AMGEN BIOSIMILARS

Biologics and biosimilars

An overview

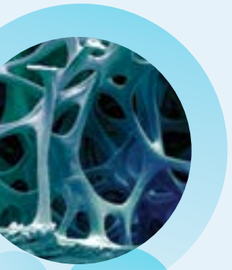
Contents

Information contained within this booklet is accurate as of August 2017.

Overall summary

"A thorough knowledge surrounding biosimilars will ensure the appropriate use of biopharmaceuticals." [1]

-The Challenge of Biosimilars. *Annals of Oncology*



Biologics and biosimilars: an overview

Biologic medicines have led to significant advances in the treatment of patients with serious illnesses.[1] These medicines are large, complex molecules that are difficult to manufacture because they are made in living cells grown in a laboratory.[2,3]

It is impossible for a different manufacturer to make an exact replica of a biologic medicine due to several factors, including the inherent complexity of biologics and the proprietary details of the manufacturing process for the original biologic medicine, often referred to as the reference product.[3]

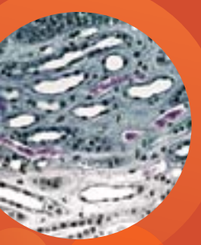
It is because of this that copies of biological products are referred to as “biosimilars”; they are highly SIMILAR but not identical to the biologic upon which they are based.[1]

In the United States (U.S.), Europe, Japan, Canada and Australia, regulatory authorities require developers to meet high-quality standards to demonstrate similarity between a biosimilar and a reference product. Manufacturers of biosimilars will be required to provide robust data to demonstrate that no clinically meaningful differences exist between a biosimilar and the original biologic medicine.[4-8]

There are a number of clinical considerations to take into account for biosimilars:

- Everyone involved in patient care should have a clear understanding of which medicine – by which manufacturer – is being administered to the patient; this can be achieved by ensuring that all biologics and biosimilars have distinguishable names. It is important that clear details of the medicine administered are captured in the patient record.
- Biosimilar labels should also be inclusive of all the relevant information supporting the safety and use of the biosimilar so that an informed choice can be made regarding the appropriate medicine for the patient.
- Transitioning, also referred to as a single switch, is a change of one medicine to another that is approved for the same therapeutic indication, and is a decision best made by healthcare providers in consultation with their patients.[9]
- Substitution (sometimes referred to as automatic or pharmacy substitution) is a practice wherein a pharmacist may dispense an alternative medicine for a prescribed medicine without the prior approval of the prescribing physician. In the U.S., this is appropriate for biosimilars that have achieved an ‘interchangeability’ designation by the Food and Drug Administration (FDA) and only in those states that have approved legislation or regulation establishing state standards for biosimilar substitution. In Europe, automatic substitution of biosimilars by pharmacists is not practiced, and several countries have implemented laws against it.[9-11]

Biosimilars are expected to play an increasingly prominent role in healthcare offering patients and physicians additional therapeutic options. Serving patients is at the core of what we do, and it is why we’re leveraging our deep scientific capabilities from more than three decades of experience in biologics to develop high-quality biosimilars.



Biologics and biosimilars

"Biotechnology has enabled the development of treatments for a variety of serious diseases. Worldwide, many million patients have already benefited from approved biological medicines. These medicines help treat or prevent many rare and severe diseases including cancers, heart attacks, stroke, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases." [9]

-European Commission, 2013

Overview

Biologic medicines have led to significant advances in the treatment of patients suffering from serious illnesses.[1]

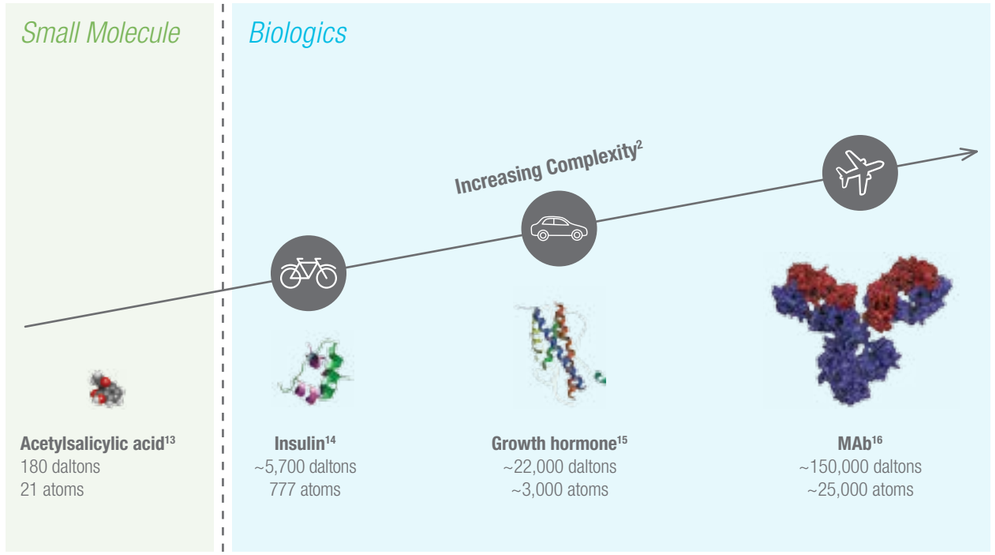
Biologic medicines are large, complex molecules that are made in living cells grown in a laboratory. They are often 200 to 1,000 times the size of a small molecule drug such as aspirin and are much more difficult to manufacture because of their complex structure.[2,3]

It is impossible for a different manufacturer to make an exact replica of a biologic medicine due to several factors, including the inherent complexity of biologics and the proprietary manufacturing process of the original biologic medicine, often referred to as the reference product.[2] It is because of this that copies of biological products are referred to as "biosimilars"; they are highly SIMILAR but not identical to the biologic upon which they are based.[1]

Biosimilars have the potential to offer patients and physicians additional options for the treatment of serious illnesses.[1]

Large-scale production of high-quality, reliably supplied biosimilars requires commitment, highly specialized biologics knowledge and experience, infrastructure and capital investment.[12]

Biologics are larger and more complex than small molecules



What is a biologic?

Biologic medicines are large, complex molecules that are made in living cells grown in a laboratory. Biologic medicines are often 200 to 1,000 times the size of a small molecule or chemical drug such as aspirin.[2,3] Due to both their large molecular size and fragile molecular structure, biologic medicines are almost always injected into the patient's body.[17]

Biologic medicines are manufactured using living cells via a complex, multi-step process

01

The isolated gene encoding the therapeutic protein of interest is placed inside a “host” cell growing in the laboratory.[3] The host cell uses this gene to make a protein which will become the medicine.[3]

03

Once sufficient quantities of the desired protein have been produced, the therapeutic protein must be isolated from the cell that produced it. Numerous purification steps are required in order to separate the therapeutic protein from impurities.[3]

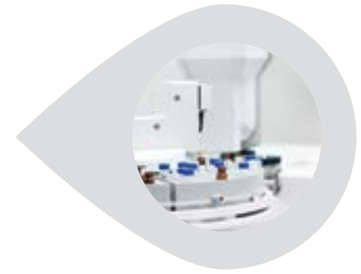
Following product approval, biologic manufacturing is carefully monitored through a tightly regulated process to ensure product consistency

02

Large volumes of these host cells are grown in a medium that has been created for optimal growth of the cells and production of the medicine.[3]

04

The purified medicine is packaged and shipped to those who need it.



Striving to ensure a reliable, high-quality supply

Biologic medicines are highly sensitive to things like temperature and pH, making them more difficult to produce on a large scale. Even minor alterations in manufacturing conditions may lead to unwanted or unintended changes in the final medicine.[12]

Manufacturers of biologic medicines are responsible for monitoring all steps during product development to ensure that the medicine is pure, has the desired strength, and is stable. Once the quality of the medicine has been verified using established tests, the medicine is packaged for eventual use by patients. Biologic medicines are very sensitive to their environment, so proper handling is critical in order to maintain production of a reliable, high-quality product.[18]

Problems or interruptions to the manufacturing process of biologic medicines may not only affect quality and safety but could also lead to delayed supplies and distribution of urgently needed medicines. Along with regulators, manufacturers have a responsibility to ensure strategies are in place to minimize incidences of drug shortages and possible supply disruption.[12]

A reliable supply of high-quality biologic medicines requires commitment, highly specialized biologics knowledge and expertise, infrastructure and capital investment.[12]

How have biologics impacted public health?

Biologic medicines have led to significant advances in the treatment of patients suffering from serious illnesses like inflammatory bowel disease (IBD), rheumatoid arthritis, psoriasis, hepatitis C, diabetes and many different types of cancers.[19]

As the mechanisms of disease progression become known, biologic medicines can be developed to target and modify the underlying cause of disease, potentially changing the course of disease rather than simply treating symptoms. For example, in rheumatoid arthritis, it has become possible to go beyond simply managing the symptoms of the disease; now the goal of treatment is disease remission. This is achieved by producing biologic medicines that specifically target pathways in the body that are involved in inflammation.

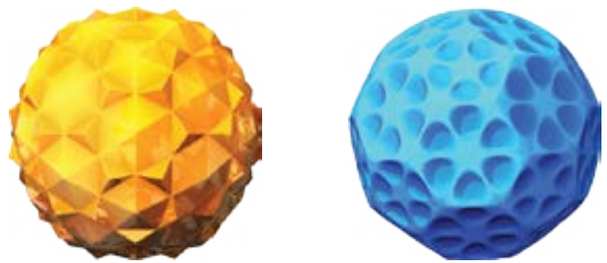
In oncology, biologic medicines can work to target the causes of cancer and may stop them from allowing the cancer to grow.

The development of new biologic medicines holds great promise for effectively treating illnesses for which there are currently no cures.

Biosimilar medicines are similar but not identical to the original biologic medicine they are based on[1]

Reference Biologic

Biosimilars



What is a biosimilar?

A biosimilar is a biologic medicine that is similar but not identical to the original biologic medicine it is based on. It is impossible to make an exact copy of a biologic medicine because they are developed using cell lines that are unique to a given manufacturer and are made using different purification processes. Therefore, the "copies" are highly SIMILAR but not identical to the original biologic upon which they are based.[1]

How do manufacturers develop and test biosimilars?

Step 1: Characterize the existing biologic medicine and develop a process to replicate it

Because of the structural complexity of biologic medicines, developing a high-quality biosimilar requires extensive scientific and manufacturing expertise. In order to develop a biosimilar, a manufacturer must have a thorough understanding of the biologic medicine that is being replicated and how it works in the body. A biosimilar developer does not have the proprietary knowledge of the manufacturing process for the original biologic medicine and must work to develop its own process to produce the biosimilar, starting with the gene that encodes the medicine.[1]

Step 2: Develop a unique cell line and manufacturing process for the biosimilar

Since biologics and biosimilars are produced in living cells in a multi-step process that is unique for every manufacturer, the manufacturing details will differ slightly between the biosimilar and its original biologic medicine. As a result, the final products will also have minor differences in their structures.

The impact of different manufacturing processes on a medicine can be compared to two different bakers who both sell chocolate chip cookies. While both recipes contain the same basic ingredients such as flour, sugar, butter and chocolate chips, the exact details of the recipe will differ. For example, whether the butter is melted or room temperature, the number of eggs used, baking time and temperature all impact the texture and taste of the cookie. Similarly, differences in biological systems (e.g., type of living cell in a laboratory environment) used to manufacture biosimilars may cause them to be slightly different from the original reference biologic, which in turn may affect the quality, safety or effectiveness of the product. It is critical to understand these differences and to demonstrate that they are not clinically meaningful, thus the biosimilar is expected to be as safe and effective as the original biologic medicine for an approved condition of use.

Step 3: Characterize the biosimilar candidate and match critical quality attributes

Like a human face, a biologic drug is enormously complex and has a large number of features. For the biologic, we call these attributes, and there are typically a hundred or more. Some of these attributes are important to the different ways the body can recognize proteins and are therefore critical to the safety, efficacy and pharmacokinetics of the drug. Features important to these functions are known as “critical quality attributes” (CQAs). These CQAs include structural aspects of the molecule that are influenced by the DNA used and by the cell line and manufacturing process.[20]

Critical quality attributes should fall within an expected range, as they may impact clinical activity, that is, how the molecule effects the patient. Evaluating the extent of similarity in the CQAs is the goal of analytical characterization. A biosimilar manufacturer may measure 100 different attributes using 40 or more analytical tests referred to as assays.[21]

Matching features between the original biologic medicine and the biosimilar is essential[20-22]

Some attributes are important on their own

- Primary structure
- Higher-order structure
- Biological function
- Receptor binding and immunochemical properties
- Product-related substances and impurities
- Process-related impurities
- Stability
- General properties and excipients

Others are important when looked at together

Step 4: Testing to demonstrate similarity to the original biologic medicine

A series of tests, including pre-clinical assays and clinical evaluations, are used to show that the biosimilar has no clinically meaningful differences from the original biologic medicine. Ultimately, all of these various types of information from analytical, non-clinical and clinical testing are integrated to provide an overall assessment called the "totality of evidence."

The following contribute to the totality of the evidence used by a manufacturer to assess the medicine.[23]

a) Analytical characterization: Testing done in the laboratory to show that the biosimilar has matched all critical quality attributes and functions of the original biologic medicine. This forms the foundation of the biosimilarity assessment.

b) Nonclinical testing: Animal studies to assess function, activity, and toxicity of the biosimilar

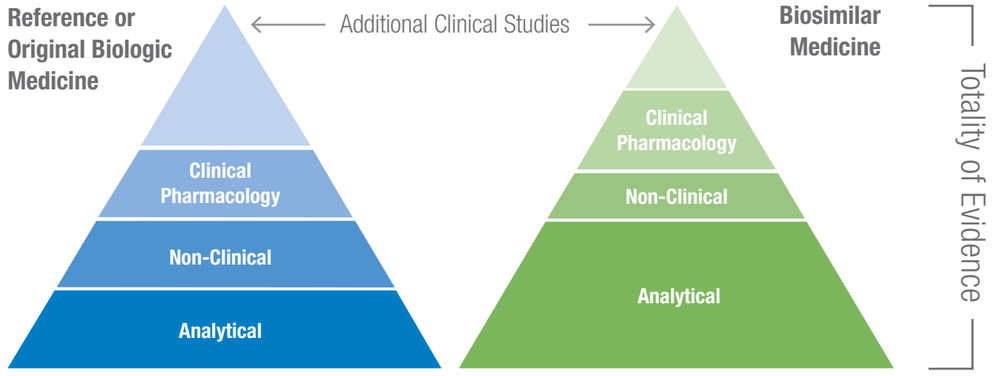
c) The final step in demonstrating biosimilarity: clinical studies in humans.

While clinical requirements differ by regulatory agency, in general, two phases of clinical studies are required – a Phase 1 study to demonstrate similar pharmacokinetics (how a medicine moves through the body) and pharmacodynamics (effect of the medicine in the body), and a pivotal Phase 3 study to demonstrate similar efficacy, safety and immunogenicity to the reference biologic.[24]

If pharmacokinetic and/or pharmacodynamic equivalence has been demonstrated, the next step in biosimilar development is to conduct a pivotal clinical trial. The objective of the pivotal trial is to demonstrate that there are no clinically meaningful differences between the proposed biosimilar and the originator biologic medicine. This means that the proposed biosimilar is neither worse (inferior) nor better (superior) than the originator biologic medicine.[4]

In conducting clinical trials for biosimilars, it is important to select the patient population that is most likely to react to any clinically meaningful differences between the original biologic medicine and the biosimilar (this population is known as the most sensitive population). The length of study should be sufficient to allow for the detection of any immune response, which can sometimes lag behind receipt of the medicine.[4]

A series of tests, including pre-clinical assays and clinical evaluations, are used to show no clinically meaningful differences[23]



With each step, the manufacturer has increasing certainty that the biosimilar will have a highly similar clinical effect as the original biologic medicine.[23]

Regulating Biosimilars

"The approach established for generic medicines is not suitable for development, evaluation and licensing of similar biotherapeutic products (SBPs) since biotherapeutics consist of relatively large and complex proteins that are difficult to characterize." [25]

-The World Health Organization

Overview

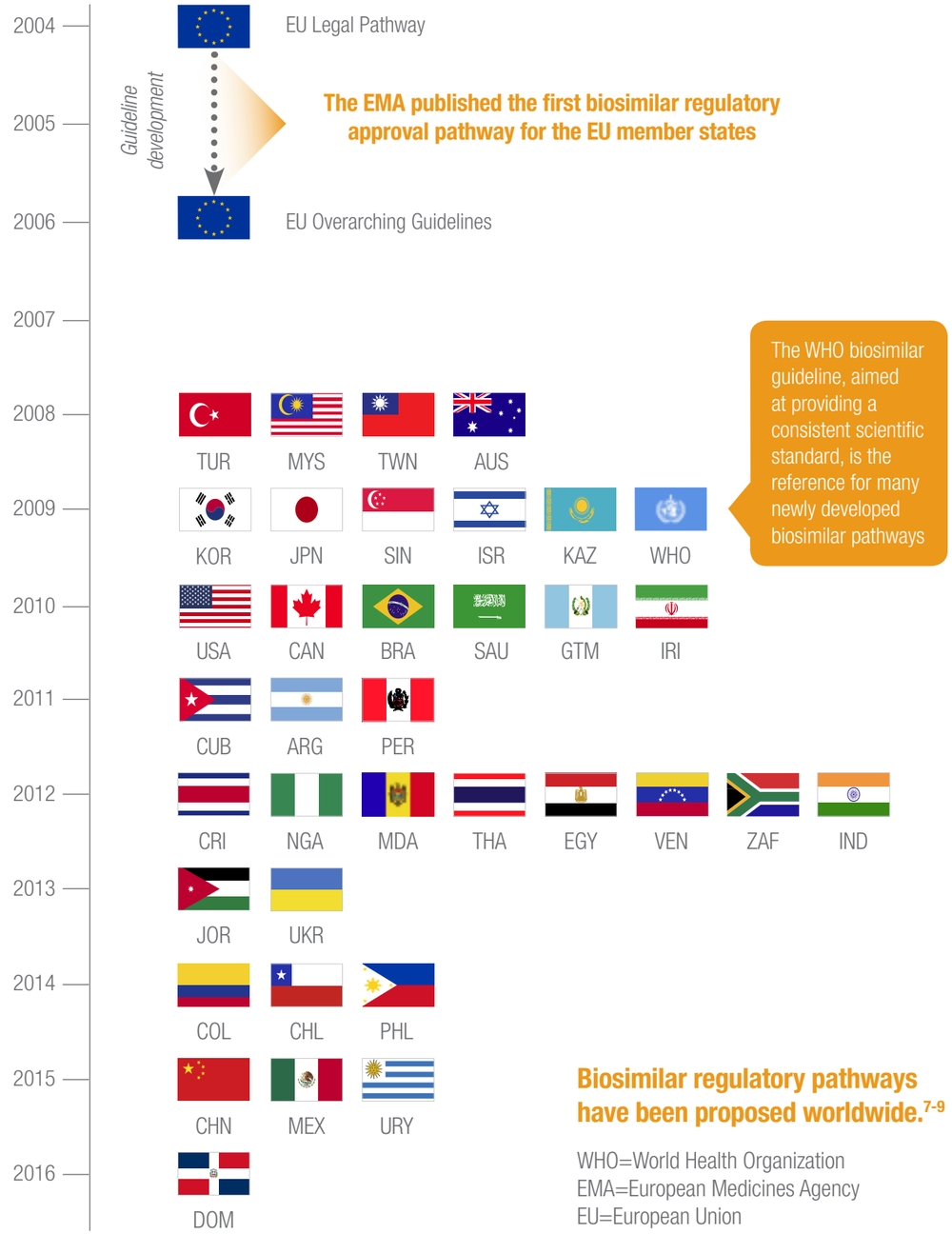
Biologics are large complex molecules that cannot be exactly replicated: only similar, but not identical versions can be made.

Early in the development of biosimilars, it was recognized that the guidelines in place for generic medicines were not suitable to govern the approval of biosimilars.[25]

Beginning with the European Medicines Agency (EMA) in 2005, regulatory agencies around the world began to develop and implement specific policies on biosimilars to ensure the production of effective, high-quality medicines.

There are now 36 countries, spread across most regions of the world, who have biosimilar regulations in place that govern the safety of these medicines.

The regulations provide manufacturers with guidance on how to demonstrate biosimilarity with the original biologic medicine as well as information on naming, demonstrating interchangeability, and labeling for biosimilar medicines.



Biosimilar regulatory pathways have been proposed worldwide.[7-9]

WHO=World Health Organization
EMA=European Medicines Agency
EU=European Union

The World Health Organization (WHO)

The WHO guidelines for biosimilars were released in 2009 with the goal of providing globally acceptable principles for evaluating and approving biosimilar products.[25]

Many countries around the world have used these guidelines as a template for generating their own, country-specific guidances.

Europe and the European Medicines Agency (EMA)

The first region to develop biosimilar guidelines was Europe, in response to emerging patent deadlines for a number of biologic medicines. The guidances were formally adopted in 2005 and were subsequently updated in 2015.[26]

The European guidances have become a template for the development of the biosimilar policies of other regions, and Australia has adopted them in their entirety.

In addition to the initial over-arching guidelines, EMA has issued guidelines specific to quality manufacturing, clinical and non-clinical requirements, immunogenicity, and manufacturing changes.[5, 27-30]

Europe has also issued a set of guidelines that describe the requirements for demonstrating biosimilarity for specific medicines.

North America: U.S. and FDA

In February 2012, FDA issued three draft guidance documents on biosimilar product development to assist those companies developing biosimilars in the U.S. In April 2015, FDA updated, revised and finalized these guidelines:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product[4]
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product[22]
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry.[11]
  The Questions and Answers guidance included some additional questions for which comment was invited.

In addition to the three overarching guidance documents, FDA has issued guidelines addressing naming, labeling, clinical pharmacology, reference product exclusivity, demonstrating interchangeability with a reference product, and how to approach formal meetings with FDA.[31-36]

Canada and Health Canada

Health Canada finalized their guidelines for biosimilars in 2010, and released an update to their biosimilars guidance in 2016.[7]

Health Canada also released a Questions and Answers document alongside the guidelines to provide additional information.[37]

Latin American Region

Argentina and ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica)[38]

In Argentina, biosimilars are known as Medicamento biológico similar (similar biological medicines).

Biosimilar guidelines were issued in 2008 by ANMAT. The guidelines follow the principles of the EU biosimilars guidance.

Brazil and ANVISA (Agência Nacional de Vigilância Sanitária)[39]

In Brazil, biosimilars are known as follow-on biological products. Brazil developed their biosimilar regulations in 2010 (Resolution no. 55/2010). The guidelines follow the principles of the WHO biosimilars guidance.

Colombia and INVIMA (Instituto Nacional de Vigilancia de Medicamentos Y Alimentos)[40]

In Colombia, biosimilars are known as productos bioterapéuticos similares (similar biotherapeutic products).

Colombia released their final guideline for biosimilars in September 2014. The decree provides for three routes for biological products: a complete route, a comparability route and an abbreviated route which aims to facilitate the approval of biosimilars.

The U.S. and EU have raised concerns with the decree as likely to put patient safety at risk and for not having sufficient detail.

In 2015, manufacturing and stability guidelines were also released.

Cuba and CECMED (Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos)[41]

In Cuba, biosimilars are called Known Biosimilar Products.

CECMED published their biosimilar guidelines in 2011. They are based on WHO guidances with some adjustments to ensure they are appropriate for the region.

Mexico and COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios)[42]

In Mexico, biosimilars are known as biocomparables.

The biocomparables guidance came into effect in April 2012. At that time, there were at least 23 non-originator biologics already available on the Mexican market. Companies who registered these biologics prior to October 2011 (known colloquially as Biolimbos) are now mandated to conduct clinical trials to prove biosimilarity.

Biosimilar guidances have also been issued in Costa Rica (2012), Guatemala (2010), Peru (2011), Uruguay (2015), and Venezuela (2012).[43-47]

Australia and the Therapeutic Goods Administration (TGA)

In Australia, the EMA biosimilar guidelines were adopted in their entirety in 2008.[8]

Asia and Asia Pacific

Japan and Pharmaceuticals and Medical Devices Agency's (PMDA) Office of Biologicals[6]

In Japan, biosimilars are known as Follow on Biologics (FOBs).

Japan developed their follow on biologics guidelines in 2009. The guidelines follow the principles of the EU biosimilars guideline.

In addition to the overarching guideline, PMDA has also issued additional guidelines addressing naming, marketing approval applications, and a questions and answers document.

Korean Federal Drug Association (KFDA)

The Guideline on Evaluation of Biosimilar Products became effective in 2010 and was updated in 2014. This was accompanied by a Questions and Answers guidance.[48]

The Korean biosimilar guideline is based on the European, Japanese and WHO guidelines.

KFDA has also issued a set of guidelines that describe the requirements for demonstrating biosimilarity for specific medicines.

Taiwan and Taiwan FDA (TFDA)

TFDA finalized their Guidance for Review and Approval of Biosimilar Products in 2008, and published two additional guidelines subsequently: Points to Consider for Review and Approval of Biosimilar Products in 2010, and Guideline for Review and Approval of Biosimilar Monoclonal Antibodies in 2013.[49]

Biosimilar guidances have also been issued in Malaysia (2008), Singapore (2009, updated in 2012), China (2015), Iran (2010), Israel (2009), Jordan (2013), Kazakhstan (2009), Philippines (2014), Saudi Arabia (2010), Thailand (2012), Egypt (2012), Moldova (2012), Nigeria (2012), South Africa (2012), Turkey (2012) and Ukraine (2013).[50-65]

India released official guidelines in 2012, before which around 20 biosimilars were already approved for use under an ad hoc abbreviated process. The WHO will continue to monitor progress.[66]

In recent years, a number of biologic medicines have begun to go off-patent, allowing for the introduction of biosimilars.

Biosimilars Approved Around the World

As of January 2017, there are eight classes of biosimilar medicines approved around the world. Not all are approved in all regions, and for those that are approved, there are variations in the specific diseases for which the medicines are approved.[70-75]

Clinical considerations

"It should be recognized that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." [26]

-European Medicines Agency

Overview

A key clinical consideration is how and when biologics and biosimilars can be safely used.

A clinician may choose to transition or switch the biologic medicine a patient is currently treated with for another biologic – either a different brand or biosimilar – that is approved and available to treat the same condition. This is a decision made by a healthcare provider in consultation with their patient.[67]

Substitution (sometimes referred to as automatic or pharmacy substitution) is a practice wherein a pharmacist may dispense an alternative medicine for a prescribed medicine without the prior approval of the prescribing physician. In the U.S., this is appropriate for biosimilars that have been designated by FDA as "interchangeable" and only in those states that have approved legislation or regulation establishing state standards for biosimilar substitution. In Europe, automatic substitution of biosimilars by pharmacists is not practiced, and several countries have implemented laws against it.[9-11]

One of the most important considerations for biosimilars is that they have distinguishable names so that health care professionals and patients clearly understand which medicine is being administered.

It is also important that the prescribing physician have clear labels describing their safety and the data behind the approval decision so that an informed choice can be made regarding the appropriate medicine for the patient.

Transitioning to a biosimilar

Transitioning, or a single switch, typically refers to a physician-guided change from one medicine to another that is approved for the same therapeutic indication in patients who are undergoing treatment.[9] If it has been demonstrated that patients can be transitioned, or switched, from the original biologic medicine to its biosimilar with no additional risks or changes in effectiveness it may be appropriate to transition a patient with the consent of a treating physician. However, unless products have been evaluated for the safety of repeated switching between the reference product and a particular biosimilar that has been designated as "interchangeable" by FDA (U.S. only), repeated switching between different biologic medicines, including biosimilars to the same product, should be avoided.[11]

Key definitions:

Substitution[10-11]	Practice wherein a pharmacist may dispense a different medicine other than that which was prescribed, without the authorization of the prescriber.
Automatic substitution[10-11]	Practice allowed by law requiring pharmacists to dispense the less costly or preferred biological medicine regardless of the prescribed medicine, and without the prior authorization of the prescriber. In the U.S., this is permitted by some states but only for biosimilars that have achieved an interchangeability designation as determined by FDA and only in those states that have approved legislation or regulation establishing state standards for biosimilar substitution.
Switching, or transitioning[9, 32]	Practice wherein a prescriber may alternate between similar biological medicines and the product a patient is currently treated with at any point during treatment. This is a decision made by a healthcare provider in consultation with their patient. • Transitioning typically refers to a single switch • Switching typically refers to repeated changing

Substitution and interchangeability

Substitution (sometimes referred to as automatic or pharmacy substitution) is a practice wherein a pharmacist may dispense an alternative medicine for a prescribed medicine without the prior approval of the prescribing physician.[10,11] This is often permitted with generic small molecules where FDA has determined the two products to be therapeutically equivalent.

Since biosimilars are complex biologics that are highly similar to their reference medicines, but not identical, different guidelines apply to biosimilar substitution.

The U.S. biosimilars pathway offers the opportunity for a drug manufacturer to demonstrate interchangeability, which is a specified designation authorized by FDA when a biosimilar can be expected to produce the same clinical result as the reference product in any given patient with no additional risk in terms of safety or diminished efficacy.

U.S. FDA

In January 2017, the FDA issued a draft guidance: 'Considerations in Demonstrating Interchangeability With a Reference Product'.[32]

To obtain an interchangeability designation, a manufacturer must successfully conduct switching studies in which patients alternate between the reference and biosimilar products with no loss in efficacy or safety versus continued use of the original biologic medicine.

If a biosimilar receives an interchangeable designation, it may be substituted at the pharmacy without the intervention of the prescribing physician, IF state law permits. The U.S. is the only country with a specific definition for an interchangeable biologic.[11]

In the U.S. as of June 2017, 35 states and Puerto Rico permit a pharmacist to substitute an interchangeable biosimilar for the original biologic medicine prescribed without physician consent.[79]

Europe EMA

Decisions on when it is appropriate for prescribers to change a patient from one medicine to another, are governed by each local health authority within each individual country within the EU, and not by the EMA.

In most European countries, there is no authorization for pharmacist-driven changes (referred to as automatic substitution).[9] In January 2014, France became the only European country to pass a law allowing biosimilar substitution by pharmacists but only under specific conditions.[80] That law has not been implemented as of the end of 2016.

Most European countries use a tendering system to procure competitively-priced medicines for patients. In this system, a country's government or authoritative body chooses the drug from the manufacturer who offers the lowest price.[81-82] In April 2016, a law came into effect, the EU Procurement Directive (2014/24/EC), which requires the introduction of the MEAT (Most Economically Advantageous Tender) design. This allows for multiple winners of the tender, to help to ensure reliability of supply.[83]

WHO

The WHO does not define standards on interchangeability or substitution for biologic medicines. The WHO believes that these decisions should be made by the national authorities.[25]

Summary of substitution policies worldwide

Information contained within this booklet is accurate as of August 2017.

Summary of U.S. state legislation

While FDA is the authority that determines the interchangeability of biosimilars, the laws that govern pharmacy substitutions are controlled by individual states.

There are currently laws in place at the state level to govern pharmacy substitution of generic medicines for brand-name prescriptions, but those laws do not address biosimilar medicines. Generic drugs have active ingredients that are identical to those of their small molecule reference products. In contrast, biosimilars are more complex than small molecule drugs and will not be identical to the original biologic medicine; therefore, these laws are not appropriate for regulating biosimilar pharmacy-level substitution. Many states have proposed legislation to regulate biosimilar substitution and ensure patient safety when using this class of medicines. As of June 2017, most states have considered legislation establishing standards for biosimilar substitution; laws have been enacted in 35 states and Puerto Rico. Clear communication among the pharmacist, physician and patient about the exact medicine that has been dispensed allows for the appropriate monitoring of a patient's response to treatment. In the case of an adverse reaction to the medicine, it will be possible to trace the problem to the correct product.

Although the provisions of the legislation vary from state to state, there are some important principles that are frequently included:[79]

- Only biosimilars deemed interchangeable by FDA should be substituted by a pharmacist.
- The pharmacist dispensing the medicine should communicate to the prescribing physician the specific biologic that was dispensed to the patient when an interchangeable product is available.
- Patients should be informed when a substitution has occurred or, in some cases, before the substitution occurs.
- Physicians retain the right to prevent a substitution they consider inappropriate for their patient by writing 'dispense as written' or 'do not substitute' on the prescription.
- A record of the substitution must be kept by the pharmacy and the physician for a set period of time.

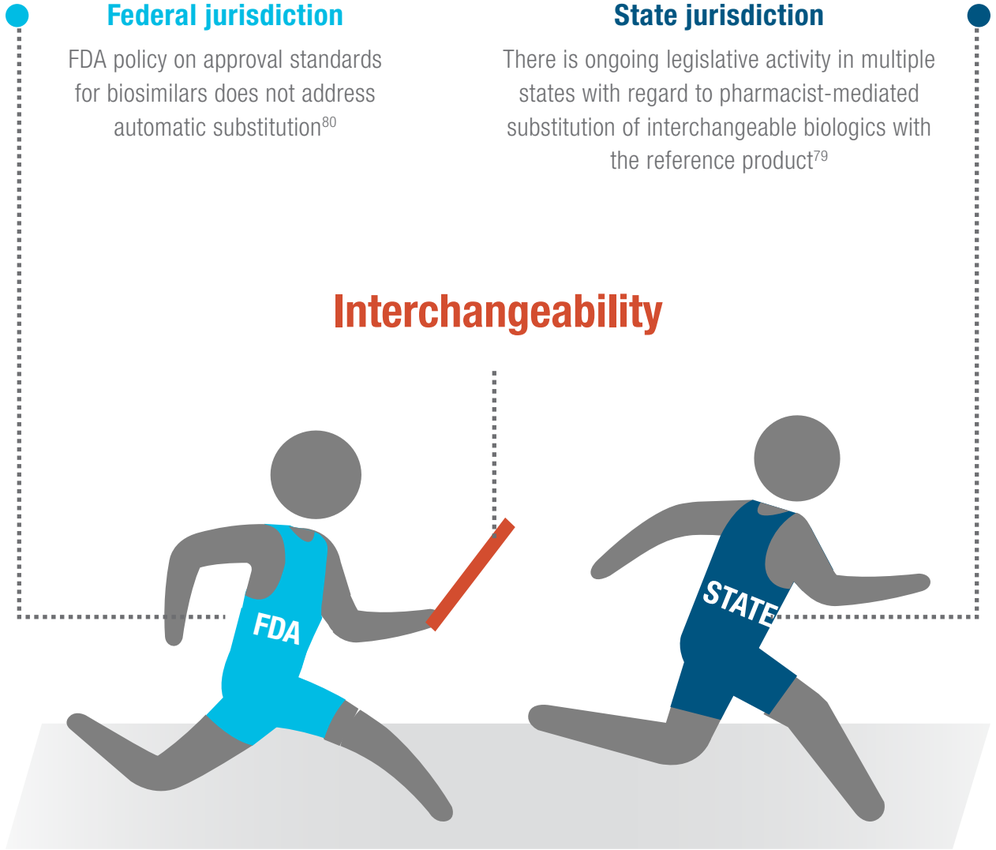
U.S. state laws governing substitution only apply to biosimilars designated by the FDA as interchangeable

Federal jurisdiction

FDA policy on approval standards for biosimilars does not address automatic substitution[80]

State jurisdiction

There is ongoing legislative activity in multiple states with regard to pharmacist-mediated substitution of interchangeable biologics with the reference product[79]

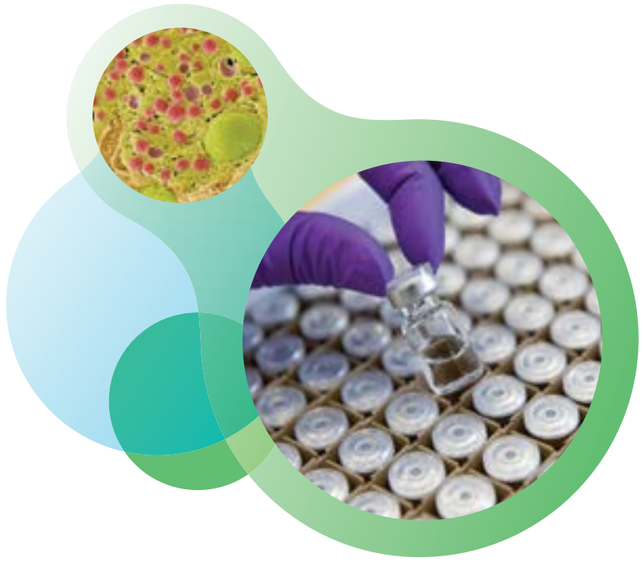


As of June 2017, 35 U.S. states plus Puerto Rico have already passed legislation regarding automatic substitution of interchangeable biologics, even though there are currently no interchangeable biologics on the market.[79]

What's in a name?

A critical part of medical care is being able to evaluate a patient's response to a specific medicine, as well as being able to monitor any side effects. One way this can be achieved is to track the use of medicines by capturing the product name in a patient's medical record. It is essential that the name allows for clear identification of the medicine received.

This is particularly important for biologics and biosimilars. Biosimilars are similar, but not identical versions of biologic medicines. These medicines are also sensitive to the manufacturing and handling process. The complexity and large molecular size of biologic medicines mean that even minor differences between two similar biologics can cause unexpected reactions in patients. Because of this, it is essential that physicians can readily identify exactly which biologic medicine a patient received, by manufacturer, so that they can appropriately care for their patients and accurately report any adverse reactions to the correct manufacturer. Ensuring manufacturers are accountable for the safety and quality of the medicines they make is good for patients.[1,31]



What's in a name? The FDA and WHO agree on names being distinguishable

WHO recommendation:
Add a four-letter biologic qualifier to the INN for biosimilars[89]

INN+_ _ _ _

FDA draft guidance:
All biosimilars will receive unique four-letter suffixes[31]

INN–_ _ _ _

Goal is to help identify patients for pharmacovigilance and avoid inadvertent substitutions[31]

INN+_ _ _ _

The EMA has not issued guidance on biosimilar nomenclature. However, the majority of EU member states do not support the WHO proposal of a qualifier for the nonproprietary name[87]

Biosimilar naming conventions around the world

In the U.S., FDA issued finalized guidance on biologic naming in January 2017.[27] Although every product may have a brand name, under FDA's guidance, the scientific – or "nonproprietary" name – will be distinct for each manufacturer. This will enable a physician to prescribe the specific biologic the patient should receive. The ability to prescribe specifically which product a patient gets is an important way to prevent inappropriate and unintended transitioning, or switching, of medicines. Equally important, if the patient has an adverse reaction to a medicine, the doctor can determine specifically which product the patient received.

In the recent guidelines on naming, FDA has recommended that the nonproprietary name for biologics be a combination of a common core name (shared by reference products and their related biosimilars to indicate that the two medicines are related) and a distinguishing suffix (so that each product may be identified by manufacturer).[27] The format of the suffix will be four lowercase letters chosen by FDA that are "devoid of meaning" and attached with a hyphen to the core name of the biologic.

Surveys have also been conducted by interest groups which show that there is strong support for memorable, meaningful suffixes – rather than randomly selected letters – that are easy for doctors and patients to use. A suffix that is an abbreviation of the manufacturer name would be an example of a memorable, meaningful suffix. This structure may help to foster effective safety monitoring of all approved biologics and support patient and physician confidence, promote manufacturer accountability and reliability of supply, and ultimately, play a key role in establishing a successful marketplace.

"Distinguishable nonproprietary names will also facilitate accurate identification of these biological products by health care practitioners and patients."[31]

-U.S. FDA Guidance: Nonproprietary Naming of Biological Products

Canada and The European Medicines Agency

In both Canada and Europe, biosimilars are generally referred to by their brand names (also called "trade names"). However, the nonproprietary names are currently identical to those of their original biologic medicine, which sometimes results in ambiguous prescribing and adverse event reporting. Health Canada, the regulatory authority in Canada, has indicated that they would like to use a distinguishable biologic qualifier for every biologic if one is adopted by the WHO.

WHO and Global Harmonization

Currently, the same biological medicine can have different nonproprietary identifiers in different parts of the world according to a protocol it has established. This nonproprietary name is used by many countries to scientifically identify the medicine so that doctors and scientists around the world can be certain they are discussing, evaluating and prescribing the same medicine regardless of where they are geographically. The nonproprietary name in the U.S. is usually the same as that assigned by the WHO; however, FDA is now giving all biologics a distinguishable suffix to ensure that each biologic is identifiable by manufacturer.[31] In Japan, a nonproprietary name is assigned to identify the biosimilar by the order in which it was approved.[88]

The lack of global consistency in nonproprietary naming can make global safety monitoring and accurate prescribing more difficult. In response to this, the WHO International Nonproprietary Naming (INN) Committee is considering assigning a distinct four-letter suffix, called the Biological Qualifier (BQ), for every biologic. The BQ would be random four-letter suffixes and could be used to distinguish among all biologics, including biosimilars.[89] For example, medicine bcfy and medicine azgt for two different medicines, each made by different manufacturers. This scheme, like all WHO names, would be optional; jurisdictions around the world could choose whether or not to adopt the BQ along with the rest of the nonproprietary name.

Biosimilar labeling

Product labels are intended to provide the information that physicians need in order to make informed decisions as to which medicine is appropriate for their patients. For biosimilars, regulators around the world have defined this differently.

Labeling policies around the world

U.S.

FDA issued a draft guidance on biosimilar labeling in 2016.[33]

The FDA expressed concern that providing data from the studies used to demonstrate biosimilarity could be confusing and irrelevant to the practicing clinician. Instead, FDA recommends that the label for biosimilars include a description of clinical data that support the safety and efficacy of the original biologic medicine highlighting any appropriate product-specific modifications that exist between the biosimilar and the original biologic medicine (e.g., differences in administration or storage).[33]

The label information will also be tailored to only include information on the indications for which the biosimilar has been approved, which may be narrower than the original biologic medicine.

Many patient and physician groups, as well as Amgen, believe that the information in a biosimilar label should:[90,91]

1. Identify the original medicine upon which the biosimilar is based.
2. Provide a clear statement as to whether the medicine is a) approved as biosimilar but NOT designated interchangeable by FDA; or b) approved as biosimilar and designated as interchangeable with the original biologic medicine.
3. Clearly identify the source of the clinical data included on the label.
4. Allow for clinical data generated by the biosimilar sponsor to be accessed – through a mechanism such as a "summary of the totality of the evidence" document or directly included in the label.

Canada

Health Canada's approach to biosimilar labeling gives prescribers more information they can consider when choosing among products. Biosimilar labels in Canada include:[7]

- A statement indicating that the medicine is a biosimilar
- Key data on which the decision for market authorization of the biosimilar was made
- Tables showing the results of the comparisons between the biosimilar and reference biologic drug
- Information on the indications approved for use

Europe

In Europe, the same label is used for the biosimilar as for the original biologic medicine. Biosimilar data (EPAR - European Public Assessment Report) is made available at the EMA website. The biosimilar label must have an inverted black triangle included, which indicates that the medicine is subject to additional monitoring.[92-93]

WHO

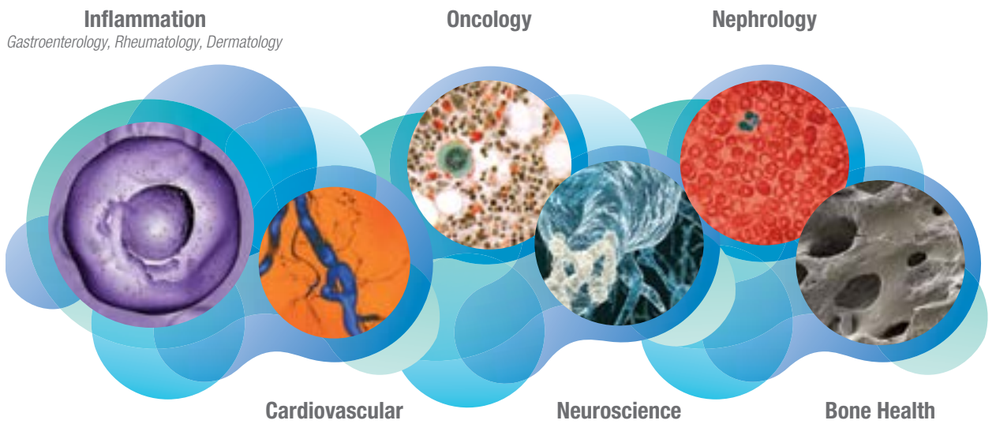
WHO does not take a formal positioning on biosimilar labeling, instead leaving national authorities to define it for their own countries.

Amgen in biosimilars

"I believe when there are multiple high-quality biosimilars – and physician confidence in these medicines – there will be meaningful options for healthcare providers." [94]

-Richard Markus, Vice President,
Biosimilars Global Development, Amgen

Amgen is committed to developing medicines across six therapeutic areas[86]



Amgen was one of the first companies to recognize the potential of modern biotechnology in developing valuable medicines for patients. Today, Amgen is applying extensive scientific capabilities from more than three decades of experience to the development of biosimilars.

At the heart of Amgen's commitment to biosimilars is our mission to serve patients. Biosimilars have the potential to offer patients additional therapeutic options and we believe we are bringing the highest quality science to this space in patient care. Due to the complexity and financial investment required for the development of biosimilars, manufacturers will benefit from having significant biologics expertise, infrastructure and capital investment to successfully bring these medicines to market.

That is why Amgen is leveraging the same personnel, services and manufacturing expertise from the company's innovative business to produce reliably-supplied, high-quality biosimilars for some of the most complex diseases.

Amgen Biosimilars will add new chapters to our story, while maintaining Amgen's commitment to connect patients with vital medicines. Our biosimilars portfolio is robust and targets key therapeutic areas. To learn more about biosimilars and Amgen's commitment in this space, visit www.amgenbiosimilars.com or follow us on Twitter (@AmgenBiosim).

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