Biosimilars

A Health Care Professional's Guide

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Pfizer Biosimilars

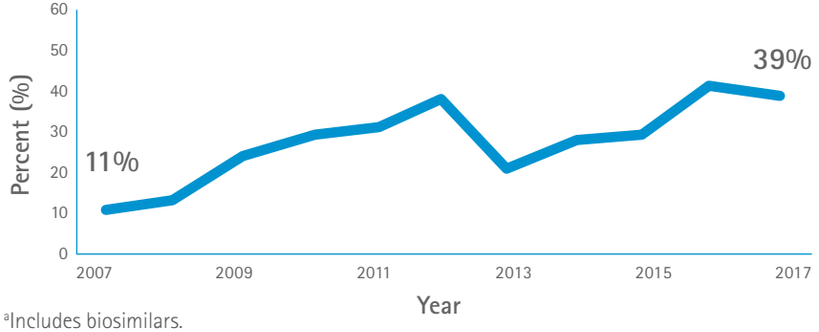
Strong demand for increased savings and efficiencies

> "While only 2% of the US population uses biologics, they account for 40% of prescription drug spending in the United States."
>
> *- Biosimilars Council*[1]

GROWTH IN BIOLOGICS

More than 30 years since their initial approval*, biologic drugs have revolutionized the treatment of patients with some of the most difficult-to-treat diseases.[2,3] They have had a meaningful impact on patient care in multiple disease states and have become an integral part of health care options in the United States and abroad.[4,5] Between 2007 and 2017, biologics more than tripled as a proportion of the total US Food and Drug Administration (FDA) drug approvals **(Figure 1)**.[6] In 2018, the FDA acknowledged more than 125 therapeutic biologic products.[7]

Figure 1. Biologics Have More Than Tripled as a Percentage of New FDA Approvals Over 10 Years[6,a]



[a]Includes biosimilars.

The growing demand for biologics in the US health care system is demonstrated by their contribution to pharmaceutical sales.[8] In 2017, half of the top 10 expenditure drugs in the United States were biologics.[9] Between 2017 and 2026, health care and prescription drug spending are projected to increase annually at an average of 5.5% and 6.3%, respectively—this, by far, exceeds the average annual increase of 1.9% projected for the gross domestic product between 2021 and 2027.[10-12] Spending on biologics, by 2020, is expected to exceed $250 billion, when nearly $5 out of every $10 the country spends on prescription drugs will be spent on biologics.[13]

*Refers to approval of the first recombinant protein.

COST-SHARING BURDEN ON PATIENTS

Considering the growing costs of biologics, high-cost sharing may impact patients in multiple ways.

Commercially insured patients

Many commercially insured patients have high coinsurance requirements for specialty drugs.[14,15]

>50% of commercial payers **require coinsurance** for specialty drugs covered under the medical benefit[14]

Based on site of care, **coinsurance rates** may average between **21%–22%**[15]

Medicare beneficiaries

For Medicare patients, annual out-of-pocket costs associated with biologic therapies may be substantial.

- After deductibles are met, Medicare patients typically pay **20% coinsurance** for most outpatient therapies[16]
- **14%** of Medicare beneficiaries **do not have supplemental insurance**[17]

Depending on the therapy, the top 10 Medicare Part B-covered biologics[a] with the highest out-of-pocket expenses may incur annual out-of-pocket costs of

~$2,500–$15,000[b]

for the 14% of beneficiaries[17,18]

Annual out-of-pocket costs may reach up to

~58%

of the median income of Medicare beneficiaries[18,19,c]

BIOSIMILARS MAY HELP MEET THE GROWING DEMAND FOR BIOLOGICS

There is a strong demand for increased savings and efficiencies for the US health care system.[8,20,21] With patents for a number of commonly used drugs either already expired or set to expire in the near future, biosimilars may potentially expand treatment options to meet the growing demand for biologic therapies and lower out-of-pocket costs for patients with cost-sharing requirements.[4,20,21]

[a]Excludes small molecules, hormones, and human immunoglobulin G therapies.
[b]Range covers multiple therapeutic areas and is based on average annual out-of-pocket costs per patient.
[c]Percentage based on an annual out-of-pocket cost for a biologic costing $15,119 and a median per capita income of $26,200, reported for Medicare population in 2016.

High-quality biosimilars may have the potential to address the growing demand for biologics and provide increased savings and efficiencies.[20]

Biosimilars require substantial time and financial investment

Bioequivalent versions of small molecule drugs are called generics. Highly similar versions of existing biologics are called biosimilars.[22,23]

BIOSIMILARS ARE NOT GENERICS

Biologics, including biosimilars, are much more complex than small molecule drugs.[4] Unlike small molecules, which are chemically synthesized, biologics are produced in living cells via a multistep process that requires significant expertise and state-of-the-art technology.[4] **Table 1** shows the differences between small molecule drugs and biologics.

In contrast to a generic drug that is bioequivalent to its brand name small molecule, biosimilars are highly similar versions of reference biologics.[4] A reference biologic is an FDA-approved biologic medicine with which a biosimilar is compared.[22] A biosimilar is highly similar to the reference biologic with no clinically meaningful differences in terms of safety, purity, and potency.[22] There are rigorous regulatory requirements in place to demonstrate biosimilarity.[22]

Table 1. Differences Between Small Molecule Drugs and Biologics[4,24,25]

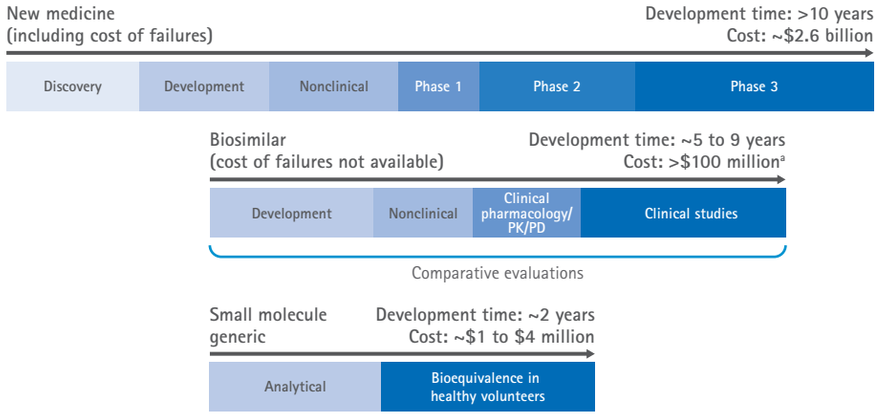
	Small Molecule (Chemical)	Biologic (Protein)
Production	Chemical synthesis	Living systems (eg, cultured bacterial, yeast, animal, or plant cells)
Characterization	Can be characterized using limited physicochemical methods	Necessary to perform comprehensive structural and functional assessment
Administration	Mostly oral delivery	Parenteral (IM, IV, SC) delivery
Immunogenicity	Mostly nonimmunogenic	Potentially immunogenic

IM, intramuscular; IV, intravenous; SC, subcutaneous.

TIME AND FINANCIAL INVESTMENT

While biosimilars have the potential to provide additional treatment options at a lower cost, development of biosimilars requires substantial investment. Development of a biosimilar may take 5 to 9 years or more at a cost of over $100 million, not including regulatory fees.[26,27] A generic version of a small molecule drug, on the other hand, may cost $1 million to $4 million to develop **(Figure 2)**.[28,29]

Figure 2. Developing a Biosimilar Requires Substantial Time and Financial Investment Compared With a Small Molecule Generic[26-29]



PD, pharmacodynamic; PK, pharmacokinetic.

[a]Not including regulatory fees.

The goal of biosimilar development is to help ensure that a consistent product is manufactured that will meet the highly similar designation with no clinically meaningful differences from the reference biologic in terms of safety, purity, and potency.[30] To this end, the regulatory process is different for biosimilars compared with small molecule generics, with far more rigorous testing required to gain regulatory approval.[22]

Potential value of biosimilars

> The successful adoption of biosimilars has the potential to provide additional treatment options at a lower cost.[20]

POTENTIAL VALUE TO PATIENTS

Biosimilars may potentially improve access to biologics

Biosimilars have the potential of offering additional treatment choices to patients, physicians, and payers at potentially lower cost.[20,31,32]

- These savings may enable more patients to have access to biologics, which could result in improved health outcomes for patients[31,32]

Biosimilars may help reduce the out-of-pocket costs of biologic medicines

It is expected that health care providers, such as clinics or hospitals, will be able to acquire biosimilars at a lower wholesale cost than their reference products.[31,32]

- Because of this, biosimilars may have the potential to lower out-of-pocket costs for patients with cost-sharing requirements, such as coinsurance and copayments[31,32]

Patients who may pay less in the form of coinsurance

Patients with Medicare Part B without supplemental coverage[16,17]

Patients with private insurance required to pay coinsurance for specialty drugs, including biologics[14,17]

POTENTIAL BENEFITS TO THE HEALTH CARE SYSTEM

As the demand for biologics continues to grow, the introduction of biosimilars has the potential to provide multiple benefits to the US health care system **(Figure 3)**.

Figure 3. Potential of Biosimilars for Patients, Payers, and Providers[20,25,33]

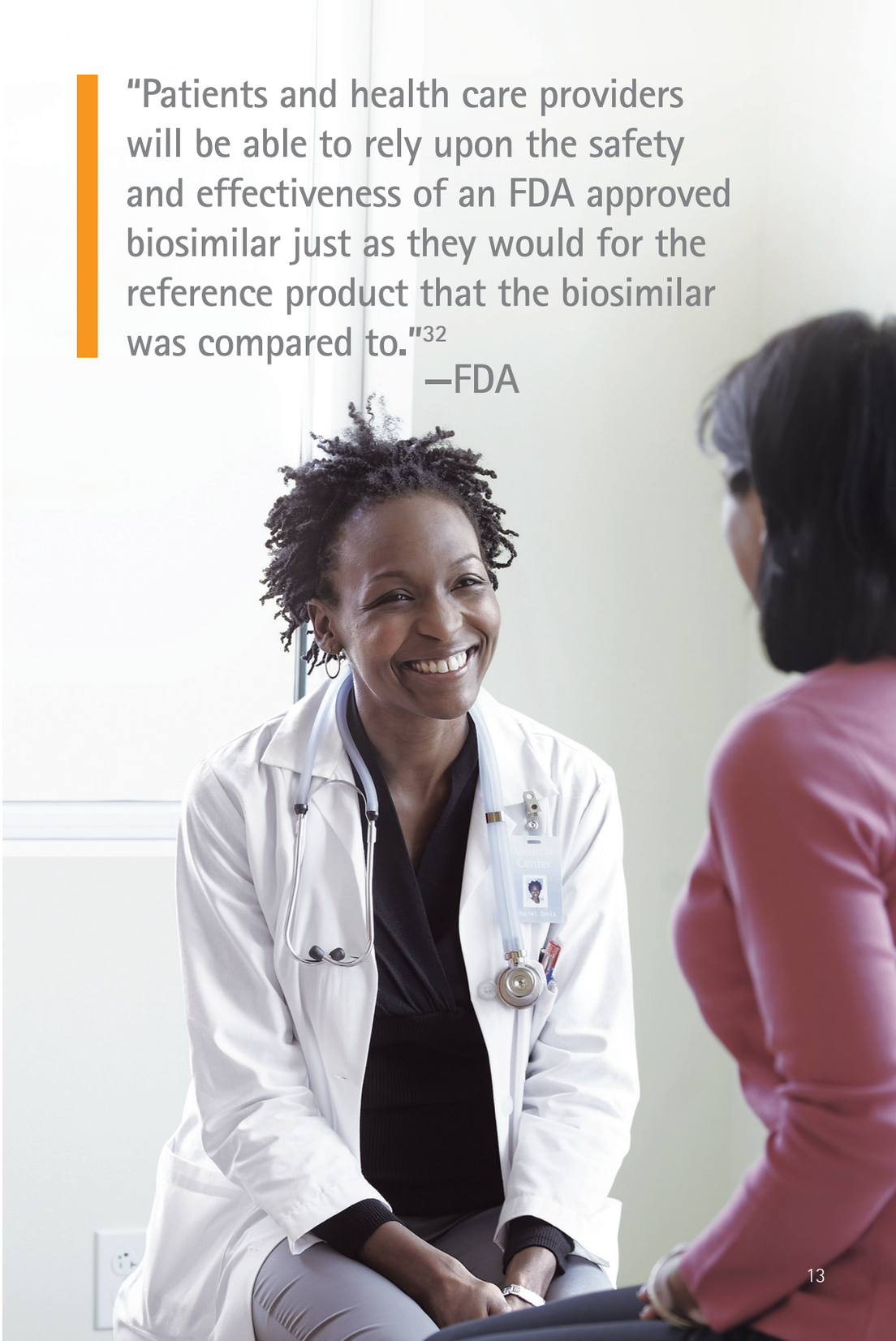
The rules for development of biosimilars may also foster innovation.[26] The Biologics Price Competition and Innovation Act (BPCIA) includes provisions to ensure 12 years of marketing exclusivity for reference biologics, as well as mechanisms for patent resolutions to mitigate any potential violations.[34] These steps may help to encourage development of new biologics with unique or improved mechanisms of action.[26]

Cost savings to health care systems due to biosimilars may be substantial. RAND corporation estimates that biosimilars may lead to savings of up to $150 billion in direct spending on biologic drugs between 2017 and 2026.[35,*] Savings realized by patients may depend on various factors, including changes in copays, coinsurance, etc, which may be more apparent in the future.[31]

*Based on an assumption of a biosimilar market share of 50% and biosimilar prices that are 50% of the reference product.

"Patients and health care providers will be able to rely upon the safety and effectiveness of an FDA approved biosimilar just as they would for the reference product that the biosimilar was compared to."[32]

—FDA

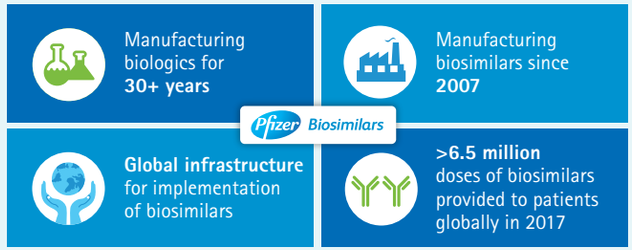


Pfizer: Working to expand treatment options, potentially improving the lives of patients

PFIZER KEEPS PATIENTS AT THE CENTER OF WHAT WE DO

Biosimilars have the potential to broaden access and provide cost savings to the health care system, leading to better health outcomes overall.[20] Building on our technical development expertise and infrastructure in manufacturing biologics, Pfizer is at the forefront of delivering biosimilar medicines to patients and physicians around the world across multiple life-threatening and chronic diseases, including inflammation, immunology, and oncology.[36,37]

Pfizer has the infrastructure and experience to make an impact with its biosimilar medicines[9,36–38]

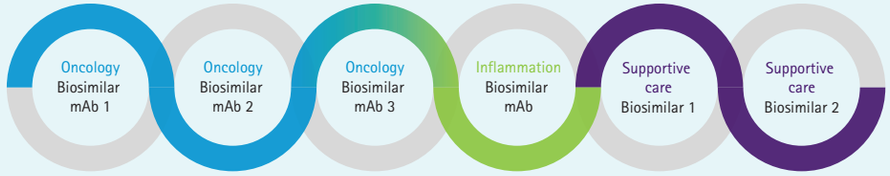


Pfizer Biosimilars is committed to working at every level to make the full potential of biosimilar medicines a reality, with

- Three biosimilars marketed outside the United States[38–40]
- First biosimilar monoclonal antibody (mAb) marketed in the United States[41]
- Three biosimilars approved in the United States[41–43]

Leveraging over 10 years of experience with biosimilars outside the United States, Pfizer is invested in the future of biosimilars with 6 in various stages of clinical development.[36,38,44]

Pfizer: Investing in biosimilars with a focus on oncology, inflammation, and supportive care[44]



Pfizer Biosimilars

A known product, a tailored process

> Biosimilar development relies on, rather than recreates, the well-established clinical profile of the reference biologic.[31]

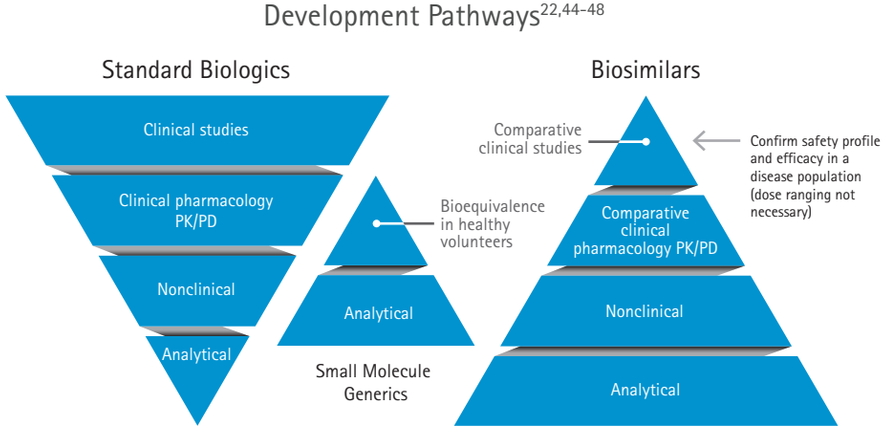
A UNIQUE APPROVAL PROCESS

As part of the Affordable Care Act, the BPCIA created the regulatory framework for an abbreviated approval process for biosimilar products.[34] The act also provides for a 12-year exclusivity period from the date of licensing of the reference product before approval of any biosimilar may occur. Potential applications are not accepted or considered until 4 years after approval.[34] It is estimated that approximately 100 biologics will lose patent or other protections by 2021.[21]

PROVING BIOSIMILARITY

The approval process for biosimilars in the United States is outlined in **Figure 4**.[22] The FDA has taken a "totality of evidence" approach to evaluating biosimilar agents.[22] All of the data are generated via a stepwise approach.[22] Each step of comparative investigation is used to establish that the potential biosimilar is "highly similar" to the reference product with no clinically meaningful differences in safety, efficacy, or potency. Demonstration of biosimilarity includes structural and functional characterization, nonclinical evaluation, comparative clinical pharmacology PK and PD data, clinical immunogenicity data, and may also typically include comparative clinical study data.[22] Using multiple state-of-the-art methods, protein structures can be extensively characterized so that the reference product and biosimilar can be directly compared, helping to ensure comparability of both functional integrity and performance in vivo.[30]

Figure 4. The Goal of Biosimilar Development Is to Demonstrate That There Are No Clinically Meaningful Differences Based Upon the Totality of Evidence, Not to Reestablish Benefit[22]

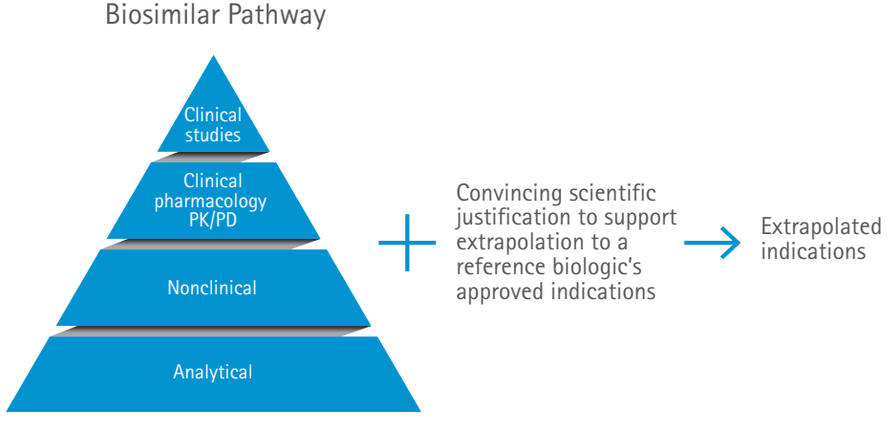


In the development of a reference biologic, the greatest contribution to clinical predictability resides at the top of the inverted pyramid (left; **Figure 4**), where the biologic drug is evaluated in a large number of patients with the aim of demonstrating superior efficacy versus placebo or comparator products and an acceptable tolerability profile.[50] In contrast to the inverted pyramid for the reference biologic, the biosimilar development pathway outlined by the FDA is focused at the bottom of the pyramid at right, where comprehensive comparisons are made to the reference biologic with respect to the structure and function of the molecule.[22,47] For a biosimilar, this molecular characterization will provide the foundation for development, which builds on the clinical experience with the reference biologic.[22,30] The aim of biosimilar drug development is to establish similarity to the reference product in terms of safety, purity, and potency, using a stepwise approach that includes analytical, nonclinical, and clinical comparability studies.[22]

EXTRAPOLATION

Once biosimilarity has been established in a specific indication, FDA guidance has indicated that a biosimilar may be licensed for additional indications of the reference biologic based on extrapolation **(Figure 5).**[22] Extrapolation is a scientific and regulatory principle that enables licensure of a biosimilar across indications approved for the reference biologic that were not directly studied with the biosimilar.[22,51] However, extrapolation is not automatic and requires scientific justification in each additional indication not clinically studied with a biosimilar.[22,52]

Figure 5. Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied[22,45,51]



Biosimilar extrapolation occurs from the reference biologic to the biosimilar, when scientifically justified based on all available data—not from the indication(s) studied with the biosimilar to other indications[53]

Scientific justification is based on a combination of experience with the reference product and the totality of evidence from the biosimilar development.[22,51] Building on high structural similarity, scientific justification in each indication not clinically studied is organized around 4 key aspects that are considered by the FDA: the mechanism of action (MOA), PK and biodistribution, immunogenicity, and expected toxicities.[22]

By potentially avoiding unnecessary clinical studies that may be burdensome to patients, extrapolation may reduce development costs, thereby making effective medicines potentially more accessible to patients and enabling resource reallocation to other areas of medicine.[51,54,55]

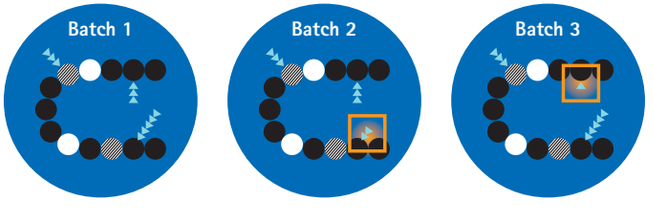
Common considerations with biosimilars

> Manufacturing consistency enables the release of a biosimilar product into the marketplace and clinic with quality attributes highly similar to those of the original reference product.[51]

HETEROGENEITY OF BIOLOGICS

Biologics are not typically a single molecule entity, but rather a complex mix of the same protein molecule under various structurally close isoforms, which results in heterogeneity.[56] While there may be interbatch variability due to the intrinsic nature of the biologic manufacturing process, a product's quality attributes must remain within an acceptable range.[57] **Figure 6** depicts an example of variability between different batches of a biologic. Variability in the reference biologic's quality attributes measured over multiple lots can be used to evaluate the acceptability of the biosimilar.[58,59]

Figure 6. Example of Variability Between Different Batches of a Biologic[60]



Orange boxes highlight sites with minor differences in glycosylation

Adapted from the European Medical Agency (EMA) website

MANUFACTURING CONSISTENCY

The manufacturing requirements for a biosimilar are equivalent to any new biologic entity, helping to ensure the production of a consistent, high-quality product.[24,30] FDA guidance on product comparability evaluates the potential significance of changes to biologics, which has been available since 1996.[30] Demonstrating biosimilarity to a reference product requires more data and information than establishing comparability between a post- and pre-manufacturing change.[30] The similarity of the biological activity, safety, and efficacy of a biosimilar product to the reference product must be established based on the totality of evidence gathered in analytical, nonclinical, and clinical studies.[22] Biosimilar developers establish independent manufacturing processes and target quality attributes of acceptable variability to establish biosimilarity based on a thorough comparison with the reference product.[51] Manufacturing processes of biosimilars are designed, developed, and understood through the science- and risk-based approaches of quality by design.[61] Quality by design uses the full understanding of how product attributes and processes relate to performance.[61] As a result, manufacturing processes can be monitored and strategies can be implemented that help ensure a consistent product is made with overall quality and attributes maintained throughout its life cycle.[61]

IMMUNOGENICITY

A common consideration for all biologics, including biosimilars, is immunogenicity. Immunogenicity is the ability of a molecule to elicit an immune response from the host. When a foreign entity enters the body, the immune system will trigger a response as a way of defending itself against bacteria, viruses, or other harmful substances. Being proteins, most biologics have the potential to induce antidrug antibodies (ADA), often resulting in no clinically relevant consequences.[22,62] However, there is the potential for these antibodies to have clinical consequences.[22,62] This reaction can result in the production of ADA, including neutralizing antibodies, which can lead to decreased efficacy[22,62]; ADA may also result in general immune effects, including allergy, "serum sickness," or anaphylaxis.[22,62] Importantly, there may be major clinical consequences if cross-neutralizing antibodies are generated that affect both the biologic product and an endogenous protein with essential activity.[22,62]

The potential for immunogenicity is evaluated through the rigorous testing of the biosimilar during its development. Biosimilars need to demonstrate no clinically meaningful differences in immunogenicity compared with the reference product.[22]

Introducing biosimilars into clinical practice

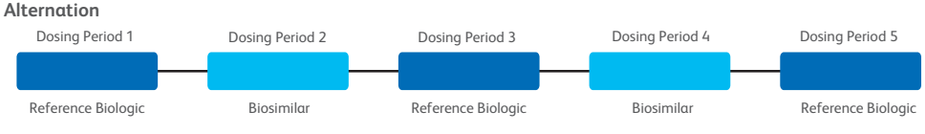
Physicians may prescribe a biosimilar in the same manner as they would prescribe other medications—this physician-directed decision may include prescribing a biosimilar for patients currently stable on the reference biologic (eg, single transition or switch).[63]

Approved biosimilars should be a potential consideration for all patients who receive treatment with biologic medications for eligible indications.[51] Acceptance by physicians that all qualifying patients can be treated with biosimilars may potentially facilitate increased access to biologic therapies for all patients.[52]

THE US FDA DESIGNATION OF INTERCHANGEABILITY

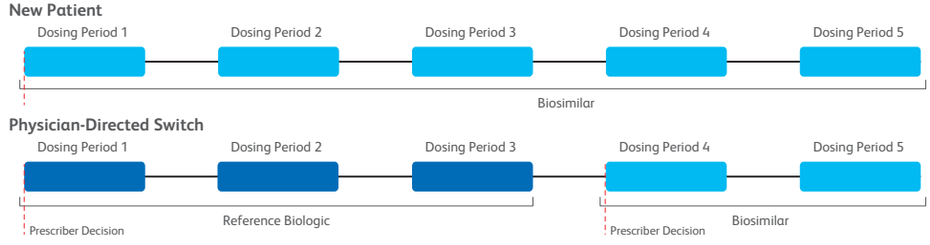
An interchangeability designation, by US law, is defined to mean a biosimilar may be substituted at the pharmacy level for the reference biologic without the intervention of the health care provider who prescribed the reference biologic.[64,65] For this reason, an interchangeability designation involves additional standards after biosimilarity is established.[65] In order to be designated interchangeable, it must be demonstrated that the biologic product is biosimilar to the reference biologic and can be expected to produce the same clinical result as the reference biologic in any given patient.[64,65] For a biologic product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biologic product and reference biologic is not greater than the risk of using the reference biologic without such alternation or switch **(Figure 7).**[64,65]

Figure 7. An Interchangeability Designation Considers the Potential for Alternation (Multiple Switches) Between a Biosimilar and Reference Biologic Without Physician Intervention[64,65]



An interchangeability designation is not required for a physician to switch a patient to a biosimilar.[64,66,67] A physician-directed switch (eg, from a reference biologic to a biosimilar) is a prescribing decision made by a patient's physician **(Figure 8).**[63] Decisions to prescribe a biosimilar to patients currently stable on the reference biologic are not restricted by FDA guidance or the BPCIA.[33,63,65] Physicians may prescribe a biosimilar in the same manner as they would prescribe other medications—this physician-directed decision may include prescribing a biosimilar for patients currently stable on the reference biologic (eg, single transition or switch).[63]

Figure 8. Physician-Directed Decisions to Start a New Therapy or Switch a Patient's Treatment (Single Transition)[64,66,67]



An interchangeability designation is not required for a physician to switch a patient to a biosimilar[64,66,67]

AT THE PHARMACY LEVEL

In January 2017, the FDA issued draft guidance describing the current thinking on expectations to meet the additional standard of the interchangeability designation.[64] When biosimilars are designated interchangeable, substitution at the pharmacy level will also be subject to state legislation.[68] Many states have considered legislation establishing standards for substitution of a biosimilar product to replace the reference biologic. Such legislation may include the following features[68-70]:

- Any substituted biosimilar must first be designated as "interchangeable" by the FDA
- The prescriber would be able to prevent substitution by stating "dispense as written"
- Prescriber must be notified of any substitution made by the pharmacy
- Product-specific safety monitoring to ensure traceability

Physicians may consult the FDA Purple Book for a complete list of biologic products licensed by the FDA, including biosimilars and biologic products with an interchangeability designation.[63]

Glossary

Biologics: Biologics include a wide range of biological products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and genetically engineered therapeutic proteins. In this guide, "biologics" refers to genetically engineered proteins produced by living cells.[23]

Biologics License Application (BLA): Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. It requires a firm that manufactures a biologic for sale in interstate commerce to hold a license for the product. A BLA is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.[23]

Biosimilar: Biologic that is highly similar to the reference product with no clinically meaningful differences in terms of safety, purity, and potency.[22]

Biosimilar labeling: According to the FDA, biosimilar manufacturers should incorporate relevant data and information from the label of the reference product, with appropriate product-specific modifications.[71] The use of a brand name in the label is recommended, where feasible and appropriate, in order to make distinctions between products as clear as possible.[71]

Biosimilar naming: Based on the final guidance by the FDA in January 2017, all biologics (including biosimilars) will be identified by a "nonproprietary" name consisting of a common "core" name plus a unique FDA-approved suffix composed of 4 letters (eg, replicamab-hjxf).[72] A clearly distinguishable nonproprietary name with a unique suffix is necessary to track adverse events related to the specific biosimilar or reference product to help ensure appropriate prescribing and dispensing as well as prevent inadvertent substitution of biologic products.[72]

Biosimilar reimbursement: As part of the final CY 2018 Medicare Physician Fee Schedule (PFS) policy, effective January 2018, an approved biosimilar will have a unique Healthcare Common Procedure Coding System (HCPCS) code and a payment limit determined by its own average sales price (ASP) calculation, allowing for greater competition within the category.[73,74] Biosimilar reimbursement is calculated as its ASP plus 6% of the reference biologic's ASP.[73,74]

Extrapolation: If a product meets FDA requirements for licensure as a biosimilar based on, among other things, data derived from a clinical study or studies that demonstrate safety, purity, and potency in one condition of use, additional conditions of use for which the reference product is licensed can be considered if the manufacturer provides sufficient scientific evidence for extrapolating clinical data to support the biosimilarity determination for each additional condition where licensure is sought.[22]

Generic drug: A generic drug is the same as a brand-name drug in dosage, safety, strength, route of administration, quality, performance, and intended use. Before approving a generic drug product, the FDA requires many rigorous tests and procedures to ensure that the generic drug can be substituted for the brand-name drug. The FDA bases evaluations of substitutability, or "therapeutic equivalence," of generic drugs on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand-name product. Drug products evaluated as "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the brand-name product.[23]

Immunogenicity: The ability of a substance to trigger an immune response or reaction (eg, development of specific antibodies, T-cell response, or allergic or anaphylactic reaction).[75]

Glossary (cont)

Interchangeability designation: To meet the additional standard of interchangeability, biosimilarity needs to be established first. An "interchangeable" biologic product must demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient. In addition, if the biologic product is administered more than once to an individual, the risk in terms of safety profile or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[65]

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.[75]

Reference product: Reference product means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application.[22]

Small molecule drugs: Small molecule drugs are usually chemically synthesized with a fixed, known structure having a molecular weight of less than 1000 daltons, and typically between 300 and 700 daltons. For reference, aspirin is 180 daltons and paclitaxel is 854 daltons.[76]

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Notes

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