Clinical and Scientific Considerations for Biosimilars

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Table of Contents

List of Figures

List of Tables

Clinical and Scientific Considerations for Biosimilars

1. Introduction to Biologics and Biosimilars

A **biologic** is a large protein-based therapeutic (e.g., monoclonal antibodies [mAbs] and recombinant proteins) made by using unique cell lines and is more complex in structure and function than chemical drugs.[1,2] Biologics are produced using proprietary cell banks optimized for manufacturing.[3] Biologics are large molecules up to 1,000 times the size of a chemical drug and have highly complex structures, including extensive protein folding and a variety of post-translational modifications (PTMs) such as glycosylation.[2,4] In contrast, chemical drugs have relatively simple, well-defined structures.[2,4] Biologics play a critical role in clinical care, both in terms of active therapy (mAbs, antibody drug conjugates, and interferons) and supportive care.[4]

A **biosimilar** is a protein-based therapeutic that is highly similar to a reference biologic and shows no clinically meaningful differences in safety, efficacy, quality characteristics, or biological activity.[5] Unlike small molecule generic drugs, biosimilars are not identical to the reference biologic or to other approved biosimilars of the same reference biologic, because they are developed using different cell lines and undergo different manufacturing and purification processes.[6,7]

Differences between biosimilars, and between biosimilars and reference biologics, are expected, because each reference biologic was developed using its manufacturer's own cell line and proprietary manufacturing processes, and biosimilar developers lack the cell banks and proprietary knowledge of the reference biologic manufacturer.[2,6] The differences between a biosimilar and its reference product must not be clinically meaningful in terms of safety, purity, and potency.[5] As therapeutic alternatives, biosimilars are not generics or generic biologics. With generics, the drug substance (pharmaceutical ingredient) is identical to the reference medicine.[6,8,9] Biosimilars are permitted to differ from a reference product by way of differences in formulation, device, or container closure, and they may not be approved for all of the reference product's indications.[10]

Regulatory authorities generally define biosimilars in a consistent fashion as biological products that are highly similar to a reference biologic:[5,11]

- "Highly similar" indicates there are no clinically meaningful differences between the biosimilar and reference product, with robust and rigorous assessment of analytical structure and function, pharmacology, and clinical safety, efficacy, and immunogenicity; these, considered together, constitute the "totality of evidence."[5]
- The US Food and Drug Administration (FDA) defines a biosimilar to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[5]

- The European Medicines Agency (EMA) states, “a biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines.”[8]
- Health Canada defines a biosimilar (previously known as a Subsequent Entry Biologic) as “a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. A biosimilar relies in part on prior information regarding safety, efficacy and effectiveness that is deemed relevant due to the demonstration of similarity to the reference biologic drug and which influences the amount and type of original data required.”[12]
- The World Health Organization (WHO) defines a biosimilar as “a biotherapeutic product, which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.”[13]

2. Development and Manufacturing of Biologics

2.1 Complexities of Biologic Molecules

Biologics are more complicated to develop and manufacture than small molecules. The characteristics of a biologic are related to each manufacturer’s unique cell line and process, including formulation and administration device, and changes in these can have clinical implications stemming from alterations in structural and functional differences in the biologic.[6,14]

The following properties of protein-based biologics contribute to the complexities associated with their development:

- *Size*: The size of a biologic may be thousands of Daltons as opposed to the size of a small molecule drug, which is typically hundreds of Daltons.[15]
- *Structure*: Biologics typically have a complex and heterogeneous structure with many options for post-translational modifications (PTMs), whereas small chemical-based drugs have a simple and well-defined structure.[15,16]
- *Characterization*: Biologics are dynamic entities that are difficult to fully characterize in the laboratory with currently available technology. In contrast, small molecule drugs are easy to fully characterize.[17,18]
- *Stability*: Biologics are sensitive to storage and handling conditions (including temperature and other environmental characteristics), whereas small molecules are relatively stable.[19]
- *Immunogenicity*: Biologics have intrinsic potential for immunogenicity, whereas immunogenicity towards a small molecule is intrinsic to the patient.[19]
- *Manufacturing*: Because biologics are manufactured in unique, living cell lines, only similar (not identical) copies can be made. Small molecule drugs are synthesized from predictable chemical processes, and identical copies can be made.[15]

The unique shape of a protein contributes to its function in the cellular environment.[15] A protein is synthesized as a chain of amino acids that undergoes a combination of conformational changes to form a three-dimensional polypeptide structure (Figure 1). Small changes in the folding of the protein can alter its function and manifest as a clinically meaningful difference in efficacy or safety.[17]

Proteins also undergo PTMs that further contribute to protein complexity, diversity, and function.[20] There are several hundred types of PTMs that have been identified, including glycosylation and other glycan-related changes, acetylation, phosphorylation, and amidation.[20,21] These modifications underlie differences in the biological properties of proteins (**Figure** 1).[22-26] Thus, changes in glycosylation of a mAb, for example, can lead to altered biological activity (e.g., in antibody-dependent cellular cytotoxicity [ADCC] and complement-dependent cytotoxicity [CDC]), altered antibody function, or altered bioavailability.[22,] An up to 100-fold enhancement of ADCC has been reported, for example, following the removal of the fucose residue from the glycocomponent of the IgG antibodies produced in Chinese hamster ovary (CHO) cell lines. On the other hand, glycoproteins produced in native plant-based systems often result in the formation of hyperglycosylated products containing xylose and fucose moieties, and bioengineering tactics to “knockout” insertion of these moieties are needed to produce antibodies with enhanced ADCC activity.[21]

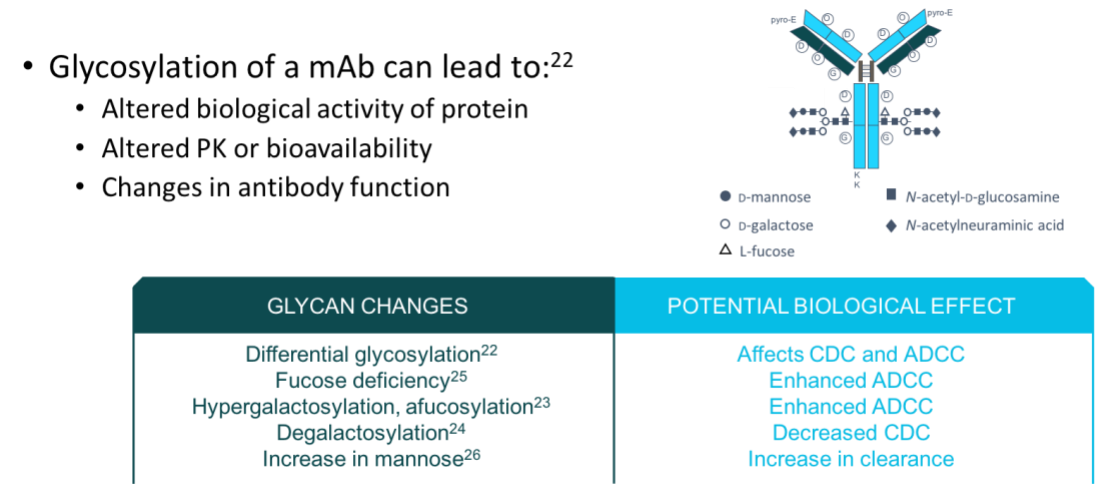


Figure 1. Post-translational modifications are a key source of functional diversity of biologics.[22-26]

CDC = complement-dependent cytotoxicity; ADCC = antibody-dependent cell-mediated cytotoxicity.

(Graphic adapted from Kozlowski, S. Slides presented at: 2015 Biomanufacturing Technology Summit; June 25, 2015; Rockville, MD)[27]

2.2 Complexities of the Manufacturing Process

The manufacturing process for a biologic medicine is more complicated and involves up to 200 additional steps compared with a chemical drug.[28] The manufacturing process begins with establishing a unique cell line, and even small changes can result in substantial changes in the critical quality attributes (e.g., activity) of any biologic produced by the cells, including a biosimilar.[6,7] Features important for the identity, purity, biological activity, and stability of a drug are called critical quality attributes.[29] Biosimilar developers do not have access to the proprietary manufacturing knowledge and cell banks of the reference product and must characterize and compare the proposed biosimilar with the reference product.[5-7] To develop a biosimilar, a biosimilar developer must create a manufacturing process for the biologic *de novo*, including creation of a unique cell line from various expression systems, growth media, bioreactor conditions, and purification conditions, and they must analytically characterize the biosimilar for similarity to the reference product in terms of critical quality attributes (e.g., purity, concentrations, structure, and biological function) using sensitive and validated assays.[6,7] Successful manufacturing of biosimilars requires expertise in protein engineering, cell line development, and large-scale cell culture.[30]

One of the first steps in the development of a biologic is to isolate the gene that encodes the protein of interest.[18] The isolated gene can be spliced into an appropriate expression vector (e.g., a plasmid or viral vector), and the resulting DNA vector is used to transfect a host cell line (e.g., hamster, rabbit, or bacterial cells).[18,31,32] The host cell is then grown in culture to produce the desired protein **(Figure 2)**.

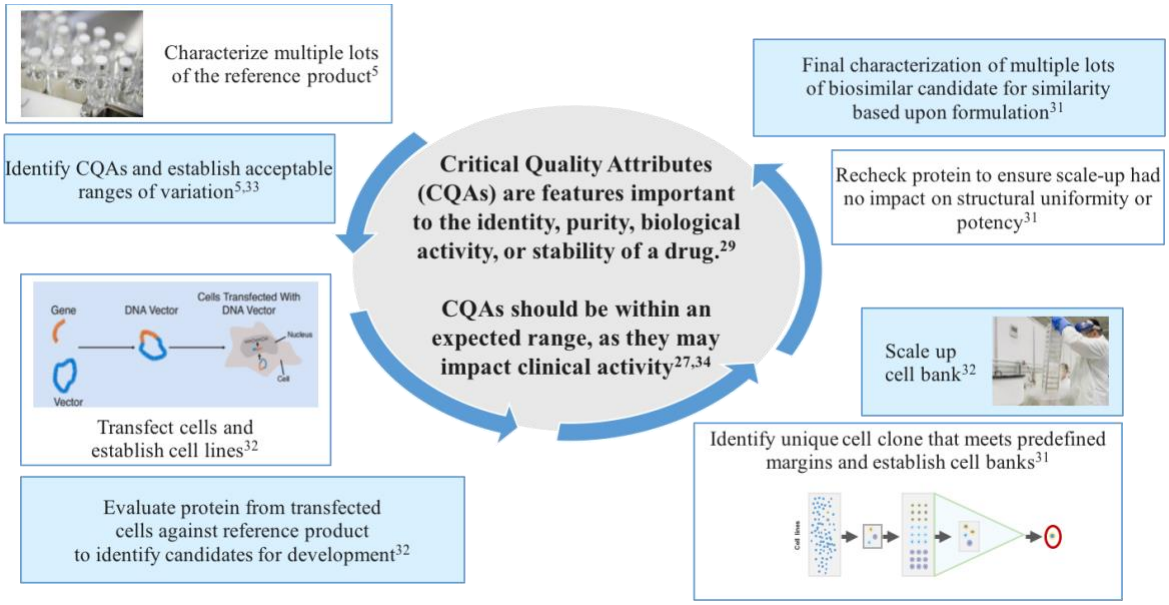


Figure 2. An overview of the biosimilar manufacturing process.[5,29,31-35]

Following transfection with the DNA vector, unique cell clones are screened for expression of the desired protein. After a positive clone is identified and expanded, a large number of vials of the cells are cryopreserved in a master cell bank.[32] Engineering and preserving an appropriate cell line for producing the protein of interest requires extensive work and careful screening. The resulting cell line will be unique for each manufacturer.[31,32]

The master cell bank houses primary cell strains that are not used for production purposes. A working cell bank is established from the master cell bank, and these cells are used for production purposes.[32] Each batch of a biologic medicine requires one vial of cells from the working cell bank, and the working cell bank is continually replenished by expanding vials from the master cell bank.[3] To begin the manufacturing process for a product batch, scientists remove and thaw a vial of cells from the working cell bank and initiate a cell culture in a flask containing a small volume of growth media. The media provides the nutrients and the optimum environment for cells to survive.[18]

The growing cells are gradually transferred into successively larger growth vessels containing larger media volumes in a "scale-up" process. The cells are constantly dividing as long as the growth environment remains favorable.[18] Therefore, more and more cells are present with each step. The greater the number of cells, the more protein product is generated. Production bioreactors can range from hundreds of liters to greater than 10,000 liters in capacity.[32]

In the downstream phase of manufacturing, the desired protein product is isolated from the cells that produced it. Often, the protein is secreted by the cells such that the recovery is a simple matter of separating cells and cell debris from the soluble components. Sometimes the protein is expressed inside the cells, and in this case recovery involves lysing the cells to release the protein product, which then has to be purified by separating from the other components that were inside the cell. Additional purification steps are always required after primary recovery in order to separate the product from other soluble impurities, including growth media, host cell impurities, and unwanted variants of the recovered protein product. Researchers verify the isolation and purification of the protein product through confirmed testing protocols.[31]

Manufacturers of biological products are responsible for all of the monitoring that is crucial to the success of the scale-up and manufacturing stages of product development.[36] Tests are performed to measure product attributes associated with product quality and manufacturing controls and are performed to assure identity, purity, strength (potency), and stability of products.[37]

The protein product is then formulated according to specifications and packaged for use by physicians and patients. Biopharmaceuticals are highly sensitive to environmental factors, such as temperature, agitation, and exposure to light. Improper storage and handling can lead to protein degradation.[31] The stages involved in a typical biotechnology manufacturing process are illustrated in **Figure 3.**[31,32]

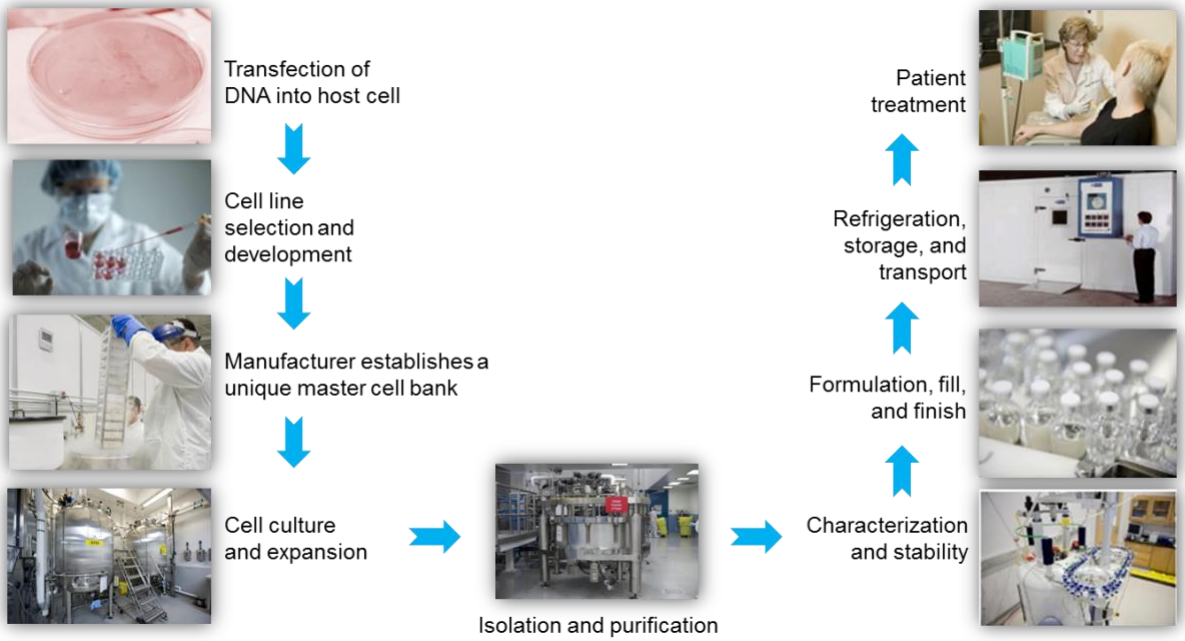


Figure 3. Biologics are produced in evolving manufacturing processes and are naturally prone to heterogeneity.[31,32]

The properties of a biopharmaceutical are dependent on the manufacturing processes, which may be similar, but not identical, between manufacturers. Differences in manufacturing processes, such as the cell line used to produce the protein and extraction/purification methods, can result in structural differences in the resulting biopharmaceutical.[5,6] Different manufacturing processes may alter a protein product in a way that could change the safety or efficacy of the product. Variations in manufacturing processes can contribute to differences in a biological product's structure, aggregation tendency, and PTMs, all of which can affect the activity profile of the protein.[38] Analytical and clinical testing is needed to evaluate the biological activity of the finished product.[31]

2.3 Manufacturing Process Changes

Manufacturers of biologics may periodically make changes to manufacturing processes in order to improve certain aspects of the process (i.e., increase scale, improve product stability, and/or comply with changes in regulatory requirements). When products undergo highly regulated *planned* process changes, the changes typically result in consistent quality within the historical lot-to-lot variability of the product. However, occasionally, they may involve a small shift in certain product attributes (i.e., outside of normal lot-to-lot variability). Process changes are always justified to show there is no adverse impact on safety and efficacy. Analytical studies, biological studies, and, occasionally, clinical bridging studies are used to evaluate and confirm that manufacturing changes do not affect the potency, safety, or immunogenicity of a product.[36]

An *unplanned* trend or shift in a quality attribute over time (away from the intended target value) is referred to as “process drift.” It is important to monitor trends in CQA attributes, i.e, chemical, physical, biological, and microbiological attributes of the product that can be well-defined, measured, and monitored on an ongoing basis to assure that these parameters remain within preset limits, particularly those attributes classified as most relevant to clinical outcomes.[33] Potential causes of drift include planned supplier-driven changes in raw materials or components and cumulative effects of minor changes in procedures, equipment, or facilities (e.g., calibration, maintenance, operator practices).[39]

An intensive investigation is performed to determine the root cause and identify measures to prevent additional drift and, if necessary, return the process to a state of control while also ensuring that the excursion has no adverse effect on product quality, safety, and efficacy.[40] Product consistency is accomplished through careful monitoring, regulation, and expertise in biologic manufacturing. Biologic manufacturing processes are regulated by manufacturers and health authorities, and data are required to demonstrate that any changes in manufacturing do not change the clinical or safety characteristics of their product.[41]

The US FDA has stated that assessing the comparability of a product before and after an innovator company makes a change to its own manufacturing process is not the same as demonstrating biosimilarity of a proposed biosimilar to a reference product.[5] In the former case, the originator company has the proprietary information and history of the biologic and its manufacturing process and applies this knowledge to make a specific post-approval change to its own product. The post-change product is, therefore, not a biosimilar. Even though some of the scientific principles used in the comparability assessment for manufacturing changes may be used in demonstrating biosimilarity of a proposed biosimilar to a reference product, more data and information are generally needed to establish biosimilarity, because there are more unknowns and hence more uncertainty.[5] Biosimilarity is a different concept whereby the sponsor develops a molecule similar in structure and function to the reference molecule using a new or different cell line and process; demonstration of biosimilarity is based on a comparative characterization of this new product, produced by a different manufacturer, with the reference product **(Table 1)**.[42]

An important consideration during the development of biosimilars is the differentiation between *comparability* and *biosimilarity*. *Comparability* refers to the comparative assessment of characteristics of the biologic product after a specific change in the manufacturing process and is implemented by a manufacturer for their own product. The implementation of such a change is supported by their comprehensive knowledge and history of the development of the product. *Biosimilarity*, on the other hand, refers to the development of a molecule that is “similar” to an existing reference product manufactured by a different manufacturer and the comparative characterization of this new product with the reference product. The US FDA defines biosimilarity to mean that the newly developed biological product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."[5,36] Because of the enormous differences between comparability and biosimilarity, it would not be accurate to state that a biologic becomes a biosimilar of itself over time.

The US FDA specifically addressed this topic in its guidance issued in April 2015:

Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. In contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Therefore, even though some of the scientific principles described in ICH Q5E (International Conference on Harmonization) may also apply in the demonstration of biosimilarity, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's postmanufacturing change product is comparable to the premanufacturing change product.[5]

Table 1. Comparability versus biosimilarity: Attributes known (√) and unknown (?) to the manufacturer.[42]

Comparability Is Not the Same as Biosimilarity

		Product history	Process evaluation	Analytical studies	Nonclinical studies	Clinical studies
Comparability Same manufacturer, same product	**Modified process** Abbreviated comparability	✓	✓	✓		
	New process Comprehensive comparability	✓	✓	✓	✓	✓
Biosimilarity Different manufacturer, new product	**Biosimilar process**	?	?	✓	✓	✓
		Knowledge gap				

3. Overview of Global Biosimilar Approval Pathways

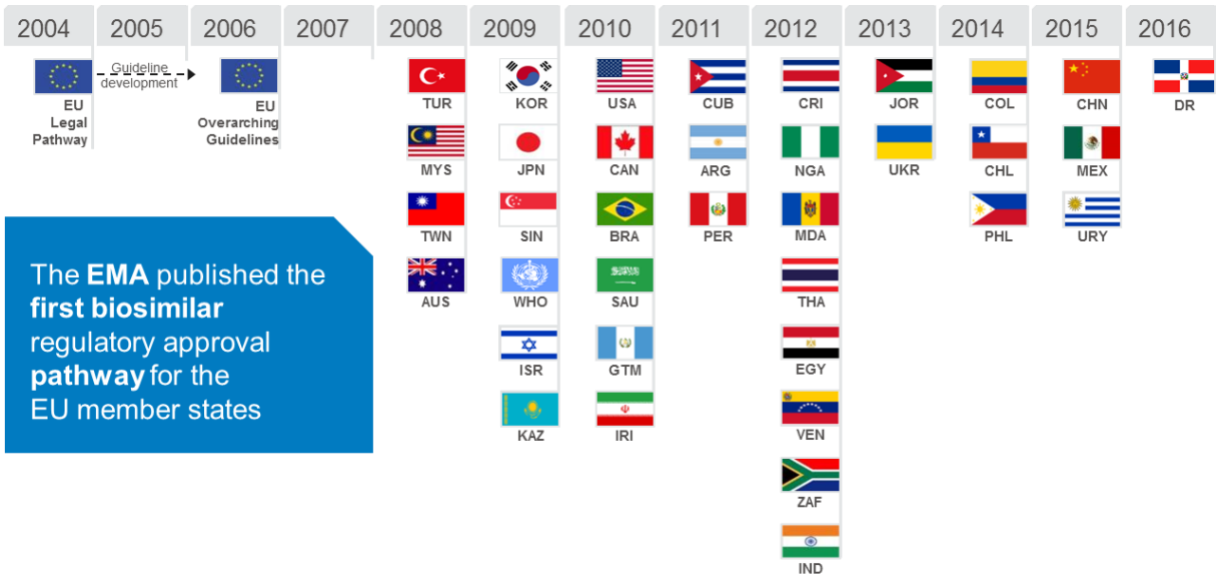
The regulatory pathways for biosimilars are rigorous and different from those for generics; approval is based on the total evidence package obtained from preclinical characterization and clinical studies.[5,35,43,44] The EMA regulatory pathway, established for the European Union (EU) member states, often serves as a reference for regulatory agencies in other regions of the world to develop guidelines on biosimilar review and approval. Many European countries that are not members of the EU do not currently have formal guidelines in place for the approval of biosimilar agents. Some of these countries (e.g., Norway, Croatia, Switzerland, and Turkey) follow the EMA guidelines or have implemented draft guidance.[45] Effective January 1, 2016, Russia and other members of the Common Market of Medicines in the Eurasian Economic Union (i.e., Armenia, Belarus, Kazakhstan, and Kyrgyzstan) adopted harmonized regulatory standards, including provisions based on EMA guidelines for biosimilar products.[46] Although many countries have based their guidelines on the EMA requirements for biosimilars, there are variations from region to region.[45]

In Latin America, the regulation of biosimilar agents varies widely among different countries. At least 11 countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Guatemala, Mexico, Panama, Peru, and Uruguay) have drafted or finalized specific requirements for the approval of biosimilars (generally based on WHO criteria). Some "intended copies" of originator biologics have already been licensed in Latin America without biosimilars regulations being in place and without adequate clinical testing performed.[44-46] In 2015, WHO finalized a Regulatory Assessment Guideline to recommend approaches for member states to review the status of nonoriginal biologics that were not licensed according to the current WHO guidelines.[46] Regulations in several Latin American countries (e.g., Mexico and Chile) include provisions to review the status of biologics licensed under prior laws.[49,50]

In Asia, government agencies in Japan, Malaysia, Saudi Arabia, Singapore, South Korea, Sri Lanka, and Taiwan have established regulatory pathways for the evaluation and approval of biosimilar agents.[37] The China Food and Drug Administration (CFDA) released guidelines on the development and evaluation of biosimilars in 2015.[51] India released new biosimilars guidance in September 2012 that outlines pre- and post-marketing regulatory requirements, including the recommendation of a stepwise approach to demonstrating biosimilarity.[51] However, India has been producing "intended copies" of already licensed biological products since 2007 under an abbreviated approval process that relies on limited efficacy data, thus allowing local biopharmaceutical manufacturers to keep production costs low and provide therapies to more patients than those who could afford the reference product.[45] These "intended copies" have not met the strict criteria for demonstration of biosimilarity that regulatory bodies such as the EMA and FDA utilize for review and approval of biosimilars.

Other nations that have implemented guidelines for biosimilar agent approval that are based on EMA regulations include Australia, New Zealand, and South Africa.[45] Since drug approval requirements for some regions vary from those of the International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, the WHO developed guidelines in 2009 in an attempt to harmonize global approval standards for

biosimilars.[13] **Figure 4** provides a timeline for the development of several global biosimilar agent approval pathways.



The flag locations reflect Amgen's best judgment of the effective dates for the pivotal implementing laws, regulations, or guidelines for reviewing a biosimilar application; information is current as of June 26, 2017.

Figure 4. EMA and WHO guidelines were catalysts for sound scientific approach to the development of biosimilar approval pathways around the globe.[13,53]

Data source: Publicly available information from national regulatory authorities and World Health Organization guidelines and data on file. EMA = European Medicines Agency; EU = European Union; WHO = World Health Organization.

In recognition that certain member states have registered nonoriginator biological products using regulatory pathways that are inconsistent with the WHO guideline for biosimilars, WHO developed a guideline in 2015 that provides a road-map for regulatory assessments of such products. The guideline clearly states that biologics registered without a comprehensive, head-to-head comparison with a reference biologic should not be called “similar biotherapeutic products” (i.e., biosimilars), that little is known about the safety or efficacy of such products, and that pharmacovigilance may be ineffective in the affected countries. The guideline recommends a stepwise process for regulatory assessment of such products, taking into consideration the benefit-risk of keeping the products on the market, the missing elements from the original dossier, and an orderly procedure for obtaining additional required data from the sponsor.[48]

In summary, it is as important to understand what biosimilars *are not* as it is to understand what biosimilars *are*. Biosimilars are not biobetters, i.e., they are not improved versions of the originator biologic. Biosimilars are not “biocopies” or “biomimics”, i.e., they are not copies of licensed biologic medicines that have not been subjected to rigorous clinical testing or evaluated according to the biosimilar regulatory pathway. Finally, biosimilars are not generic drugs, i.e., they are not small-molecule, chemically synthesized drugs using the same active ingredient, strength, dosage

form, route of administration, and conditions of use as the reference product. Biosimilars are biologics that are developed and approved according to the biosimilar regulatory pathway.

4. US Approval Pathways for Drugs and Biologics

The US approval pathways for chemically based, small molecule drugs and biologics differ. New small molecule drugs are evaluated and approved under a New Drug Application (505[b][1] or 505[b][2] pathway) as authorized by the Food, Drug, and Cosmetic Act (FDCA).[43]

A subsequent generic of a small molecule drug can be approved via an Abbreviated New Drug Application (505[j] pathway) that shows the drug is an exact replica of the reference drug.[43,54] The Abbreviated New Drug Application for generics is solely based on analytical and pharmacokinetic (PK) evaluation and does not require evidence of clinical efficacy or safety.[43]

As authorized by the Public Health Services Act (PHSA), new biologics are evaluated and approved under a Biologics License Application (351[a] pathway).[55] The Patient Protection and Affordable Care Act of 2010 (PPACA) added the Biologics Price Competition and Innovation Act of 2009 (BPCIA), or Biosimilars Act, that amends the PHSA and other statutes to create an approval pathway for biosimilars (351[k] pathway) that can be demonstrated to be highly similar to an FDA-licensed biologic.[55] These pathways are summarized in **Table 2**.

Table 2. Approval processes for drugs and biologics in the US.[38]

Product *Governing Act*	Application Type	Pathway	Requirements
Drugs– **Approved via *Food, Drug, and Cosmetic Act (FDCA)***	NDA	505(b)1	Full clinical evaluation of safety and efficacy
	NDA	505(b)2	Sponsor may rely (in part) on US FDA's findings of safety and/or effectiveness for a previously approved drug; however, sponsor must provide necessary data to ensure that differences from reference product do not compromise safety and effectiveness
	Abbreviated NDA	505(j)	No clinical study required (duplicate of an already approved product); only bioequivalence must be demonstrated
Biologics– **Approved via *Public Health Services Act (PHSA)***	Biologics license application (BLA)	351(a)	Full clinical evaluation of purity, safety, and potency
	Biosimilar application	351(k)	Proposed biosimilar is demonstrated to be highly similar (i.e., no clinically meaningful differences) to a 351(a) product in terms of safety, purity, and potency For an interchangeable biologic, proposed biosimilar must be approved as a biosimilar AND have expectation of same clinical result in any given patient AND exhibit no additional risk to safety or efficacy as a result of switching (for a product administered more than once)

Adapted from Lucio SD, et al. Am J Health-Syst Pharm. 2013;70:2004.

FDA = Food and Drug Administration; NDA = New Drug Application.

5. US FDA Guidance for Biosimilars

The US FDA has provided several guidance documents to assist biosimilar developers:

- *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*:[5] Intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product via a 351(k) application to FDA. This draft guidance describes a risk-based "totality-of-the-evidence" approach that FDA intends to use to evaluate the data and information submitted in the 351(k) application.
- *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*:[35] Provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting a 351(k) application (including the importance of extensive analytical, physicochemical, and biological characterization).
- *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*:[56] Intended to assist sponsors with the design and use of clinical pharmacology

studies to support a decision that a proposed therapeutic biological product is biosimilar to its reference product.

- *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*:[10] Provides answers to common questions from parties interested in developing biosimilar products pertaining to the early stages of product development, differences in formulation, delivery device, routes of administration, indications from the reference product, extrapolation, and how to request exclusivity.
- *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry:*[55] Provides answers to common questions from parties interested in developing biosimilar products pertaining to product development, including pharmacokinetic/pharmacodynamic (PK/PD) studies, drug-drug interaction studies, clinical studies, and pediatric assessment, and how to request exclusivity.

Procedural:

- *Reference Product Exclusivity for Biological Products Filed Under 351(a) for the Public Health Service Act (PHSA)*:[58] Describes how FDA will determine the critical "date of first licensure" for the purposes of determining when the period of 12-year market exclusivity for the reference product begins and ends.
- *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*:[59] Provides recommendations to industry on formal meetings between FDA and sponsors or applicants relating to the development and review of biosimilar biological products.
- *Naming Guidance*: In addition to these biosimilar-specific guidance documents, the US FDA published a guidance regarding the nonproprietary naming of biological products in January 2017.[60] Within the guidance, the US FDA proposes a nonproprietary name designation for originator biological products, related biological products, and biosimilar products that will include a core name and a unique suffix composed of four lowercase letters.[60] The purpose of this suffix is to aid in differentiating among biological products that have not been determined to be interchangeable and to improve pharmacovigilance.[60]

- *Interchangeability Guidance:* This draft guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). To support a demonstration of interchangeability, section 351(k)(4)(A) of the PHS Act provides, among other things, that a sponsor must show that the proposed product "is biosimilar to the reference product." Where a product is first licensed as a biosimilar, that licensure may be referenced to support a showing for this statutory criterion for demonstrating interchangeability.[61] In addition, section 351(k)(4)(A) of the PHS Act provides that an application for an interchangeable product must include information sufficient to show that the proposed interchangeable product "can be expected to produce

the same clinical result as the reference product in any given patient." FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use. The data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use may vary depending on the nature of the proposed interchangeable product and may include, but need not be limited to, an evaluation of data and information generated to support a demonstration of a biological product's biosimilarity.[61]

- *Labeling Guidance:* This draft guidance is intended to assist applicants in developing draft labeling for submission in applications for proposed biosimilar products under section 351(k) of the Public Health Service 16 Act (PHS Act) (42 U.S.C. 262(k)). The US FDA requires that all prescription drug labeling must provide sufficient information to enable healthcare practitioners to "use the drug safely and for the purposes for which it is intended." Consistent with this requirement and the definition of a biosimilar product as a biological product with no clinically meaningful differences with a reference product in terms of safety, purity, or potency, the FDA recommends that biosimilar product labeling include relevant information from the reference product label (i.e., information and data from clinical studies) along with appropriate biosimilar product-specific information (e.g., biosimilar name) or modifications (e.g., indications and usage information that is specific to the approved indications for the biosimilar). Of note, clinical data generated from phase 3 pivotal studies evaluating a proposed biosimilar is not generally included on the label of the biosimilar product.[62] The understanding is that clinical studies supporting biosimilar licensure are designed to demonstrate no clinically meaningful differences between the proposed biosimilar and the reference product and not designed to independently demonstrate efficacy and safety of the biosimilar.[61]

5.1 US FDA Takes a "Totality-of-the-Evidence" Approach

Given the complex nature of biologics, it is unlikely that a "one size fits all" assessment of biosimilarity can be developed. The US FDA will likely need to integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product.[63] In a 2011 publication in the *New England Journal of Medicine*, members of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) published US FDA's perspective on developing the approval pathway for biosimilars and discussed a "risk-based totality-of-the-evidence approach" to the evaluation of biosimilarity.[63] The US FDA suggested a stepwise approach to evaluate attributes of biosimilar products. At each step, the US FDA recommends that the sponsor evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty. This stepwise approach involves the following (**Figure 5**):

- *Step 1*: Extensive structural and functional characterization of both the biosimilar product and the reference product is the foundation for the biosimilar development program. This

analytical characterization includes the determination of differences in relevant critical attributes between a biosimilar and the reference product using appropriate methodology. If rigorous structural and functional comparisons show minimal or no differences between the proposed biosimilar product and the reference product, there is a stronger justification for a more selective and targeted approach to animal and/or clinical testing.[5]

- *Step 2*: Consider the need for animal data to assess toxicity when uncertainties remain about the safety of a biosimilar after extensive structural and functional characterization. Nonclinical studies may not be warranted if a biosimilar has been demonstrated to be highly similar to a reference product through analytical characterization.[5]
- *Step 3*: Comparative human PK and pharmacodynamic (PD) studies.[5]
- *Step 4*: Comparative safety and effectiveness data will be needed to address any residual differences with unknown clinical relevance that exist after steps 1 through 3. A variety of factors can influence the type and extent of clinical efficacy and safety studies needed, including the nature and complexity of the reference product, the mechanism of action of the reference product and disease pathology (can also impact extrapolation and/or indications granted by the US FDA), the extent of clinical experience with the reference product and its therapeutic class, the extent to which differences in structure and function studies predict differences in clinical outcomes, and the extent to which PK/PD studies predict clinical outcomes (e.g., are sensitive PD markers available?).[5]
- Clinical immunogenicity studies – the US FDA will generally expect at least one clinical study that includes a comparison of immunogenicity of the proposed biosimilar to the reference product. The goal of immunogenicity studies is to establish there are no clinically meaningful differences in incidence and severity of human immune response between the biosimilar and the reference product that can impact both safety and efficacy of the biosimilar. Immunogenicity can be tested during clinical safety and efficacy studies, including PK/PD studies. Immunogenicity studies should be conducted in a sensitive population and include assessments of binding and neutralizing antibodies.[5]
- In all cases, US FDA has discretion under BPCIA to determine that certain studies are not required.[5]

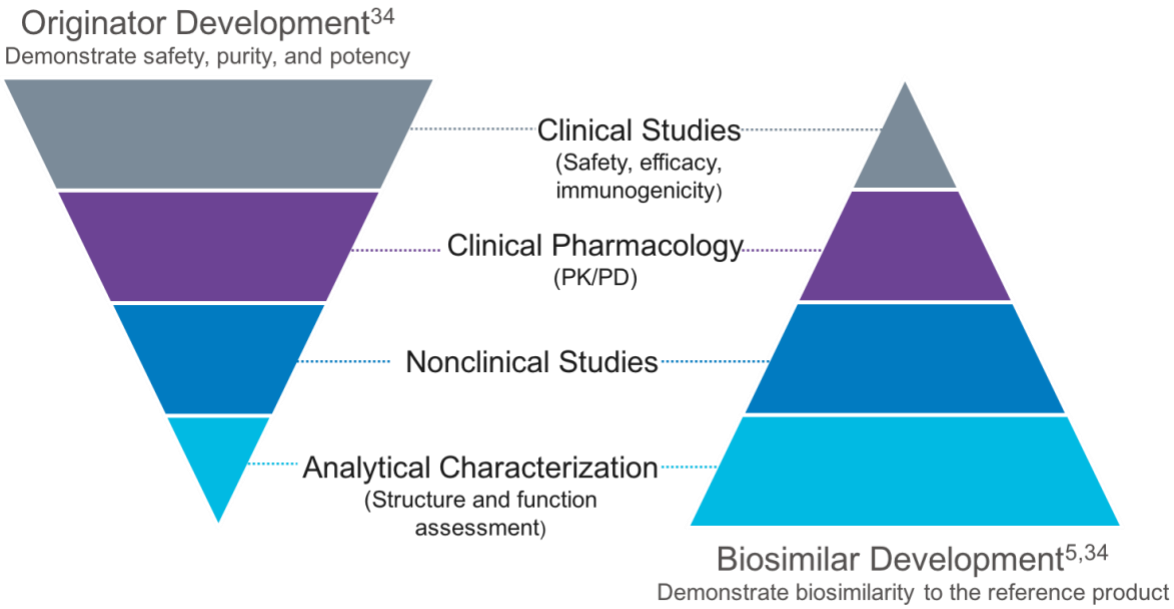


Figure 5. US FDA recommends a "totality-of-the-evidence" and stepwise approach for the demonstration of biosimilarity.[5,34]

PD = pharmacodynamics; PK = pharmacokinetics.

Under the BPCIA, biosimilars can be approved as either a "biosimilar" or as an "interchangeable biologic" to a reference product. To be granted an "interchangeability" designation, a product must demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient (**Figure 6**).[35,55,61] For products administered more than once to a patient, the safety and/or diminished efficacy risks of alternating or switching between the biosimilar and the reference biologic cannot be higher than the risks associated with using the reference product alone. In January 2017, the US FDA issued a draft guidance indicating what data would be sufficient to deem a biological product interchangeable with the reference product.[61] The type and amount of data needed to demonstrate interchangeability are determined by the US FDA on a case-by-case basis depending on a composite of factors, such as the complexity of the biologic product, its physicochemical characterization, clinical experience with the reference product, and the potential for risk of immunogenicity. The US FDA expects that applicants will include data from one or more switching studies in one or more appropriate conditions of use to assess the risk, in terms of safety and diminished efficacy, of alternating or switching between the products.[61] The number and duration of switches between the reference product and the proposed interchangeable product should consider the clinical condition to be treated, the dosing of the product, and the duration of the exposure interval to each product that would be expected to cause the greatest concern in terms of immune response and the potential impact of such response on safety and efficacy, if any.[61] Further, the treatment lead-in period should be of sufficient duration to ensure an adequate baseline (e.g., steady state of pharmacokinetics) before randomization to the switching period of the study. The switching arm should incorporate at least two separate exposure periods to each of the two

products (i.e., the study should include at least three switches, with each switch crossing over to the alternate product) **(Figure 6)**.[61]

It should be noted that a first biosimilar designated as "interchangeable" with a reference product will be granted a period of exclusivity during which time another biological product may not be assigned as "interchangeable" with that same reference product.[59.] In the US, an interchangeable product may be used as a substitute for a reference product, provided that state regulations allow such substitution by a pharmacist who may dispense an interchangeable biologic in place of the prescribed biologic without prior prescriber approval. Many state laws, however, also include provisions whereby a prescriber may prevent substitution by stating "dispense as written" or "brand medically necessary."[61,64]

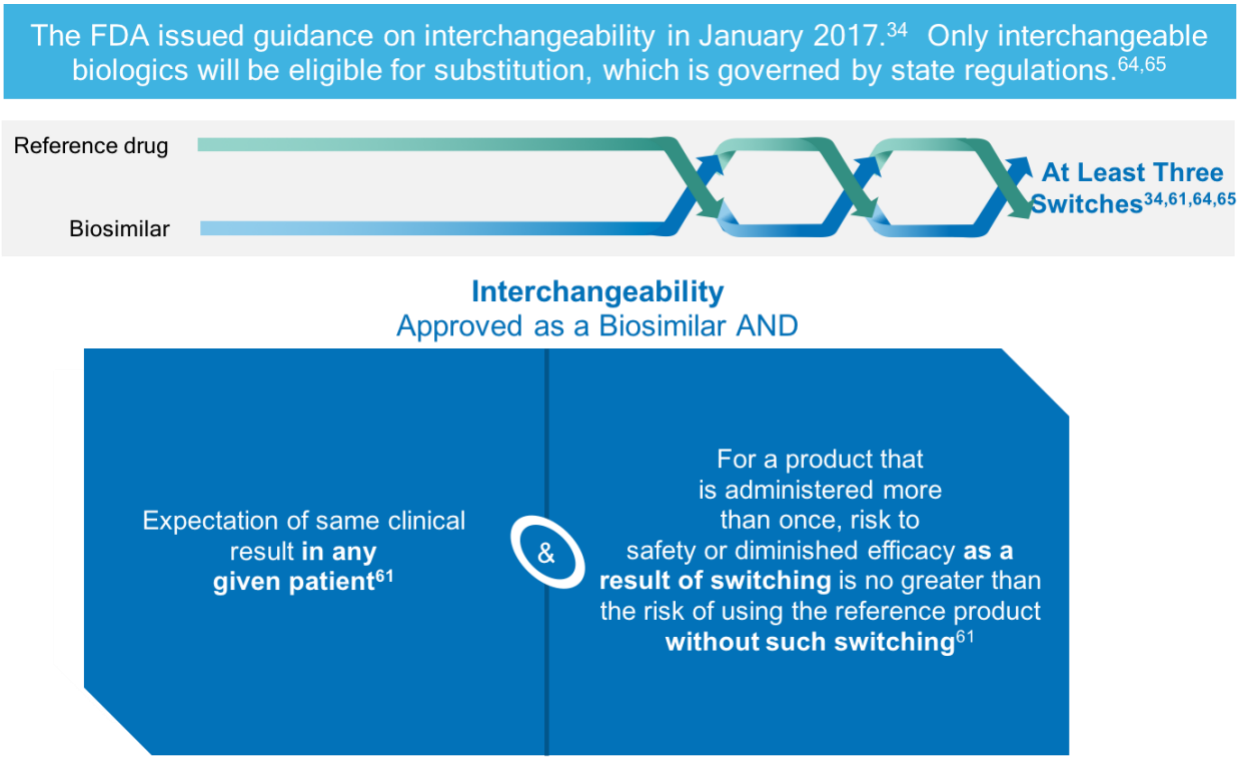


Figure 6. Demonstration of biosimilarity is the first step, while demonstration of interchangeability has additional requirements.[61,64,65]

6. The European Experience With Biosimilars

The EMA is a decentralized agency of the EU responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU.[66] The EU was the first region to develop a biosimilar approval pathway due to the earlier expiration of patents for biotechnology-produced medications in European countries.[67]

The EU established legislation for biosimilars in 2004, and EU regulators developed a regulatory approval pathway for biosimilars starting in 2005;[68] the first biosimilar was approved in Europe in 2006.[69]

Currently, there are nine classes of biosimilar medicines approved in Europe:[69,70]

- Recombinant erythropoietins
- Recombinant granulocyte colony-stimulating factors (G-CSFs)
- Recombinant human insulin
- Recombinant human growth hormone (GH)
- Recombinant follicle-stimulating hormone (FSH)
- Recombinant parathyroid hormone (PTH)
- Fusion protein (TNF inhibitor)
- Monoclonal antibodies (mAbs)
- Low molecular weight heparins

6.1 EMA Guidance

EMA has provided three guidelines that cover the basic principles, quality, and nonclinical and clinical considerations related to biosimilars:

- *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues* (EMEA/CHMP/BWP/247713/2012):[44] Developed in 2006 and effective December 2014, this document addresses the requirements regarding manufacturing processes, the comparability exercise for quality, the choice of reference product, analytical methods, physicochemical characterization, biological activity, purity, and specifications of the similar biological medicinal product.
- *Guideline on Similar Biological Medicinal Products* (CHMP/437/04 Rev 1):[71] Developed in 2005 and effective April 2015, this document describes and addresses the application of the biosimilar approach, the choice of reference product, and the principles of establishing biosimilarity.
- *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues* (EMEA/CHMP/BMWP/42832/2005 Rev 1):[11] Developed in 2006 and effective July 2015, this document provides an overview of the requirements for nonclinical studies and clinical studies when evaluating biosimilar products as well as the risk management plan with special emphasis on immunogenicity.

In addition, EMA has developed individual product-specific guidelines on developing biosimilars. Class-specific guidelines are available for certain types of biosimilar products.

6.2 Nonidenticality Versus Clinically Meaningful Differences

The EMA's experience with evaluating biosimilars has demonstrated the value of clinical data in the assessment of biosimilarity. The EMA approval standards have been applied to a significant set of candidate biosimilar products and have successfully screened those with substantial analytical and clinical similarity from products with incomplete or unacceptable results.

A majority of biosimilar products reviewed by the EMA have received marketing authorization. Some biosimilar products that were evaluated by the EMA for marketing authorization were rejected or withdrawn by their sponsors after the EMA raised concerns during the review process.[8,71] In one example, the EMA rejected approval of an alpha-interferon biosimilar based on results that showed statistically significant biophysical differences and clinical variations (PK, efficacy, and tolerability) between the biosimilar and reference product treatment groups.[72] Other concerns raised by the CHMP included: impurities, insufficient stability data, significant difference in adverse event rates, and lack of sufficient validation in the immunologic response tests and manufacturing process.[14,72] Similarly, three applications for human insulin biosimilar candidates in the EU were withdrawn after the products failed to demonstrate PD similarity to the reference product.[14,72] Finally, a biosimilar of a recombinant human GH is an example of a biosimilar product that received marketing approval by EMA after initial safety concerns were addressed.[14,72] In a pre-authorization clinical study that compared the biosimilar to the reference product, a higher number of patients that received the biosimilar developed non-neutralizing anti-GH antibodies as compared to those that received the reference product. Consequently, changes to the purification steps of the biosimilar product's manufacturing process were made, and the immunogenicity issues were resolved. [14,72]

There is no expectation for biosimilars to be identical to the reference biologic. The use of unique cell lines and different manufacturing processes results in proteins that have unique structural characteristics compared to the original protein. For example, there have been documented differences in biosimilars in the EU compared to the reference product in terms of PTMs such as glycosylation, phosphorylation, acetylation, and sialylation.[73] These biophysical variations between biosimilar and reference formulations were observed in the absence of statistically significant variations in clinical parameters. In 2013, the EMA approved the first biosimilar anti-tumor necrosis factor (TNF) mAb.[74] Although some differences in biological activity were detected in an in vitro assay, this difference was not interpreted to be clinically meaningful since it did not affect the activities of the biosimilar in experimental models regarded as more relevant to the pathophysiological conditions in patients.[74] Regulatory agencies around the world continue to emphasize the importance of clinical testing to evaluate the clinical impact, if any, of these minor biophysical variations.

Other guidelines relevant to biosimilars include:

- Comparability of biotechnology-derived medicinal products after a change in the manufacturing process – non-clinical and clinical issues[75]

- ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products[36]
- Immunogenicity assessment of biotechnology-derived therapeutic proteins[76]
- Immunogenicity assessment of mAbs intended for in vivo clinical use[77]

7. Practical Considerations for Biosimilars

Biologics play an essential role in disease treatment and supportive care. Therefore, when biosimilar agents enter the market as potentially less-expensive biologic competitors, prescribers and other healthcare professionals will likely require more clinical data than typically utilized for review of small molecule generic drugs in order to make informed decisions.[78]

In a 2012 survey of US institutional pharmacists, only 40.7% knew that the BPCIA had granted the US FDA the authority to create an expedited pathway for biosimilars.[79] In May 2013, the North American Center for Continuing Medical Education carried out a survey where over 400 healthcare professionals, including oncologists, pharmacists, rheumatologists, and primary care providers, were evaluated on their knowledge of biosimilars.[80] The results indicated there was a low level of understanding regarding the differences between biosimilars and generics (54% rated their understanding as fair or poor), as well as that of the differences between biosimilars and their reference products (67% rated their understanding as fair or poor).[80]

An educational needs assessment of more than 200 practicing clinicians (including more than 50 pharmacists) in the United States indicated that although there is a significant interest in utilizing biosimilars in practice, there are clear knowledge gaps regarding the definition of biosimilars and their regulatory approval process. Almost all respondents (97%) indicated the need for more education related to biosimilars.[81] Similarly, a 2013 survey of 470 European physicians conducted across five European countries (France, Germany, Italy, Spain and the UK) by the Alliance for Safe Biologic Medicines indicated that only 22% of physicians considered themselves as very familiar with biosimilars.[82] Almost one-fourth of the physicians surveyed could not define biosimilars or had not heard of biosimilars before. Additionally, 37% of surveyed prescribers were unaware that clinical trials for a single indication led to approval for multiple indications.

One of the most significant issues that will potentially hinder the adoption of biosimilars is a lack of information about these agents on the part of physicians, nurses, and other healthcare professionals.[83] Some key considerations related to the use of biosimilars in clinical practice are discussed below.

7.1 Interchangeability and Substitution of Biosimilars

Substitution (sometimes called automatic substitution, led by the pharmacist without consent from a physician) is often permitted for generic products that are considered to be therapeutically equivalent or clinically identical.[28] The practicalities of substitution vary from country to country. For example, in some European countries, the physician is encouraged to prescribe substitutable medicines by international nonproprietary name (INN), leaving the pharmacist to decide which product (generic or reference product) to dispense, whereas in other EU countries the pharmacist

may dispense a generic of a substitutable medicine, even where the physician has prescribed the reference product by brand.[28,84] As of November 2015, across the EU, decisions on prescribing practices such as substitution are made at the national level. In many countries (e.g., Italy and Germany), biologic medicines are specifically excluded from lists of products suitable for substitution, whereas in other countries where substitution is permitted only for INN-only prescriptions (e.g., Sweden and UK), physicians routinely prescribe biologics by brand. In 2013, France passed a law permitting a restricted form of substitution, wherein pharmacists may dispense a biosimilar product for a patient who is initiating therapy and has been prescribed the reference product.[35]

The US is the only country with a specific definition for an interchangeable biologic (**Figure 7**).[78] The US FDA can designate a biosimilar as an interchangeable biologic when all of the following criteria are met:[55,61]

1) The biological product is biosimilar to the reference biological product.
2) The biological product can be expected to produce the same clinical results as the reference product in any given patient.
3) For a biological product administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is no greater than the risk of using the reference product without such alternation or switch.

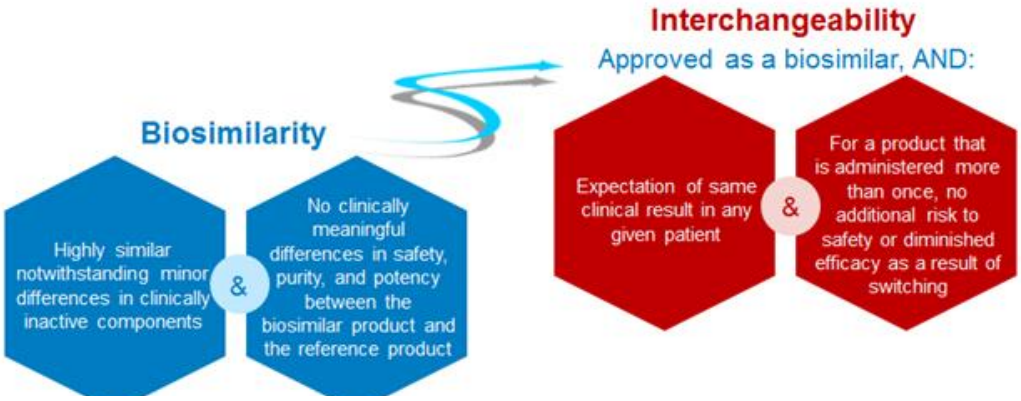


Figure 7. Additional standards are required by the US FDA for an interchangeability designation.[55,61]

Although interchangeability in the US will be determined by the FDA, the regulation of substitution is governed by state pharmacy practice acts. States vary on the terms of substitution for traditional chemical drugs, and it is anticipated that states will vary in how they apply substitution to biologics.[65] As of July 2017, 35 states and Puerto Rico have adopted laws regarding substitution of biologic medications by the pharmacist without the intervention of the prescribing physician, although the prescriber can prevent substitution by stating “dispense as written” or “brand medically necessary”. In each of those 35 states, substitution is limited to products deemed “interchangeable” by the US FDA.[65]

Legislation has been introduced and considered in several states to address pharmacist-initiated substitution of an interchangeable biologic for the reference product in a retail pharmacy setting. Although language between states varies, proposed legislation granting pharmacists the authority to substitute a biosimilar for its reference product often contains a combination of the following principles:[85]

1) Only biologics deemed by the FDA to be "interchangeable" should be eligible for substitution under the state pharmacy practice laws;
2) The prescribing physician should retain the authority to require that the pharmacist dispense as written (DAW);
3) The pharmacist should inform the patient or patient's representative of the substitution;
4) For dispensed biologics where an interchangeable product is available, the pharmacist should communicate with the prescribing physician the name and manufacturer of the product dispensed to their patient within a reasonable period of time after dispensing. Such communication should rely on prescriber-accessible electronic systems, if available, or any other prevailing means of communication if such systems are not in place. No communication is necessary for refills where there is no change from the product originally dispensed; and
5) Records should be maintained to reflect the actual product received by the patient to facilitate accurate attribution of any adverse events.

Automatic Substitution:* a practice mandated by law (or government payer policy) wherein a pharmacist must dispense the less costly or preferred biologic medicine regardless of the prescribed biologic medicine and without the prior approval of the prescriber.†

Substitution:*‡ a practice allowed by law wherein a pharmacist may dispense an alternative biologic medicine for a prescribed biologic medicine without the prior approval of the prescriber.†

Switching: a practice wherein a prescriber (or the prescriber's delegate, under direct supervision of the prescriber) may change the prescription from one biologic medicine to another biologic medicine.

*In some US states, there is ongoing dialogue regarding post-dispensing notification and documentation.

†Prescribers may indicate "DAW" and patients may request the originally prescribed biologic medicine.

‡Private organization management of substitution may vary based on formulary decisions and other factors.

Unlike the US FDA, the EMA does not have the authority to evaluate and approve products as safe for switching with another product during a course of treatment without the intervention of the prescriber.[86] There are no formal "interchangeability standards" – that is, guidance on when and whether it is safe to switch between products – set forth by the EMA. Across the EU, decisions on prescribing practices, such as when it is appropriate for a prescriber to switch a patient from one product to another (referred to as "switching" in the EU), are made at the national level. In many countries, biologic medicines are specifically excluded from lists of products suitable for substitution without the involvement of the prescriber.[87] In 2015, drug regulatory agencies from several EU member states, including Finland, the Netherlands, and Germany, issued statements stating that prescribers could safely switch patients from the originator product to a biosimilar. These statements clearly differentiated this practice from pharmacy substitution, and they emphasized the need for the prescriber to be involved.[88,89] The WHO does not define standards on interchangeability for biologic medicines.

The WHO recognizes that a number of issues associated with the use of biologics should be defined by the national authorities.[13]

In 2015, The Australian Pharmaceutical Benefits Advisory Board (PBAC) issued a policy permitting the PBAC to designate certain biosimilars as suitable for substitution at the pharmacy. The PBAC should make this decision based on the absence of evidence of clinically relevant differences from the reference product, data from any switching studies, and other considerations.[90] In 2015, the PBAC applied this policy to permit pharmacy substitution of an anti-TNF biosimilar mAb.[90,91]

7.2 Extrapolation of Indications

A biosimilar sponsor is not required to perform clinical trials in all indications for which the reference product was approved and for which approval for use is sought for the proposed biosimilar. In the US, a biosimilar sponsor may provide scientific justification to extrapolate to an indication that has not been formally investigated for the biosimilar but is approved for the reference product.[5] This means that a biosimilar that was clinically studied in one tumor type or disease state may potentially be approved for use in additional tumor types or diseases without supporting clinical data. To support the approval of an extrapolated indication in a biosimilar, the sponsor will need to demonstrate that the biosimilar has the same mechanism of action, target-binding characteristics, PK, and biodistribution in the clinically tested and the extrapolated indications, as well as address any expected differences in toxicity or effectiveness.[5] This may be done based on the available knowledge of the reference product as well as the totality of evidence generated during development of the proposed biosimilar **(Figure 8).** Extrapolating indications does not, on its own, indicate that a biosimilar is interchangeable with its reference product.[5] It is also important to note that a manufacturer may be unable to seek approval for all indications of the reference product, if some indications are still protected by patents or exclusivity at the time of application submission. Concerns have been raised by various organizations about the efficacy and safety of biosimilars in extrapolated indications that have not been formally evaluated in clinical studies.[92-94]

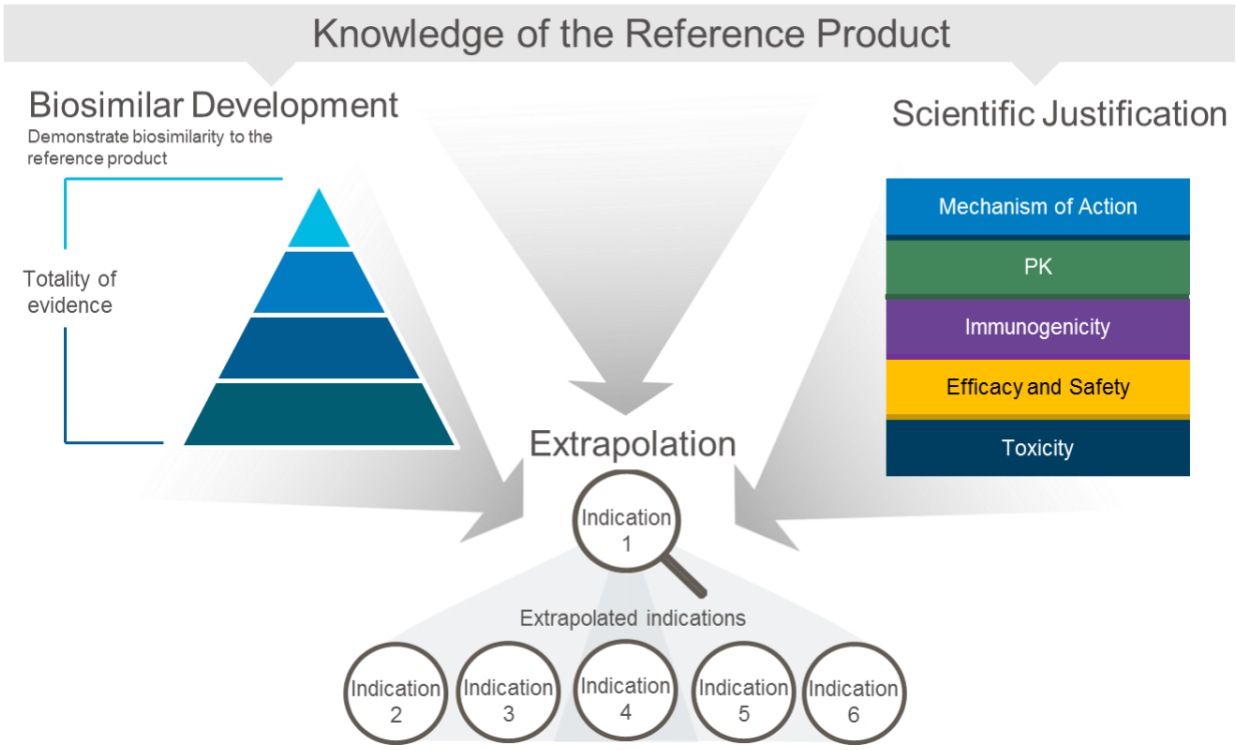


Figure 8. Extrapolation of indications for the proposed biosimilar is based on the knowledge of the reference product and scientific justification.[5]

Extrapolation is determined by health authorities on a case-by-case basis and therefore biosimilar indications may differ from country to country. As an example, the first biosimilar anti-TNF mAb was approved in the EU in 2013 and Canada in 2014.[95] Although approval of the biosimilar by the EMA included full extrapolation to all the reference product's indications, Health Canada did not originally grant extrapolation from autoimmune arthritis to inflammatory bowel disease (IBD) due to the differences in ADCC activity observed with relation to the Fc-region of the anti-TNF mAb, which may be implicated specifically in IBD.[74] Subsequently, however, in 2016, the mAb was approved for the adult IBD indications. This was based on previously submitted clinical data that had demonstrated comparable efficacy and safety in patients with rheumatoid arthritis and comparable PK in patients with ankylosing spondylitis as well as new physicochemical and biological data and rationales addressing the potential mechanism of action (MOA) of the agent and the relationships of these MOAs to clinical outcomes in IBD.[96]

7.3 Pharmacovigilance and Postmarketing Surveillance

Post-marketing surveillance is a key health authority requirement for all biologics to help ensure the safety of these products.[5] Due to their molecular size, biologics (both reference biologics and biosimilars) have the potential to stimulate unwanted immune reactions. Furthermore, because biologics are large, complex molecules and made in living cells, they are generally very sensitive to the manufacturing process, environmental conditions, container closure systems, and handling, and structural changes in the molecule can occur after the product has been approved.[18,31]

Although many may be of either no or minor clinical consequence, some structural changes can have an impact on the safety and efficacy of the medicine. When biologics (reference biologics or biosimilars) cause unexpected or rare adverse reactions in patients, it is essential that these reactions be attributed to a specific product and manufacturer so that any problem with a product can be promptly identified and addressed to ensure product efficacy and patient safety.[18,31]

According to the US FDA, post-marketing safety monitoring should first take into consideration any particular safety or efficacy concerns already associated with the use of the reference product (and/or its therapeutic class), as well as the proposed biosimilar product in its development and clinical use. Rare, but potentially serious safety risks (e.g., immunogenicity) may not be detected during pre-approval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through postmarketing surveillance or studies. In addition, like any other biological product, the US FDA may take any appropriate action to help ensure the safety and efficacy of a proposed biosimilar product, including, for example, requiring a post-marketing study to evaluate certain safety risks.[5]

Post-marketing safety monitoring for a proposed biosimilar product should have adequate mechanisms in place to differentiate between the adverse events associated with the proposed product and those associated with the reference product.[5] There are several data sources that have been suggested as tracking methods:[97]

- ***Development of a Prospective Registry***: Such registries have typically been instituted as part of programs to improve the benefit and reduce the risks associated with products known to have potentially serious adverse events. Some registries require the provider to record each administered dose of a product in a product-specific central database. Adherence to data-entry requirements is enforced by restricting distribution of the product to providers who have joined the registry. The major advantage of this model is that it maintains very complete data on exposures, and possibly outcomes, for as long as the registry is maintained. The major disadvantage is that these registries are very expensive to establish and maintain and are very burdensome for healthcare providers to use. Thus, the utility of product-specific registries has been limited to very risky products.[97]
- ***Electronic Medical Records* (*EMRs*)**: Post-approval safety studies use large databases derived from administrative (e.g., billing) and/or EMR data, which are used to measure exposures and outcomes. The great advantage of this approach versus the use of prospective registries is that EMRs are integrated into a system to capture routinely collected data, thus greatly reducing the burden on the healthcare system. At present, the population that is accessible for post-approval safety studies using EMRs is quite limited, so the focus has been on claims-based data sources.[97]
- ***Use of Claims Data***: In the US, drugs and biologics administered on an outpatient basis are typically identifiable in claims data in one of two ways, principally driven by billing procedure requirements: (i) National Drug Codes (NDCs), for agents dispensed by outpatient pharmacies, and (ii) Healthcare Common Procedure Coding System (HCPCS) codes, for agents administered by providers (e.g., via infusion) in an ambulatory care setting. Biological products with different brand names in a class may be billed under a

patient's medical benefit using the same HCPCS J-code, making these codes an inaccurate method for identifying the specific biological product administered to a patient.[97] While NDC numbers are unique identifiers of labeler, product, and trade package size in the US, these numbers are typically not available from the primary packaging (e.g., a syringe) at the time an adverse event is reported, and the need to record long numerical identifiers may increase the likelihood of transcription errors. Lot numbers are also unique identifiers, but they are infrequently and inconsistently used.

Systems for tracing biologics in the US currently exist, but their effectiveness is predicated on a single-source manufacturer. The approval and entrance of biosimilars into the US will shift the market from single-source with clear accountability to multisource and the potential for ambiguous accountability.[78] Associating adverse events with the correct product and manufacturer may become more challenging with the arrival of biosimilars, unless each biologic has a distinguishable nonproprietary name.[78] In the absence of distinguishable nonproprietary names, other significant policy measures would be necessary to facilitate product-level identification of all biologics in patient medical records and adverse event reporting. For example, the European law requires each biological product to be identified by a trade name and each member state to take measures to ensure that important identifiers are accurately recorded in patient medical records and adverse event reports.[96] It is unclear whether analogous policy measures could be applied in the US.

7.4 Biosimilar Naming

The naming convention applied to biosimilars represents another potential challenge relating to the entrance and management of biosimilars in the global marketplace. An internet-based survey of US prescribers conducted by the Alliance for Safe Biologic Medicines (ASBM) indicated that over 75% of respondents perceived products with the same INN as structurally identical, and almost 70% interpreted a shared nonproprietary name to mean that a patient could receive either product safely and expect the same results.[82] For biosimilars, brand names are not required, and prescribers and other healthcare providers are not required to use them. In contrast, nonproprietary names (sometimes referred to as the "United States Adopted Name", "INN", or "active ingredient name") are required for all drugs and biologics and are often preferentially used in prescribing and health records. The question has been raised about whether biosimilars should have unique nonproprietary names to ensure that they are not treated like multisource generic drugs for purposes of prescription ordering, health records, and pharmacovigilance (**Figure 9**).[99,100] Effective pharmacovigilance requires that all biologics within a product class can be distinguished from each other to facilitate accurate attribution of adverse events to the correct product.[78] Furthermore, assigning the same nonproprietary name to all biosimilars of a given reference product could create challenges in prescribing and reimbursement if not all biosimilars are granted the same indications via extrapolation.[100]

Analyses have shown that reporters (e.g., healthcare professionals and patients) often attribute adverse events to the reference product, when in fact the patient likely took a generic product with the same nonproprietary name. Furthermore, complete and conclusive product-identifying information (e.g., lot number, NDC, etc) is usually not submitted by reporters. Using data from FDA's Adverse Event Reporting System (AERS), an assessment of eight small molecule drugs

that became subject to generic competition between 2005 and 2011 revealed serious limitations in the product-identifying information included in the reports, supporting the need for distinguishable nonproprietary names for biosimilars and helping to ensure that adverse events are traced to the correct product. It is important that health authorities, sponsors, healthcare professionals, and patients can rely on timely and accurate adverse event data to make critical decisions regarding the use of biologics.[101]

There is currently no global consensus on naming conventions for biosimilars. The BPCIA did not include provisions for the naming of biosimilars.[102] In January 2017, the US FDA published a final guidance based on its current thinking, proposing a naming system comprised of a shared nonproprietary name for all biologics, followed by a unique meaningless suffix composed of four lowercase letters for each version of a biologic (originator, related biologic product, and biosimilar product).[60] At present, there is no specific guidance that categorically addresses the naming of interchangeable biosimilars. The Japanese regulatory authority, the Pharmaceutical and Medical Devices Agency, requires that biosimilars be assigned a distinguishable nonproprietary name with a suffix consisting of "BS" plus the manufacturer's name added to the INN.[103] The current WHO policy for assigning INNs to biologics (there is no specific policy for biosimilars) follows two different approaches, depending on whether the product is glycosylated.[102] Nonglycosylated biologics with the same amino acid sequence are considered to have highly similar PTMs and receive the same INN. In contrast, glycosylated biologics are considered comparable to but distinct from a previously approved product and could, in principle, receive the root INN of the reference product plus a Greek letter suffix to indicate different glycosylation patterns.[102] To date, distinguishable INNs have been assigned for two biosimilar versions of an erythropoiesis-stimulating agent. The WHO policy for glycosylated biologics has not been enforced consistently by EMA, and biosimilars with different glycosylation patterns from their reference products have been authorized with the same INN.[78] In 2015, the WHO proposed a complementary "biological qualifier" system to be used in conjunction with the INN. Similar to the US FDA's proposal, the biological qualifier would be a unique four-letter code that could be used as a suffix in conjunction with the INN.[60,103] In the US, the FDA has implemented this naming system by assigning the name "filgrastim-sndz" to its first approved biosimilar. Since then, several additional biologics and biosimilars have been approved in the US and named using the FDA naming guidance of a nonproprietary name with a four-letter suffix.[60,103]

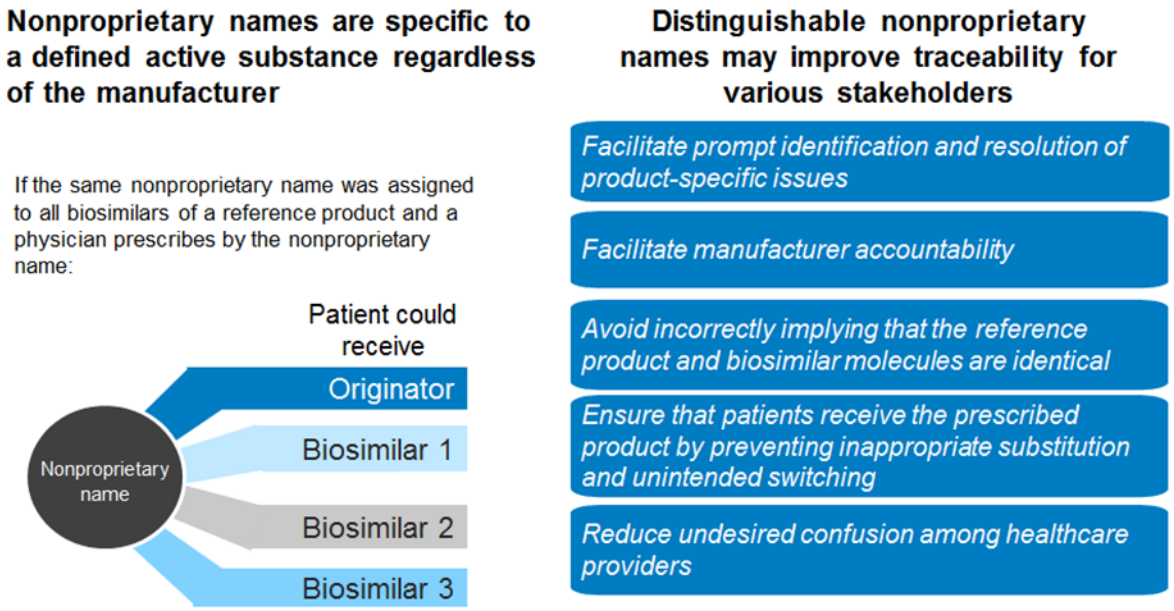


Figure 9. Distinguishable nonproprietary names and clear labeling may assist with traceability measures.[104,105]

7.5 Formulary Evaluations for Biosimilars

Given the differences between biologics and small molecule drugs, biosimilars will require a more thorough evaluation by healthcare professionals on Pharmacy and Therapeutics (P&T) Committees compared with P&T reviews of generic medications.

7.6 Clinical Data

The overall clinical program for demonstration of biosimilarity is abbreviated compared with the program required for reference biologics, but requires additional evidence beyond the requirements for a generic drug (**Figure 10).**[43] Analytic and preclinical similarities provide the foundation for the abbreviated clinical development program for biosimilars.[5,35,71] Animal studies may be abbreviated or not necessary, depending on uncertainties about the safety or activity of the biosimilar following structural and functional characterizations.[5,106]

Clinical studies supporting biosimilar development are designed as equivalence studies, as required by regulatory agencies. Equivalence studies are explicitly designed to determine whether there are clinically meaningful differences between the two products; they are not designed to re-establish efficacy or safety.[5,11,107] Equivalence studies are fundamentally different from superiority studies. Superiority studies aim to demonstrate that one agent provides superior efficacy over another by ruling out the equivalency of the two agents. Lack of superiority in a study does not prove equivalence.[107] In contrast to superiority studies, equivalence studies aim to establish statistical evidence that the proposed product is neither inferior nor superior to the reference product by more than a prespecified margin to rule out any clinically meaningful differences.[5,11,107]

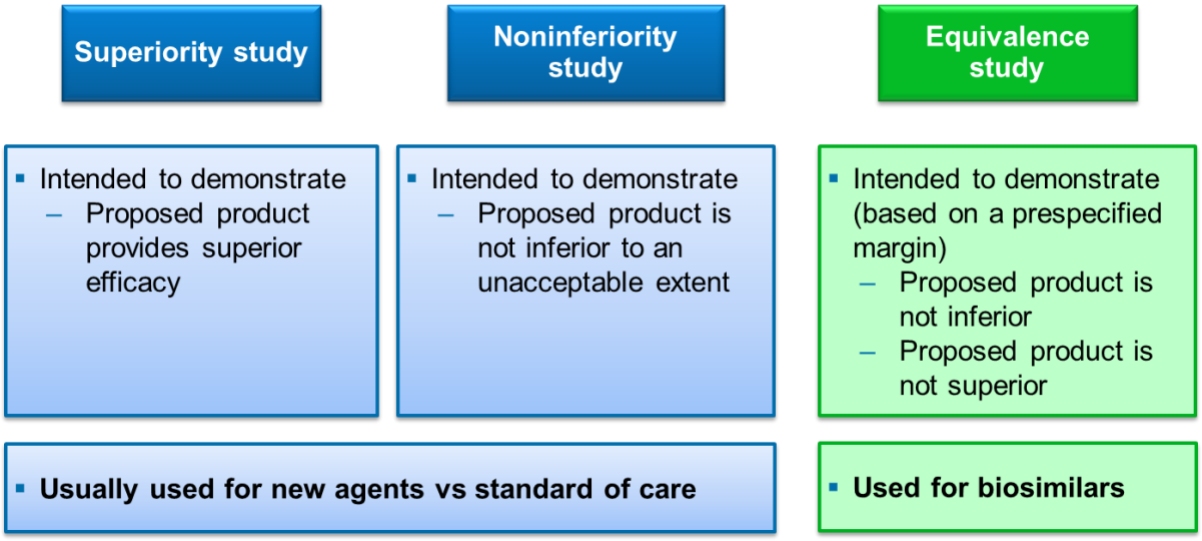


Figure 10. Equivalence studies demonstrate biosimilarity.[5,107]

The goal of the clinical development program for a biosimilar is to demonstrate the absence of any clinically meaningful difference relative to the reference product. Efficacy and safety studies should be performed in populations that are sensitive enough to detect clinically meaningful differences between the proposed biosimilar and the reference product if such differences exist.[5] The objective of the comparative clinical studies is to demonstrate the biosimilar candidate has neither a decreased nor an increased efficacy relative to the reference product, and that it does not have an increased safety risk when compared to the reference product. The most straightforward study design is one in which the null hypothesis, based on a prespecified equivalence margin, is a two-sided test procedure that demonstrates the proposed biosimilar is neither inferior nor superior to the reference product. The margins should be scientifically justified and adequate to enable detection of clinically meaningful differences in effectiveness, if a difference exists. An acceptable equivalence margin is chosen based on historical data and relevant clinical and statistical considerations for each given molecule. The efficacy endpoint can be that of clinical benefit, or alternatively, a meaningful surrogate for efficacy. Preferably, safety is assessed in the same study as efficacy. The choice of patient population should also include considerations of sensitivity for detection of differences with respect to safety. Typically, this may be a population for which the investigational product is used as monotherapy. An additional consideration is the use of surrogate endpoints that can play a key role in biosimilar development. Further, clinical study designs for evaluation of biosimilars may include a single switch or transition phase in which the study population in the comparator arm (reference product) is re-randomized to either receive the proposed biosimilar or to continue in the comparator arm. The key objective is to ensure there are no immunogenicity concerns after switching from the reference product to the proposed biosimilar.[108]

As with any biologic medicine, ongoing post-marketing assessment may further characterize differences between a biosimilar and its reference product that were not fully characterized during testing for initial biosimilar registration.[109,110] Biosimilars will be approved by regulatory authorities

as safe and effective; therefore, healthcare professionals should evaluate available biosimilar data in comparison to the characteristics of the reference product in this context. Specific considerations should include molecule functions, PD (if a marker exists), and available clinical data. Product characteristics (such as formulation or excipients that impact patient tolerability and stability of the biologic) and delivery devices would also be considered in the clinical data evaluation.[109,110]

7.7 Clinical Practice Questions and Operational Issues

Healthcare professionals should consider the implications of interchangeability, approved indications of biosimilar products (noting that biosimilars may not be approved for all the same indications as the reference product), product naming, and information technology requirements.

For health systems considering therapeutic substitution of a biosimilar, the distinction between biosimilars with and without an interchangeable designation is particularly important. Consideration should be given to whether an interchangeable biologic has been approved as interchangeable for all of the approved indications of the reference product as opposed to selected indications only. Another issue that will be important to address relates to transitions of care. Decisions made regarding practices for patients who receive a given product (i.e., biosimilar or reference product) in a particular care setting and then move to a different care setting, should minimize potential inadvertent product switches and the impact on patients during this transition.[109,110]

Consideration should also be given to the operational details and the extent of information technology support necessary to manage and accurately track multiple versions of biological products and biosimilars.[109,110] Healthcare systems must have mechanisms in place to accurately track the specific drug(s) a patient received as well as any adverse events uniquely associated with a biosimilar that have not been observed previously with the reference drug.[38]

It may be necessary to implement special procedures, if biosimilars have the same nonproprietary name as the reference product.

7.8 Drug Supply

Drug shortages impact nearly all facets of clinical care. Interruptions in the supply of critical medications may result in serious consequences, such as the need to ration drugs, delay or cancel treatments, utilize drugs with a different efficacy or safety profile, require unplanned switching between different biological products during the course of treatment, or incur additional time and expense associated with locating alternative medications.[111]

Whether or not a manufacturer has fostered confidence in the integrity and uninterrupted supply of a product may be a key criterion for formulary inclusion of a biosimilar product.[109,110] Since virtually all drug shortages are preceded by disruptions in drug production, manufacturers have the responsibility of establishing appropriate practices and conditions that help ensure a reliable provision of quality products in an uninterrupted manner.[111] In October 2013, the US FDA published a document entitled *Strategic Plan for Preventing and Mitigating Drug Shortages,* which

encouraged hospitals, pharmacies, and other group-purchasing organizations to utilize public data on a manufacturer's historical ability to produce quality products when they make purchasing decisions.[113] The US FDA stated that better utilization of this information could help incentivize manufacturers to focus on quality and, ultimately, prevent shortages.

7.9 Economic Considerations

Given the evolving nature of the regulatory and competitive landscape of biosimilars, it is difficult to estimate the potential savings of biosimilar products. Biosimilar manufacturers have to appropriately invest in clinical development, manufacturing, and post-approval safety monitoring programs similar to that of innovators, which can be expensive.[114]

Physicians, pharmacists, health systems, and payers should evaluate the potential economic savings from incorporating biosimilars into clinical practice in the context of any differences between the biosimilar and its reference product in the following areas:[83]

- Out-of-pocket costs for patients
- The financial impact on the institution
- Inpatient costs of administration
- Outpatient margin
- Potential additional monitoring costs when there is therapeutic interchange
- The influence of bundled contracting approaches and patient assistance programs on cost

8. Summary

A biosimilar is a biological product that is demonstrated to be highly similar (but not identical) to a reference biologic. Biologics and biosimilars are more complicated to develop and manufacture than small molecule drugs, and the manufacturing process of biosimilars will not be identical to that of the reference biologic manufacturer. The variations in manufacturing process can potentially contribute to differences in a biological product's structure, aggregation tendency, and post-translational modifications, all of which can affect the activity profile of the protein. Health authorities have published guidance documents in an effort to provide biosimilar developers with direction on the data necessary for submission of a comprehensive application for a proposed biosimilar product. Given the complex nature of biologics, health authorities need to integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product.

Now that pathways for the approval of biosimilars have been established, biosimilar products are entering the global market. Since biosimilars may provide alternative choices of biologic treatments for patients, healthcare organizations should be educating staff now and ensuring that infrastructure will be in place to support timely evaluation and appropriate use of biosimilars. There will also be a number of issues that healthcare professionals should consider in order to make informed decisions about incorporating biosimilars into clinical practice. One issue to consider is the evaluation of substitution practices and how these may affect patient care. Healthcare professionals play a primary role in adverse event reporting and should consider how pharmacovigilance requirements and biosimilar naming conventions may affect safety monitoring. The current process for documentation of administered products may also change, particularly if there are multiple products that may be switched over a patient's planned course of treatment. Potential cost savings of biosimilars should be evaluated in the context of differences between the biosimilar and reference product in manufacturer assistance programs, patient copayments, and institutional costs associated with education and support. The manufacturer's ability to ensure reliable, high-quality drug supply should also be considered to avoid forced and undesired switching of a patient's biologic treatment. A good understanding of biosimilars and their unique considerations is crucial in order for the healthcare professionals to prepare for their use in clinical practice.

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