Clinical and Scientific Considerations for Biosimilars

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Clinical and Scientific Considerations for Biosimilars

1. Introduction to Biological Products and Biosimilars

Biological products are large, protein-based therapeutics (e.g., monoclonal antibodies [mAbs], vaccines, interleukins, hormones, recombinant proteins, and blood products) that have highly complex, heterogenous structures, including extensive protein folding and a variety of post-translational modifications (PTMs), such as glycosylation.[1-5] Biological products are generally made using living cells that are highly sensitive to changes in manufacturing conditions. These highly complex products may be up to 1,000 times the size of small-molecule drugs, such as aspirin, which in contrast may have relatively simple, well-defined structures.[1-3] Biological products play a critical role in clinical care,[2,6] both in terms of active therapy (e.g., mAbs,[2] antibody drug conjugates,[7] and interferons[2]), preventive care (vaccines),[4] and supportive care (e.g., granulocyte-colony stimulating factors[8]).

A **biosimilar** is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that has no clinically meaningful differences in terms of safety, purity, and potency from the reference product. The "reference product" is an originator biological product approved by a national regulatory agency.[9] Biosimilar products undergo intensive characterization and quality testing during development, but due to the unique cell lines and proprietary manufacturing processes used by the manufacturer of the reference product, slight differences in the biosimilar compared to the reference product are expected. However, these differences are not expected to result in clinically meaningful differences in terms of safety, purity, or efficacy.[3,9-11] Biosimilar products have a primary amino acid sequence identical to that of their reference products, but minor differences in the tertiary and quaternary structures (primarily the result of PTMs) may be accepted if the manufacturer demonstrates that these differences have no effect on the safety or efficacy of the biosimilar.[9,10,12] Biosimilars are also expected to have the same strength, dosage form, and route of administration as the reference biological product.[13] However, biosimilars may differ from a reference product in formulation, delivery device, or container closure.[14] In addition, a biosimilar may be approved for fewer than all of the indications of the reference product, as the biosimilar sponsor may elect to not seek approval for all of the reference product's approved indications.[15] A biosimilar approved for fewer than all indications of the reference product should not be viewed as inferior to the reference product or to another biosimilar of the same reference product with additional indications.[16]

Most stringent regulatory authorities have established common expectations for biosimilar products.[17-20]

Definitions for Biosimilar Products Across Regulatory Authorities

- United States (US) law defines a biosimilar as "a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that has "no clinically meaningful differences from the reference product in terms of the safety, purity, and potency."[17]
- The European Medicines Agency (EMA) defines a biosimilar product as "a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product and demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise."[21]
- Health Canada defines a biosimilar product (previously known as a subsequent entry biologic) as "a biologic drug that enters the market subsequent to a version previously authorized in Canada, with demonstrated similarity to a reference biologic drug. A biosimilar relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference biologic drug and which influences the amount of and type of original data required."[19]
- The World Health Organization (WHO) defines a biosimilar product as "a biotherapeutic product, that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product."[20]

Noncomparable biotherapeutics (NCBs, also known as biocopies, biomimics, me-too biologics, etc.) are not biosimilars. These products are intended copies of licensed biological products, but they have not been directly compared to a reference product and have not been approved in alignment with robust, scientifically appropriate approval guidelines, such as those published by the WHO.[22,23] There are limited or no data about the clinical safety or efficacy of an NCB when used in place of another biological product. The continuation of licensing of NCBs in some jurisdictions under regulatory pathways that are not appropriate for biotherapeutic medicines and that do not require rigorous scientific standards to demonstrate biosimilarity may put patients at risk with respect to safety or may alter expected clinical outcomes, and can diminish providers' and patients' confidence in biosimilar products.[24-28]

2. Development and Manufacturing of Biological Products

2.1 Complexities of Biological Molecules

Biological products are more complicated to develop and manufacture than small-molecule drugs.[1,29]

The characteristics of a biological product are often related to each manufacturer's unique and proprietary cell line and manufacturing process, including formulation and administration device. Changes in these variables in any biological product, including biosimilars, can have clinical implications stemming from alterations in structural and functional characteristics.[1,29]

The properties of protein-based biological products contribute to the complexities associated with their development, as illustrated in **Table 1**.

Table 1. Properties of Biological Products and Small-Molecule Products

Property	Biological Products	Small-Molecule Products
Size[30]	> 100,000 Daltons	Hundreds of Daltons
Structure[30,31]	Complex, heterogenous, many types of PTMs	Generally simple, well defined
Characterization[1]	Complex, resource-intensive, > 2000 in-process quality tests during manufacturing	< 100 in-process quality tests during manufacturing
Stability	Sensitive to storage and handling conditions, such as temperature and other environmental characteristics[32]	Relatively stable[33]
Immunogenicity[33]	The biological product has an intrinsic potential for immunogenicity	Immunogenicity is less likely and is intrinsic to the patient
Manufacturing	Manufactured using proprietary techniques in living cell lines, and similar (not identical) versions can be made[30]	Generally synthesized from predictable (and sometimes proprietary) chemical processes, and identical copies are possible[34]

The unique shape, or structure, of a protein contributes to its function in the cellular environment.[30] A protein is synthesized as a chain of amino acids that undergoes a combination of conformational changes to form a three-dimensional polypeptide structure. Small changes in the folding of the protein can alter its function and manifest as a clinically meaningful difference in efficacy or safety.[35]

Proteins can also undergo PTMs that further contribute to protein complexity, diversity, and function.[36] There are several hundred types of PTMs that have been identified, including glycosylation and other glycan-related changes, acetylation, phosphorylation, and amidation.[36,37] These modifications underlie differences in the biological properties of proteins.[38-42] Thus, differences in glycosylation of a mAb, for example, can lead to altered biological activity, altered pharmacokinetics (PK) or bioavailability, changes in antibody function, or changes in immunogenicity (**Figure 1**).[39] An up-to-100-fold enhancement of antibody-dependent cell-mediated cytotoxicity (ADCC) has been reported following the removal of the fucose residue from the glycocomponent of the immunoglobulin G (IgG) antibodies produced in Chinese hamster ovary 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; in this case, bioengineering tactics are needed to "knock out" insertion of these moieties to produce antibodies with enhanced ADCC activity.[37]

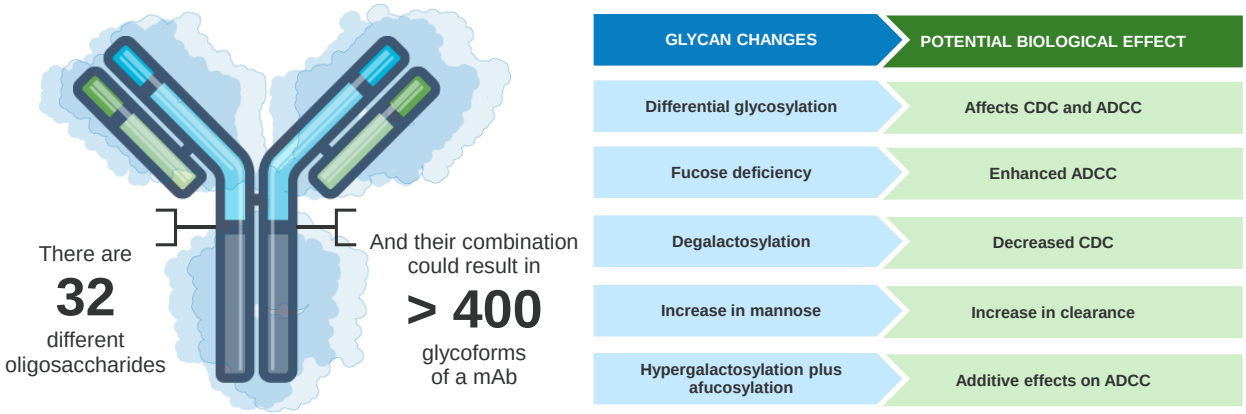


Figure 1. PTMs Are a Key Source of Functional Diversity of Biological Products[38-44]

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; mAb, monoclonal antibody; PTM, post-translational modification.

2.2 Complexities of the Development and Manufacturing Process for Biosimilars

The manufacturing process for a biological product, including a biosimilar, is more complicated than the process for a small-molecule drug[45]; and successful manufacturing requires expertise in protein engineering, cell line development, and large-scale cell culture.[29,46]

The manufacturing process for a biosimilar product begins with identification of the critical quality attributes (CQAs) of the reference product.[47] The CQAs are features critical to the identity, structure, purity, biological activity, and stability of a biological product.[11,47] **Figure 2** lists the eight categories of CQAs that are generally evaluated.

Once the reference-product CQAs are identified, the biosimilar manufacturer must establish its own unique development and manufacturing process—starting with selection of a cell line and moving through formulation, fill, and finish of the final biosimilar product—to manufacture a product with highly similar CQAs.[11]

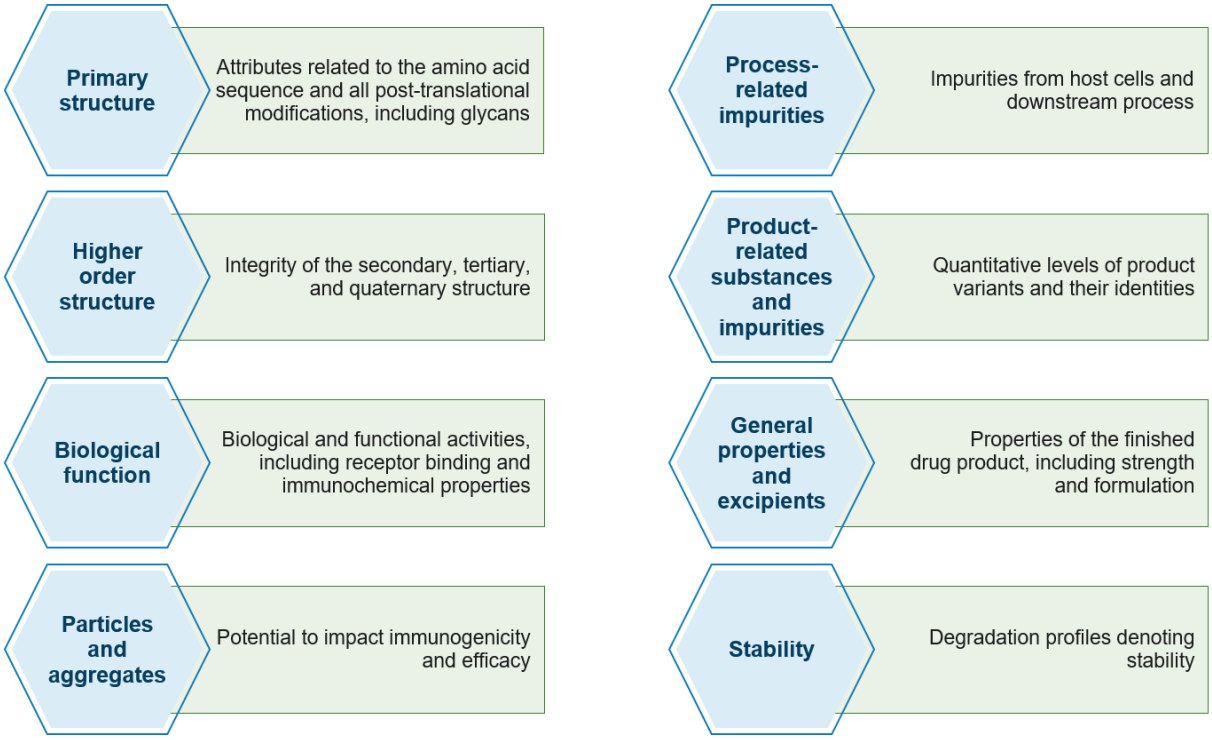


Figure 2. Analytical Characterization Is Used to Evaluate Reference Product CQAs[9,12,48,49]

As is the case for biological products in general, there are many steps that comprise the development process of a biosimilar, as illustrated in **Figure 3**. One of the first steps is to isolate the gene that encodes the protein of interest.[50] 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).[50,51]

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.[51,52] Engineering and preserving an appropriate cell line for producing the protein of interest requires extensive work and careful screening. The resulting cell line is unique to each manufacturer.[32,51]

The primary cell strains housed in the master cell bank are not used for production purposes. Instead, a working cell bank is established from the master cell bank, and these cells are used for production purposes.[51] Each batch of a biological product 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.[52] 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 that provides the nutrients and the optimum environment for cells to survive.[50]

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.[50] 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 more than 10,000 L in capacity.[51]

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 primary recovery can be 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, primary recovery involves lysing the cells to release the protein product, which then has to be purified by separating it from the other components of the cell. Additional purification steps are always required after primary recovery 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.[32] Because even small differences in the manufacturing process can result in substantial changes in the CQAs of a biological product, the biosimilar manufacturer must plan to analytically characterize the biosimilar product in terms of CQAs using sensitive and validated assays.[11,29]

The protein product is then formulated per specifications and packaged appropriately. Biopharmaceuticals are highly sensitive to environmental factors such as temperature, agitation, and exposure to light. Improper storage and handling can lead to protein degradation.[32]

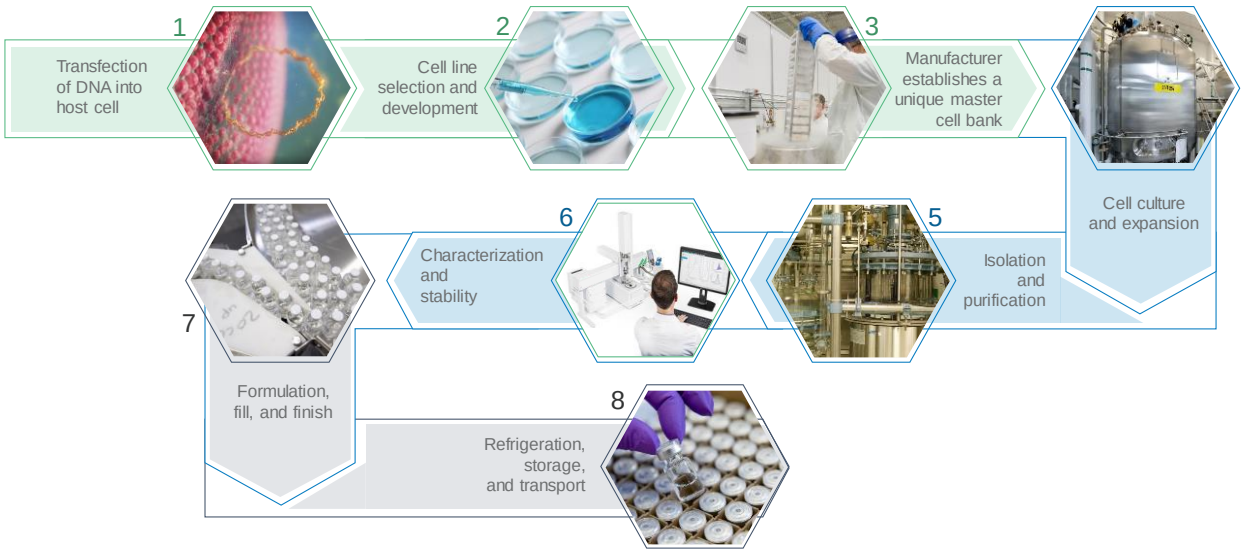


Figure 3. The Steps of a Typical Biological Product Manufacturing Process[32,51]

Manufacturers of biological products are responsible for all of the monitoring crucial to the success of each product's development, scale-up, and manufacturing process. Because the manufacturing process is critical to producing a consistent product (i.e., with the expected quality, safety and efficacy), it is necessary to implement appropriate testing.[53] Tests are performed to measure product attributes associated with product quality and manufacturing controls and to assure the identity, purity, strength (potency), and stability of the products.[53,54]

2.3 Manufacturing Process Changes

Manufacturers of biological products may periodically choose to alter manufacturing processes 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, they generally result in consistent quality within the historical lot-to-lot variability of the product. However, planned process changes occasionally result in a small shift in certain product attributes (i.e., outside of normal lot-to-lot variability). Health authorities and the manufacturers themselves, therefore, require data demonstrating that any changes in manufacturing do not change the clinical or safety characteristics of the product.[53]

An *unplanned* trend or shift in a quality attribute is referred to as "process drift" or, if it occurs gradually over time, "evolution." Potential causes of process drift include planned supplier-driven changes in raw materials or components and cumulative effects of minor changes in procedures, equipment, or facilities. After a process drift is identified, an intensive investigation is performed to determine the root cause and identify measures that will 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.[55]

2.4 Comparability for a Post-manufacturing Process Change vs Biosimilarity

The US Food and Drug Administration (FDA) emphasizes the distinction between assessing the *comparability* of a product before and after a manufacturer makes a change to its own manufacturing process and demonstrating *biosimilarity* of a proposed biosimilar to a reference product. This topic was discussed in guidance issued in April 2015:[9]

> *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.*[9]

Although some of the scientific principles used in the comparability assessment for within-product manufacturing changes may be similar to those used to support a demonstration of biosimilarity for a proposed biosimilar to a reference product, more data are needed to establish biosimilarity due to the use of different proprietary cell lines and manufacturing processes by the reference product and biosimilar product manufacturers. Because a biological product manufacturer can assess an iteration of a post-manufacturing change for a biological product against its pre-change product, it would not be accurate to state that a biological product becomes a "biosimilar" of itself over time.[9]

The requirements for demonstrating comparability after a within-product manufacturing process change vs demonstrating biosimilarity are delineated in **Table 2**.[56]

Table 2. Major Differences Between Biosimilarity Assessment and Manufacturing Changes[56]

Biosimilarity Assessment	Manufacturing Process Changes
Newly developed cell line	Typically, same cell line*
Entirely new process, with no access to originator's process history	Typically, incremental change to an existing process, which is amenable to stepwise comparisons*
Comprehensive structural and functional comparison with selected samples of a reference product with no access to reference-product historical testing data	Comprehensive structural and functional comparison at all relevant steps (intermediate, drug substance, and final product) and reference to complete historical testing records
Reference-product substance lots not available	Reference material available at each step

*Higher-risk manufacturing changes may include a new cell line or significant re-engineering of several process steps and may therefore require additional comparability data

3. Global Biosimilar Approval Pathways

In highly regulated regions, the regulatory pathways for biosimilar products are rigorous and approval is based on the total evidence package obtained from comparative analytical characterization and comparative preclinical and clinical studies.[9,48,57,58]

3.1 EMA Approval Pathway

The EMA is a decentralized agency of the European Union (EU) responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU.[59] The EU was the first region to develop a biosimilar approval pathway for biotechnology-produced medications.[60]

The EU established legislation for biosimilars in 2004, and EU regulators developed a regulatory approval pathway for biosimilars starting in 2005.[61] The first biosimilar was approved in the EU in 2006.[62]

Currently, there are nine classes of biosimilar medicines approved in the EU:[63,64]

1. Recombinant erythropoietins
2. Recombinant granulocyte colony-stimulating factors (G-CSFs)
3. Recombinant human insulin
4. Recombinant human growth hormone (GH)
5. Recombinant follicle-stimulating hormone (FSH)
6. Recombinant parathyroid hormone (PTH)
7. Fusion proteins (tumor necrosis factor [TNF] inhibitor)
8. mAbs
9. Low molecular weight heparins

The EMA has three guideline documents that cover the basic principles, quality, and nonclinical and clinical considerations related to biosimilars. A list of these documents can be found in **Appendix A.1** of this white paper.

The EMA regulatory pathway, established for the EU member states, often serves as a reference for other regulatory agencies to develop guidelines on biosimilar review and approval. Although many non-EU European countries 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.[25] 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.[65,66] Other nations that have implemented guidelines for biosimilar product approval based on EMA regulations include

Australia, New Zealand, and South Africa.[25,67,68] It is worth remembering that despite many countries basing their guidelines on the EMA requirements for biosimilars, there are variations from region to region.[25]

3.2 US Approval Pathway

The US approval pathways for small-molecule drugs and biological products differ. New small-molecule drugs are evaluated and approved under a New Drug Application [section 505(b)(1) or 505(b)(2) pathway] as authorized by the Federal Food, Drug, and Cosmetic Act.[69]

A subsequent generic of a small-molecule drug can be approved via an Abbreviated New Drug Application [505(j) pathway] that shows the drug has the same active ingredient as, and is bioequivalent to, the reference drug.[57,69] The Abbreviated New Drug Application for generics is solely based on an analytical and bioequivalence evaluation and does not require evidence of comparative clinical efficacy or safety.[57]

As authorized by the Public Health Services Act (PHSA), new biological products are evaluated and approved under a Biologics License Application (BLA) 351(a) pathway. The Patient Protection and Affordable Care Act of 2010 added the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which amended the PHSA and other statutes to create an abbreviated licensure pathway for biological products under a BLA 351(k) pathway that are demonstrated to be highly similar to, and have no clinically meaningful differences from, a US FDA-licensed biological product.[70] These pathways are summarized in **Table 3**.

Table 3. Approval Processes for Drugs and Biological Products in the US[15]

Product *Governing Act*	Application Type	Pathway	Requirements
Drugs ***FDCA***	NDA	FDCA §505(b)(1)	Full product-specific evaluation including clinical demonstration of safety and efficacy
	NDA	FDCA §505(b)(2)	Sponsor may rely (in part) on the 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
	ANDA	FDCA §505(j)	Demonstration of same active ingredient and bioequivalence required; no product-specific clinical safety and efficacy evaluation required
Biological product ***PHSA***	BLA	PHSA §351(a)	Full product-specific evaluation including clinical demonstration of safety, purity, and potency
	BLA	PHSA §351(k)	Proposed biosimilar is demonstrated to be highly similar to, and to have no clinically meaningful differences in terms of safety, purity, and potency from, a reference biological product licensed under 351(a) of the PHSA

ANDA, Abbreviated New Drug Application; BLA, Biologics License Application; FDCA, Food, Drug, and Cosmetic Act; NDA, New Drug Application; PHSA, Public Health Services Act

3.3 Regulatory Pathways in Other Countries

Regulatory standards for biosimilar products vary widely by region and by country; some regions have established and are maintaining some of the most rigorous regulatory standards globally (e.g., US FDA, EMA), while other countries have not developed or are still developing laws or regulations. Many countries rely on the recommendations/approvals from regulated markets (e.g., EU, US, Canada, Japan, and Australia) through the Certificate of Pharmaceutical Product (CPP) certification scheme implemented by the WHO. Through CPP, maturing regulatory authorities can rely on the previous thorough evaluation of the quality, safety, and efficacy of a product, and instead focus on providing added-value rather than duplicative assessment activities.[71] In some countries where biosimilar regulatory pathways were only recently developed, or where they do not exist at all, noncomparables were licensed outside of an established regulatory pathway and without comparative data to demonstrate biosimilarity.[72]

Similar to the US and EU, the biosimilar regulatory pathways in Canada and Australia are well established and considered stringent.[67,73] In both of these latter countries, only global biosimilar developers with approvals from the EMA or US FDA have registered biosimilar products.[73,74] To

receive licensure for a biosimilar product from Health Canada, applicants must present a comprehensive data package to demonstrate biosimilarity and quality.[19] Similarly, the regulatory framework in Australia also requires applicants to provide a comprehensive data package. Australia's biosimilar regulatory pathway aligns closely to that of the EMA, with the Therapeutic Goods Administration (TGA) adopting the EMA guidelines in 2008 and formally publishing TGA guidance that remain based on EMA guidelines in 2013.[67]

In Latin America, the regulation of biosimilar products varies widely among different countries. Several countries have drafted or finalized certain requirements for the approval of biosimilars (e.g., Argentina, Brazil, Chile, Colombia, Costa Rica, Guatemala, Mexico, Panama, Peru, and Venezuela).[22,75] While many of these countries have based regulations on the 2009 WHO criteria, others have aligned with regulations from stringent regulatory authorities (SRAs) or developed their own guidelines that are not aligned with SRAs or the WHO (e.g., Colombia).[75] Some noncomparable biotherapeutics were licensed in Latin America prior to biosimilar regulations being in place and without adequate clinical testing being performed, and in some circumstances, are now mandated to conduct appropriate comparative testing, including clinical trials, to prove biosimilarity (e.g., Mexico, Chile).[24,25] In 2016, the WHO finalized a Regulatory Assessment Guideline to recommend approaches for member states to use in reviewing the status of non-original biological products that were not licensed according to the current WHO guidelines.[76] In 2019, the Panamerican League of Assocations for Rheumatology (PANLAR) created a consensus statement and recommendations on biosimilars in rheumatology to address the inconsistency of regulations regarding biosimilars among Latin American countries.[77]

Similar to Latin America, the regulation of biosimilar products in the Middle East and Africa varies widely by country. Several countries have established certain requirements for the approval of biosimilars (e.g., Turkey, Egypt, Saudi Arabia, Jordan, South Africa), whereas others are currently developing guidelines (e.g., United Arab Emirates [UAE], Lebanon, Morocco, Algeria, Tunisia).[78,79] However, there are many countries in the region that currently do not have any established biosimilar guidelines (e.g., Kuwait, Oman, Qatar, Bahrain, Iraq).[79] Of the countries with regulatory guidelines established or under development, many are based on the WHO, EMA, and/or US FDA guidelines (e.g., UAE, Jordan).[79] Countries in the Middle East and Africa also rely on CPP dependence as part of the regulatory framework, requiring data from a previous filing in a foreign country (e.g., US, EU, Canada, Australia, Japan, EU-5 Nordics). Some noncomparable biotherapeutics are licensed in certain countries within the region without adequate clinical testing (e.g., Egypt, Iraq, Lebanon).[79]

In Asia, many NRAs have established regulatory pathways for the evaluation and approval of biosimilar agents (e.g., China, Japan, Malaysia, Singapore, South Korea).[25] Japan has established stringent regulatory requirements that require submissions to include data from comparative clinical trials, details of manufacturing methods, long-term stability data, and information on overseas use.[80] Although Thailand is now considered to have stringent regulatory standards, prior to establishing biosimilar regulations it licensed noncomparable biotherapeutics

solely based on bioequivalence data, and did not include the preclinical or clinical studies that are required today.[81] Some NRAs in the region have recently made significant progress in establishing regulatory pathways. The National Medical Product Administration (NMPA; formerly the China Food and Drug Administration) initially released guidelines on the development and evaluation of biosimilars in 2015.[82] In 2020, NMPA released additional guidelines, including the "Technical guidelines for the similarity evaluation and indication extrapolation of biosimilar drugs" and several product specific guidelines pertaining to clinical trials of biosimilars.[83]

In contrast, while stringent regulatory guidelines may be established by many NRAs in the region, other countries continue to license noncomparables. India released biosimilars guidance in September 2012, which was revised in August 2016.[84] The revision outlines pre- and post-marketing regulatory requirements, including the recommendation of a stepwise approach to demonstrating biosimilarity, and takes the EMA and WHO guidelines into account.[84] However, India has been producing noncomparable "intended copies" of already licensed biological products since 2007 under an abbreviated approval process that relies on limited data, which allows local biopharmaceutical manufacturers to keep production costs low and provides therapies to patients who cannot afford the reference product.[25] However, these "intended copies" have not met the rigorous criteria for demonstration of biosimilarity that stringent regulatory bodies such as the EMA and US FDA utilize for review and approval of biosimilars.[25,85]

As noted above, the WHO developed guidelines in 2009 in an attempt to provide globally accepted norms and standards for biosimilars.[20] In recognition that certain member states have registered NCBs using regulatory pathways inconsistent with the 2009 guidelines for biosimilars, in 2015 the WHO developed a guideline that provides a road map for regulatory assessments of such products. The guideline clearly states that biological products registered without a comprehensive, head-to-head comparison with reference biological products 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 and risk of keeping the products on the market, the elements missing from the original dossier, and an orderly procedure for obtaining additional required data from the sponsor.[76]

In summary, biosimilars are developed and approved according to a country's or region's biosimilar regulatory pathway, which can vary considerably with some countries continuing to develop guidelines. However, adherence to globally accepted regulatory standards, such as the 2009 WHO Guidelines on Similar Biotherapeutic Products, is fundamental to assuring patients and the medical community that approved biosimilar products are safe and efficacious, and ensuring that adverse events (AEs) can be accurately tracked and identified.

4. Demonstrating Biosimilarity

The goal of a biosimilar development program is to demonstrate that the candidate biosimilar is highly similar to (and has no clinically meaningful differences from) the reference product, not to independently establish de novo the safety and efficacy of the biosimilar. The US FDA has provided several guidance documents to assist biosimilar developers. A list of these documents and a description of their contents can be found in **Appendix A.2** of this white paper.

4.1 US FDA's "Totality-of-the-Evidence" Approach

Given the complex nature of biological products, a "one size fits all" assessment to evaluate biosimilarity is not appropriate. In a 2011 article 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) discussed a "risk-based totality-of-the-evidence approach" to the evaluation of biosimilarity.[86] The US FDA suggested a stepwise approach to generating data to support a demonstration of biosimilarity (**Figure 4**). 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 the next steps to try to address that uncertainty. This stepwise approach involves the following:[9]

- *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 using appropriate methodology to determine the differences in relevant CQAs between a biosimilar and the reference product. 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.[9] Although advanced in vitro and in silico technologies can be used for analytical characterization to support the demonstration of biosimilarity, they are not, by themselves, sufficient to show that there are no clinically meaningful differences in efficacy, safety, and immunogenicity between a biosimilar and its reference product.[48]
- *Step 2:* Consider the need for animal data to assess toxicity when uncertainties regarding the safety of a biosimilar remain after extensive structural and functional characterization. However, nonclinical studies may not be warranted if a biosimilar has been demonstrated to be highly similar to a reference product through analytical characterization.[9]
- *Step 3:* Comparative human PK/pharmacodynamics (PD) studies are necessary because of the general inability to adequately predict the human PK and PD profiles of a protein product using functional assays and/or animal studies. Therefore, PK and PD studies in humans, comparing the proposed biosimilar to the reference product, are fundamental to demonstrating biosimilarity. Selection of the human PK and PD study populations and parameters should take into account the relevance and sensitivity of the populations and parameters. The populations and parameters studied for the licensed reference product

and current knowledge of within- and between-subject variability of human PK and PD of the reference product should also be considered.[9]

- *Step 4:* Comparative safety and effectiveness data will be needed to address any residual uncertainties 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 (MOA) of the reference product and disease pathology (which can also influence 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., whether sensitive PD markers available).[9]
- *Clinical immunogenicity studies:* The US FDA will generally expect at least one clinical study that includes a comparison of immunogenicity of the proposed biosimilar vs that of the reference product. This can be incorporated into the comparative PK/PD study, the comparative clinical study, or both or be a stand-alone study. The goal of immunogenicity studies is to establish that there are no clinically meaningful differences in incidence and severity of human immune response between the biosimilar and the reference product. Immunogenicity can be tested during clinical safety and efficacy studies or PK/PD studies. Immunogenicity studies should be conducted in a sensitive population and include assessments of binding and neutralizing antibodies.[9]

In all cases, the US FDA has discretion under US law to determine that certain studies are not required.[9]

As illustrated in **Figure 4**, the steps for developing an originator biological product and a biosimilar are the same, but the amounts of time and data that need to be generated at each step differ.

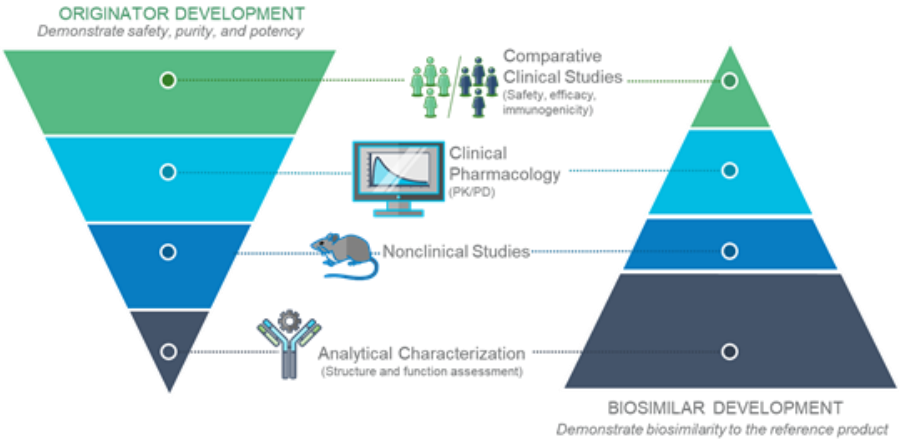


Figure 4. The US FDA's Approach to the Demonstration of Biosimilarity[9,43]

4.2 Clinical Studies

The overall clinical program to support a demonstration of biosimilarity is different from that required for the approval of the reference product. To demonstrate biosimilarity, regulatory agencies generally require comparative clinical studies to resolve residual uncertainty about whether there may be clinically meaningful differences between the proposed biosimilar and the reference product; these studies are not designed to re-establish efficacy or safety, which were already demonstrated by the reference product.[9,22,87,88] Comparative clinical studies, as part of a biosimilar development program, should be performed in populations and use endpoints that are adequately sensitive to detect clinically meaningful differences between the proposed biosimilar and the reference product, if such differences exist.[9,87]

Comparative clinical studies generally include an evaluation of comparative PK, PD (when there are relevant PD endpoints), immunogenicity, efficacy, and safety. There is no “pivotal” clinical study that demonstrates biosimilarity. Necessary studies are determined based on observed differences between the proposed biosimilar and the reference product and the ability to evaluate the impact of the differences; these differences are identified from the structural and functional comparisons and various product-specific factors.[9]

Comparative efficacy studies are typically designed as equivalence studies.[9] Equivalence studies are fundamentally different from superiority studies and non-inferiority studies (**Figure 5**).[9,22,87,89] Superiority studies aim to demonstrate that one product provides superior efficacy over another by ruling out the equivalency of the two agents.[89] Non-inferiority studies aim to demonstrate that the proposed product is not inferior to an unacceptable extent.[89] Lack of superiority, or demonstration of non-inferiority, does not prove equivalence.[87] Equivalence studies intend to establish statistical evidence showing 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.[9,87]

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 that the proposed biosimilar is neither inferior nor superior to the reference product (**Figure 5**).[9,88] 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 the same as that used to demonstrate the clinical benefit of the reference product; alternatively, sensitive and meaningful endpoints reflective of in vivo activity and therapeutic effect (e.g., PD endpoints) may be used.[9]

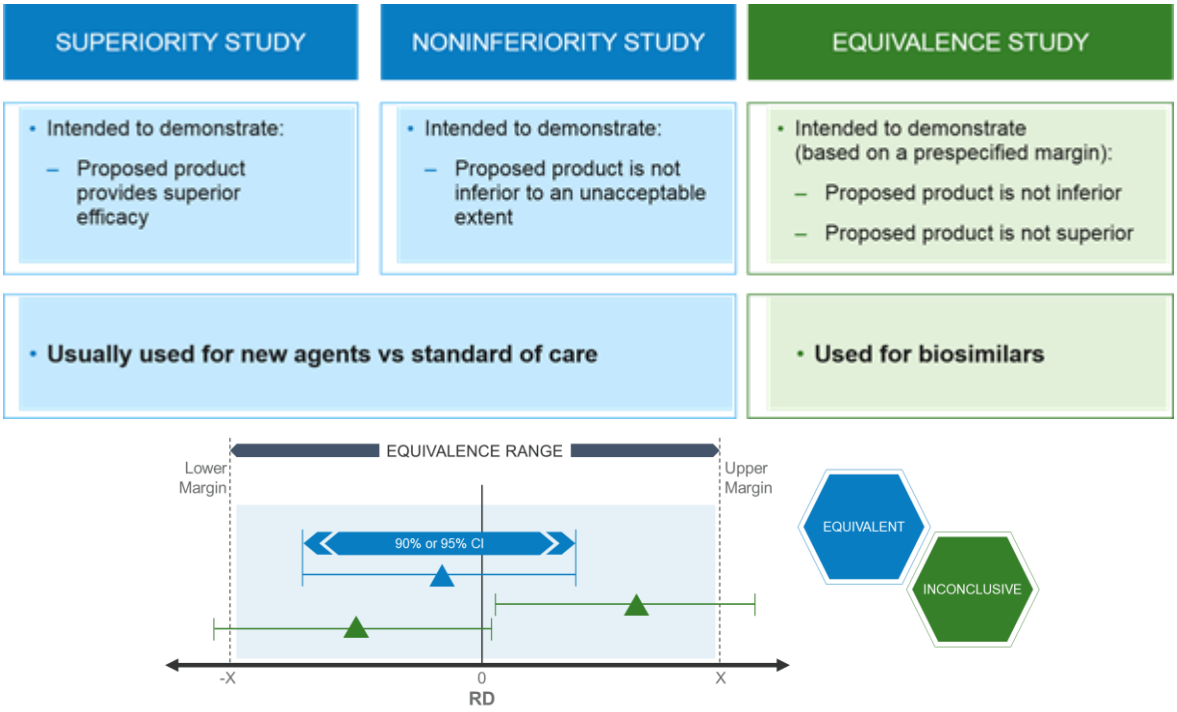


Figure 5. Equivalence Studies Help Demonstrate Biosimilarity[9,22,87-89]

CI, confidence interval; RD, risk differential.

Preferably, comparative safety and immunogenicity are assessed in the same study as comparative efficacy. The choice of patient population should also include considerations of sensitivity for detection of differences with respect to safety. With regard to sensitivity to detect difference, a population for which the investigational product is used as monotherapy should be considered.[9]

In some circumstances, comparative clinical study designs for evaluation of biosimilars may include a single transition in which the study subjects in the comparator arm (reference product) are re-randomized either to receive the proposed biosimilar or to continue in the reference product arm. The key objective is to ensure that there is no hypersensitivity, immunogenicity, or other reaction after transitioning from the reference product to the proposed biosimilar.[90] (More information on this subject is provided in Section 5.)

The comparative clinical studies may also include sensitivity analyses. These analyses help assess the credibility of the study results and conclusions by testing whether the results would change when something about the assumptions or the approach to the data analysis changes. Such scenarios could include (but are not limited to) definitions of outcomes, missing data, or outliers. If the sensitivity analyses findings are consistent with those of the primary analysis and

would lead to similar conclusions, then the underlying factor(s) likely had little or no influence or impact on the primary conclusions, and the results or conclusions are considered to be "robust".[91]

4.3 The Importance of Robust, Scientifically Appropriate Regulatory Standards

The EMA's experience with evaluating biosimilars has demonstrated the value of scientifically appropriate regulatory standards, including comparative clinical data in the assessment of biosimilarity. Although regulators may not require the same amount of comparative clinical data for all biosimilars, comparative clinical testing is important and remains an expectation in most robust regulatory reviews.[92] EMA approval standards have been applied to more than 60 candidate biosimilar products and have successfully screened those with substantial analytical and clinical similarity from products with incomplete or unacceptable results.[63]

While a majority of proposed biosimilar products reviewed by the EMA have received marketing authorization, some proposed biosimilars 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.[63] In one example, the EMA declined to approve 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.[93] Other concerns raised by the Committee for Medicinal Products for Human Use (CHMP) included impurities, insufficient stability data, significant difference in AE rates, and lack of sufficient validation in the immunologic response tests and manufacturing process.[1,93] 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.[93]

In another example, applications for some biosimilar candidates to pegfilgrastim were initially withdrawn from or rejected by the EMA for several reasons including: (*1*) study results were unable to show that blood concentrations of pegfilgrastim were similar after taking the reference biological product and the biosimilar; (*2*) lack of a certificate of Good Manufacturing Practice (GMP) for the biosimilar's manufacturing site; and (*3*) study results were unable to show bioequivalence.[94,95] The agency did eventually approve several pegfilgrastim biosimilars, but the initial rejections and withdrawals are evidence of the critical importance of robust scientific standards to evaluate biosimilarity.[63]

In some cases, the EMA may have concerns that initially preclude approval of the biosimilar, but approval is granted after those concerns are appropriately addressed. For example, a preauthorization clinical study that compared the biosimilar of a recombinant human growth hormone to the reference product found that a higher number of patients who received the biosimilar developed non-neutralizing anti-GH antibodies compared to those who received the reference product. Consequently, changes were made in the purification steps of the biosimilar product's manufacturing process and the immunogenicity issues were resolved, resulting in approval by the EMA after these initial safety concerns were adequately addressed.[1,93]

As discussed, biosimilars are not expected to be identical to the reference biological product.[96] For example, in 2013, the EMA approved the first biosimilar anti-TNF mAb.[63] Although some differences in biological activity were detected in an in vitro assay, this difference was not interpreted to be clinically meaningful because it did not affect the activities of the biosimilar in experimental models that were regarded as more relevant to the pathophysiological conditions in patients.[97] Regulatory agencies around the world continue to rely on scientifically appropriate clinical testing to evaluate the clinical impact, if any, of these minor biophysical variations.[9,20,21]

4.4 Extrapolation

Extrapolation is a critical part of a biosimilar development program, and is defined as the approval of a biosimilar for use in an indication held by the reference product that has not been directly studied in a comparative clinical trial with the biosimilar.[98] Approval of additional indications via extrapolation is based on scientific rationale that considers all available data in the biosimilar marketing application, knowledge of the reference product, and consideration of various scientific factors for each indication sought. Extrapolation refers to the extrapolation of data and the totality of evidence; efficacy and safety from the indication(s) studied using the biosimilar are not extrapolated to other non-studied indications that are approved for the reference product and sought for the biosimilar.[9,21]

To support the approval of an indication via extrapolation, the sponsor generally will need to provide a scientific justification addressing differences, if any, in the MOA, PK, biodistribution, immunogenicity risk, expected differences in toxicity, and any other relevant factor between the clinically tested and the sought additional reference product indications.[9] Differences with respect to the factors described do not necessarily preclude extrapolation, but the scientific justification should address the differences and the potential impact on biosimilarity. Such differences may be addressed based on the available knowledge of the reference product as well as the totality of evidence generated during development of the proposed biosimilar (**Figure 6**).[9] Independent of the mechanism by which a biosimilar sponsor seeks approval for additional indications, it is also important to note that a manufacturer might not seek approval for all indications of the reference product at a given time, e.g., in instances where some indications may be protected by patents or exclusivity.[99]

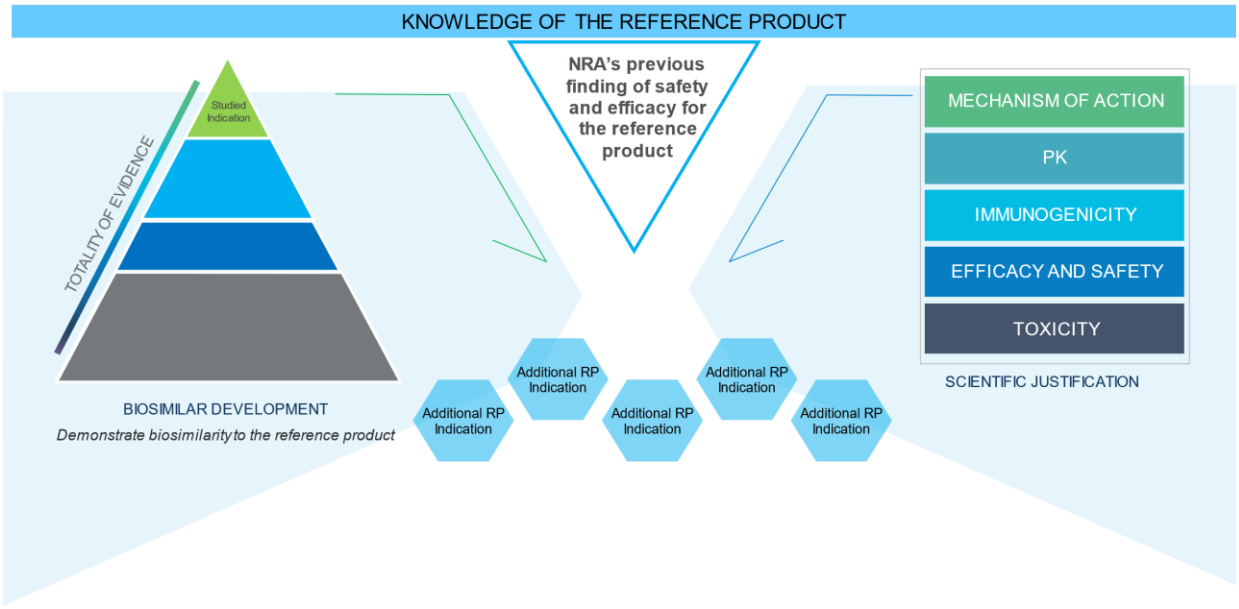


Figure 6. Extrapolation[9,21]

Approval of additional indications for the biosimilar, which are approved for the reference product, via extrapolation is determined by regulatory authorities on a case-by-case basis. Therefore, approved indications for a biosimilar 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.[100,101] Although approval of the biosimilar by the EMA included approval of all the reference product's indications, Health Canada did not originally allow extrapolation to support the inflammatory bowel disease (IBD) indications due to the differences in ADCC activity observed with relation to the fragment crystallizable (Fc)-region of the anti-TNF mAb, which may be implicated specifically in IBD.[97,101] However, subsequently, in 2016, the mAb was approved by Health Canada for 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 MOA of the agent, and the relationships of these MOAs to clinical outcomes in IBD.[101]

5. Switching, Interchangeability, and Substitution

The terms “switching,” “interchangeability,” and “substitution” have different meanings across regions, and there are also regional differences between switching and substitution practices, as reviewed in this section.

5.1 Switching

“Switching” is defined as the practice by which a physician may elect to prescribe one medicine in place of another with the same therapeutic intent.[102] In relation to biosimilars, a physician may elect to prescribe a biosimilar in place of the reference product. Switching is a prescriber-led action. Physicians should practice evidence-based medicine and consider the risks/benefits of switching patients between a reference product and its biosimilar. In Europe, in the context of biosimilars, the term *“*switching*”* has been used synonymously with the term *“*interchangeable.”[45] As described below, the term “interchangeable” has a specific legal and regulatory meaning in the US that differs from switching. It is therefore important to understand the intended meaning of the terms when used.

5.2 Interchangeability

In the US, under the BPCIA of 2009, biosimilars can be approved as “biosimilar to” a reference product or, in addition, can be approved as a biosimilar that is “interchangeable with” a reference product. To be granted an “interchangeability” designation, a biosimilar product must demonstrate biosimilarity and that it can be expected to produce the same clinical result as the reference product in any given patient.[70,103] 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 biological product cannot be higher than the risks associated with using the reference product alone.[103]

In May 2019, the US FDA issued guidance describing what data and information would be needed to support a demonstration of interchangeability. The type and amount of data needed to demonstrate interchangeability is determined by the US FDA on a case-by-case basis depending on a composite of factors, such as the complexity of the biological product, the extent of comparative and functional characterization, clinical experience with the reference product, and the potential risk of immunogenicity. For products administered more than once to a patient, the US FDA generally 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 proposed interchangeable product and the reference product.[103] The number and duration of switches between the reference product and the proposed interchangeable product should consider the clinical condition being treated, the dosing of the product, 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.[103] Further, the treatment lead-in period should be of sufficient duration to ensure an adequate baseline (e.g., steady state of PK) 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 7**).[103]

In the US, an interchangeable biosimilar product may be substituted for the reference product without prior prescriber approval, consistent with state pharmacy law. Many state laws also include provisions whereby a prescriber may prevent substitution by stating "dispense as written" or "brand medically necessary."[103,104]

Interchangeability as described here is a regulatory standard that only exists in the US. Amgen does not support the automatic substitution at the pharmacy of biosimilars that have not met a US-like standard for "interchangeability." Only those biosimilars that have undergone additional analyses and have been determined by a regulatory authority to be "interchangeable" per a US-like standard should be eligible for automatic substitution by a pharmacist (without consulting the prescriber). Also, automatic substitution should occur only if appropriate communication and recordkeeping requirements are in place.

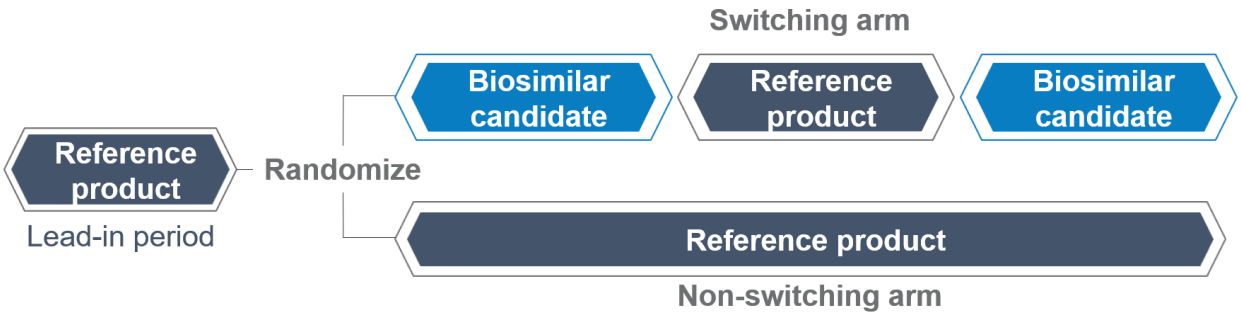


Figure 7. US FDA Guidance for Demonstrating Interchangeability[103]

5.3 Pharmacy Substitution of Biosimilars

In the US, as of February 2021, 49 states, the District of Columbia, and Puerto Rico have adopted laws regarding substitution of biological products by the pharmacist without the intervention of the prescriber. Although language between states varies, such substitution laws often contain a combination of the following principles:[104,105]

1. Only biological products deemed by the US FDA to be "interchangeable" are eligible for substitution.[104,106]
2. The prescribing physician retains the authority to require that the pharmacist dispense as written (DAW).[104,106]
3. The pharmacist informs the patient or patient's representative of the substitution.[104,106]

4. For dispensed biological products where an interchangeable product is available, the pharmacist must make available to the prescribing physician the name and manufacturer of the product dispensed; this notification must take place within a reasonable period of time after dispensing. Such communication may 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.[104]
5. Records must be maintained to reflect the actual product received by the patient to facilitate accurate attribution of any AEs.[104]

Unlike the US FDA, the EMA does not have the authority to evaluate and approve products as safe for substituting with another product without the intervention of the prescriber.[64] There are no formal “interchangeability standards”—that is, no legal standard or EMA guidance on when and whether it is safe to substitute products. In many countries, biological products are specifically excluded from lists of products suitable for pharmacy substitution without the involvement of the prescriber.[107]

Across the EU, decisions on prescribing practices—such as a prescriber determining whether to switch a patient from one product to another (see description of “switching” above)—are generally deferred to the national level. In some countries (e.g., Norway, France, and Finland), physician-led switching is encouraged for a patient already treated with a reference biological product.[102] In Germany, recent guidelines have been published stating that prescribers should consider switching a patient who is currently on therapy to a less expensive biological product, unless there is a medical reason not to do so.[108]

In 2015, the Australian Pharmaceutical Benefits Advisory Board issued a policy permitting the designation of certain biosimilars as suitable for substitution at the pharmacy. These decisions were based on the absence of evidence of clinically relevant differences from the reference product, data from any switching studies, and other considerations.[109]

The WHO does not define standards on interchangeability or substitution of biological products. It recognizes that a number of issues associated with the use of biological products should be defined by national authorities.[20]

6. Pharmacovigilance and Naming

6.1 Pharmacovigilance and Post-marketing Surveillance

Post-marketing surveillance is a key health authority requirement for all biological products to help ensure the safety of these products.[9] Biological products (both reference biologics and biosimilars) have the potential to stimulate unwanted immune reactions.[110] Further, because biologics are typically complex molecules that are often made in living cells, they are generally very sensitive to the manufacturing process, environmental conditions, container closure systems, and handling, and therefore, structural changes in the molecule can occur after the product has been approved.[32,50] Although many of these changes may be of no (or minor) clinical consequence, some structural changes can affect the safety and efficacy of the medicine. When biological products do cause unexpected or rare adverse reactions in patients, it is essential that the specific product and manufacturer responsible are identified so that any problem with a product can be promptly addressed to ensure patient safety.[32,50]

Rigorous pharmacovigilance is essential for all biologics, including biosimilars, to protect patients. According to the US FDA, post-marketing safety monitoring of biosimilars 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. As with any biologic, rare, but potentially serious safety risks (e.g., immunogenicity) may not be detected during preapproval clinical testing because the size of the exposed population will likely not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through post-marketing surveillance or studies. In addition, the US FDA may take similar appropriate action as may have been done for the reference product to help ensure the safety and efficacy of a proposed biosimilar product, including, for example, requiring a post-marketing study (e.g., a registry) to evaluate certain safety risks.[9]

Post-marketing safety monitoring should have adequate mechanisms in place to differentiate between the adverse events associated with the biosimilar product and those associated with the reference product or other biosimilar products.[9] Several data sources have been suggested as tracking methods to support rigorous pharmacovigilance of biological product:[111]

- *Development of a Prospective Registry:* Such registries have typically been instituted as part of programs to reduce the risks associated with products known to have potentially serious adverse events. Some, but not all, prospective registries require the provider to record each administered dose of a product in a product-specific central database. In these cases, adherence to data-entry requirements may be 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 disadvantages of such registries are that they may be very expensive to establish and maintain and may be very burdensome for healthcare

providers to use. The high cost and time requirements could limit the utility of the product-specific registry.[111]

- *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, 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.[111]
- *Use of Claims Data:* In the US, drugs and biological products 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.[111] Prior to January 1, 2018, the Centers for Medicare & Medicaid Services required that claims include a modifier that identified the manufacturer of the specific product. These modifiers were used to distinguish between biosimilar products that appear in the same HCPCS code but were made by different manufacturers. However, in 2018, a new payment policy was put into place assigning unique HCPCS codes for biosimilars and made the use of these modifiers in claims unnecessary.[112]

Rigorous pharmacovigilance is essential for all biological products to protect patients, facilitate the quick detection and accurate reporting of adverse events, and enable an adverse event to be attributed to the correct product and manufacturer. As such, it is important that all biologics have a unique, distinguishable identifier to accurately identify the product in medical and pharmacy records. In the absence of a distinguishable identifier that is carried through all systems that feed into pharmacovigilance, other significant policy measures are necessary to facilitate product-level identification of all biological products in patient medical records and adverse event reporting.[34] For example, 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.[113,114]

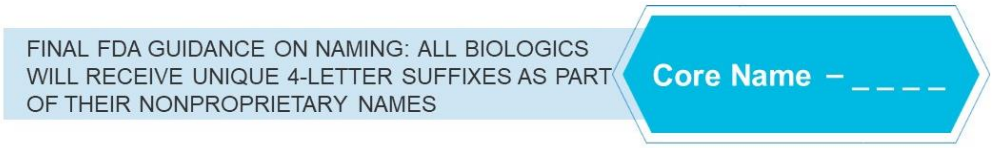
6.2 Biosimilar Naming

In the US, brand names are not required for medicinal products, and prescribers and other healthcare providers are not required to use them. In contrast, non-proprietary names are required for all drugs and biological products and are often preferentially used in prescribing and in health records.[115,116] Effective pharmacovigilance requires that all biological products within a product class can be distinguished from each other to facilitate accurate attribution of AEs to the correct product.[34] Assigning the same non-proprietary 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.[99,117,118] Further, as discussed above, it is important that each biological product

has a unique, distinguishable identifier to accurately identify the product in all systems that feed into pharmacovigilance to facilitate targeted regulatory action, when warranted, to protect patient safety and facilitate patient access.[34,64,119]

Analyses related to small-molecule drug products have shown that AE reporters (e.g., healthcare professionals [HCPs] and patients) often attribute AEs to the originator product, when in fact the patient likely took a generic product with the same non-proprietary name.[118] Furthermore, complete and conclusive product-identifying information (e.g., lot number, National Drug Code) is usually not submitted by reporters. Using data from the US FDA's Adverse Event Reporting System, 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 non-proprietary names for biosimilars to help to ensure that AEs are traced to the correct product. It is important that health authorities, sponsors, HCPs, and patients can rely on timely and accurate AE data in order to make critical decisions regarding the use of biological products.[118]

There is currently no global consensus on naming conventions for biosimilars. The 2009 BPCIA did not include provisions for the naming of biosimilars. Under the US FDA's naming policy, the agency will designate to each newly approved biological product (biosimilar or originator) a non-proprietary name ("proper name") comprising the "core name" and a distinguishing suffix composed of four lowercased letters devoid of meaning.[119] The "core name" refers to the component an originator biological product shares with any related biological product, biosimilar product, or interchangeable product.[119] If a product has been approved as a biosimilar and determination of interchangeability is successfully sought at a later time, the non-proprietary name and suffix of the approved biosimilar will not change.[119] The US FDA first implemented this naming system, which is applicable to all biological products, by assigning the name "filgrastim-sndz" to its first approved biosimilar. Since then, the US FDA has approved more than 25 biosimilars and approximately 50 351(a) biological products with four-letter suffixes.[119-121] Some examples are listed in **Figure 8**.



Some FDA Approved Biologics With Four-Letter Suffixes					
adalimumab-atto	etanercept-szzs	infliximab-qbtx	trastuzumab-dttb	erenumab-aooe	moxetumomab pasudotox-tdfk
adalimumab-adaz	filgrastim-aafi	pegfilgrastim-cbqv	trastuzumab-pkrb	pegvaliase-pqpz	fremanezumab-vfrm
adalimumab-adbm	filgrastim-sndz	pegfilgrastim-jmdb	calaspargase pegol-mknl	mogamulizumab-kpkc	galcanezumab-gnlm
bevacizumab-awwb	infliximab-abda	rituximab-abbs	vestronidase alfa-vjbk	emapalumab-lzsg	cemiplimab-rwlc
epoetin alfa-epbx	infliximab-dyyb	trastuzumab-dkst	burosumab-twza	cenegermin-bkbj	elapegademase-lvlr

Figure 8. Examples of US FDA Non-proprietary Naming for Biological Products[120,121]

The US FDA describes its policy on the non-proprietary naming of biological products as intending to: facilitate accurate identification of products by healthcare practitioners and patients, improve pharmacovigilance, and help to minimize inadvertent pharmacy substitution of non-interchangeable biosimilar products.[119]

In Japan, the naming convention requires the biosimilar to use the non-proprietary name of the reference product, plus 'biosimilar' and a number indicating the order in which the biosimilar was approved.[122]

The current WHO policy for assigning international non-proprietary names (INNs) to biological products (there is no policy specific to biosimilars) follows two different approaches, depending on whether the product is glycosylated. Non-glycosylated biological products with the same amino acid sequence are considered to have highly similar post-translational modifications and receive the same INN. In contrast, glycosylated biological products 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. For example, distinguishable INNs have been assigned for two biosimilar versions of an erythropoiesis-stimulating agent.[34] 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.[119,123]

The WHO policy for glycosylated biological products has not been enforced consistently by EMA, and biosimilars with different glycosylation patterns from their reference products have been authorized with the same INN in the EU.[34]

The Alliance for Safe Biologic Medicines (ASBM) recently conducted a survey of 202 US prescribers of biological products focused on the US FDA draft guidance on biological products and biosimilar naming. Approximately 85% of responding prescribers agreed with the US FDA's decision to use four-letter suffixes to clearly distinguish biosimilars from their reference products (as well as from other biosimilars to that product) and about 67% agreed with the US FDA's decision to not rename biosimilars subsequently designated as interchangeable, but to have instead those biosimilars retain the unique suffix given at time of approval.[124] Similarly, the International Society of Oncology Pharmacy Practitioners (ISOPP) supports the use of two identifiers: the generic name stem and either the brand name or a four-letter suffix.[125]

7. Clinical Practice and Operational Considerations

Biological products play an essential role in disease treatment and supportive care. When biosimilar products enter the marketplace, they may provide additional treatment options with the potential to bring meaningful cost savings to the healthcare system.[34]

7.1 Prescriber Attitudes Toward Biosimilars

Prescriber confidence in biosimilars continues to increase. A 2019 survey of biologics prescribers in Europe, commissioned by The Alliance for Safe Biologic Medicines (ASBM), found that a strong majority of respondents (90%) identified themselves as either being “familiar” or “very familiar” with biosimilars, which increased from 76% in the 2013 survey results. Furthermore, a strong majority of respondents (82%) feel that it is either “very important” or “critical” for them to decide which biologic medicine is dispensed to their patients, and more than half of prescribers (58%) are uncomfortable with switching their patients to a biosimilar for non-medical reasons. This percentage increased to 73% when asked about a third party initiating such a switch.[126]

In the US, a recent survey of 297 physicians who commonly prescribe biological products for their patients (dermatologists, gastroenterologists, and rheumatologists) indicated that the majority of them (84%) did not support switching to a biosimilar for non-medical reasons in a patient who was stable on their current medication. Reasons cited included a negative impact on the mental health of the patient (59%), efficacy (57%), safety (53%), and management of the office (60%).[127]

7.2 Formulary Evaluations for Biosimilars

Considering the differences between biological products and small-molecule drugs, biosimilars will require a more thorough evaluation by HCPs on Pharmacy and Therapeutics (P&T) Committees compared to generic medications.[128] (**Figure 9**).

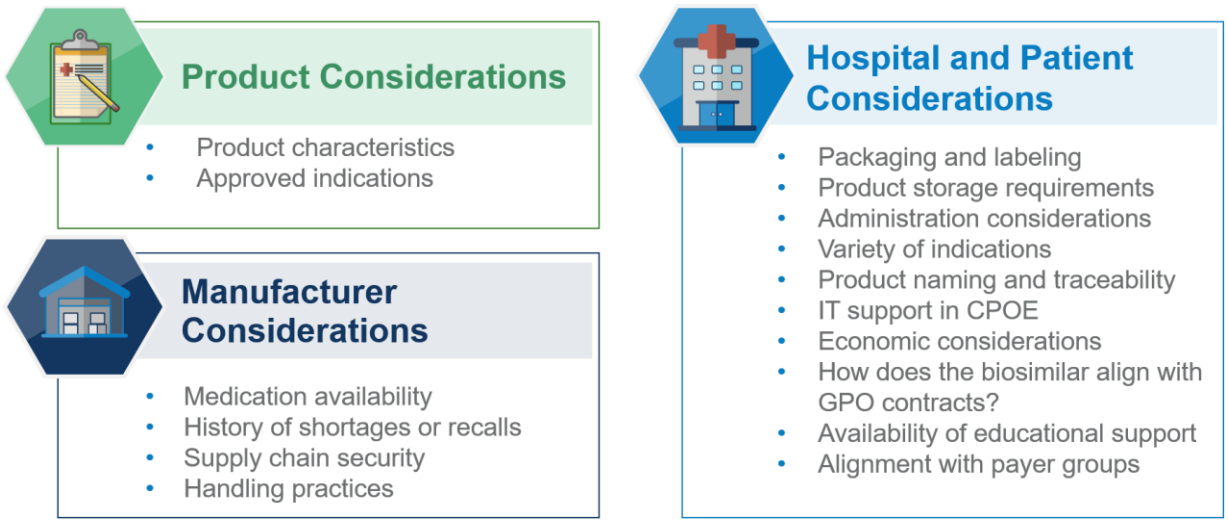


Figure 9. Evaluating Biosimilars for Formulary Inclusion[128]

Biosimilars approved by regulatory authorities are safe and effective for their labeled conditions of use. Therefore, HCPs should compare the approved labeling for a biosimilar to the approved labeling for the reference product.[128,129] HCPs should also evaluate product characteristics (such as formulation or excipients that impact both patient tolerability and the stability of the biological product) and delivery devices.[128]

For health systems considering therapeutic substitution of a biosimilar, consideration should be given to whether the biosimilar has been approved for all of the approved indications of the reference product, as opposed to approved for selected indications only.[15,128] Another important issue to address relates to transitions of care. In situations where patients who receive a given product (i.e., biosimilar or reference product) in a particular care setting are transitioned to a different care setting, healthcare providers should be aware of, and try to avoid, inadvertent switching of products.[128]

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.[128] Healthcare systems must have mechanisms in place to accurately track the specific drug(s) a patient receives, as well as any product-specific AEs.[15] In situations where multiple versions of a biological product have the same non-proprietary name, it may be necessary to implement unique tracking measures.

7.3 Drug Supply

Drug shortages can 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, to delay or cancel treatments, to utilize drugs with a different efficacy or safety profile, to effect unplanned switching between different biological products during the course of treatment, or to incur additional time and expense associated with locating alternative medications.[130-132]

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.[128] In most cases, drug shortages are preceded by disruptions in drug production; therefore, manufacturers have the responsibility of establishing appropriate practices and conditions that help promote a reliable source of quality products in an uninterrupted manner. The US FDA also encourages hospitals, pharmacies, and other group purchasing organizations to use public data on a manufacturer's historical ability to produce quality products when making purchasing decisions. The US FDA states that better utilization of this information helps give manufacturers the incentive to focus on quality and, ultimately, prevent shortages.[133]

Amgen knows that it is imperative for patients to receive an uninterrupted supply of medicine and that gaps in supply can have serious consequences. In previous years, Amgen manufacturing plants have withstood earthquakes, fires, and hurricanes.[134] While COVID-19 has disrupted the

global supply chain across multiple industry sectors, as of this writing, Amgen manufacturing teams have continued to produce and deliver an uninterrupted supply of medicines to patients.[135]

7.4 Potential to Contribute to a Long-term, Sustainable Marketplace

Robust competition with originator biological products and between biosimilars can result in cost savings and the conditions needed for a long-term, sustainable marketplace with biosimilars.[136] These savings can also be deployed to support newer, innovative treatments and technologies, while potentially expanding treatment options for patients.[136] In the US, the potential cost savings from switching from originator biological products to biosimilars is projected to be between $40 and $250 billion by 2025; and in Europe, cost savings are already estimated to be more than €10 billion.[136,137] Healthcare markets are already experiencing savings as a result of the introduction of biosimilars. For example, with the use of biosimilars the United Kingdom's National Health Service saved around £300 million on the cost of a single drug.[138]

Biosimilars are available in the US marketplace in the fields of oncology, oncology/nephrology supportive care, and inflammation therapeutics.[134] In oncology, biosimilars of trastuzumab, bevacizumab, and rituximab are available (as of March 2021) and represent between 40%–60% of sales by volume.[139] Biosimilars of pegfilgrastim, filgrastim, and epoetin alfa are available for oncology/nephrology supportive care and account for 30%, 72%, and 40% of the market share, respectively.[139] In the inflammation therapeutic area, biosimilars to infliximab represent a 20% market share.[134] As more biosimilars become available, reference products may lower prices in order to compete more effectively.[6]

While financial savings are important for driving biosimilar uptake, they are not the only consideration for payers and providers. The manufacturer's reputation for producing high-quality products and reliably supplying the products, along with understanding not only provider and payer decision-making drivers but also clinical, economic, and operational needs, are also important.[128,140,141]

Current policies support the strong wave of biosimilars that have entered, and continue to enter the marketplace – and these should be preserved. In the US, the Centers for Medicare and Medicaid Services has made important changes to the current reimbursement system, such as establishing separate Healthcare Common Procedure Coding System codes and payment rates for biosimilars.[142] Additionally, the US FDA established the Biosimilars Action Plan in 2018 with the goal of accelerating biosimilar competition.[6]

The 2020 edition of Amgen's annual Biosimilar Trends Report demonstrated that the US marketplace has already launched and is poised to welcome many new biosimilars, spurring additional competition that will potentially lead to significant savings for the healthcare system.[134]

8. Summary

A biosimilar is a biological product that is demonstrated to be highly similar (but not identical) to, and has no clinically meaningful difference from, a reference biological product. A biosimilar cannot be identical to the reference biological product primarily because of the proprietary nature of the manufacturing process and use of unique cell lines to produce the reference biological product. Variations in the manufacturing processes 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 globally have published guidance documents 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 biological products, health authorities need to integrate various types of information to provide an overall assessment that a biological product is biosimilar to an approved reference product.

Now that regulatory pathways for the approval of biosimilars are established in several regions, biosimilar products are entering the global market. Because biosimilars can provide additional treatment options for patients, healthcare organizations should make efforts to educate staff and ensure that infrastructure is in place to support timely evaluation and appropriate use of biosimilars. There will also be several issues that healthcare providers (HCPs) should consider in order to make informed decisions about incorporating biosimilars into clinical practice, including the evaluation of switching practices and how these practices may affect patient care.

HCPs play a primary role in AE reporting and should understand pharmacovigilance requirements and that biological product naming conventions, or the use of other distinguishable product identifiers, are important components of successful safety monitoring. The current process for documentation of administered products may also need to change, particularly if there are multiple products that may be switched during a patient's planned course of treatment. There is a need for ongoing awareness of and education on biosimilars for HCPs, so as to guide them in making treatment decisions for their patients.

9. Appendix

A.1 Select EMA Guidance Documents for Demonstrating Biosimilarity

- Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues (revision 1) (EMEA/CHMP/BWP/247713/2012)[58]
- Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)[92]
- 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)[21]

Note: The EMA has created individual product-specific guidelines on developing biosimilars. Class-specific guidelines are available for certain types of biosimilar products.

Other EMA guidelines relevant to biosimilars include:

- Comparability of Biotechnology-Derived Medicinal Products After a Change in the Manufacturing Process–Nonclinical and Clinical Issues[143]
- ICH Q5E Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process: Comparability of Biotechnological/Biological Products[53]
- Guideline on Immunogenicity Assessment of Therapeutic Proteins[110]
- Immunogenicity Assessment of mAbs Intended for In Vivo Clinical Use[144]

A.2 US FDA Guidance Documents for Demonstrating Biosimilarity

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product[9]
- Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations[48]
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product[145]
- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)[13]
- Questions and Answers on Biosimilar Development and the BPCI Act[14]
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants[146]
- Considerations in Demonstrating Interchangeability With a Reference Product[103]
- Labeling for Biosimilar Products[147]

Other guidance relevant to biosimilars includes:

- Nonproprietary Naming of Biological Products—Update[119]
- Reference Product Exclusivity for Biological Products Filed Under 351(a) for PHSA[148]

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