Biosimilars
A Health Care Professional's Guide

Visit PfizerBiosimilars.com to learn more about biosimilars.
High-quality biosimilars may have the potential to increase access to biologic therapies and provide savings and efficiencies to health care systems.¹
It is anticipated that health care spending in the United States will increase from 17.4% in 2013 to 19.6% of gross domestic product (GDP) by 2024, and the cost of prescription drug spending is projected at an average 6.3% annual growth rate from 2015 through 2024. Health care spending is expected to grow 5.8% on average from 2015 through 2024, 1.1% faster than GDP. Twenty-seven percent of pharmaceutical products approved in 2015 were biologics. Figure 1 shows national health care spending as a percentage of GDP.

More than 30 years since the approval of the first biologic, biologic drugs have revolutionized the treatment of patients with some of the most difficult-to-treat diseases. They have had a meaningful impact on patient management in multiple disease states. The growing demand for these biologics in health care worldwide is demonstrated by the dramatic increase in their global share of pharmaceutical sales. Global biologic sales are projected to exceed $390 billion by 2020, accounting for up to 28% of the global market value for pharmaceuticals. Biologics account for nearly half of approximately $85.5 billion spent on the top 15 drugs in 2015. Patents for a number of the most commonly used biologic drugs have already expired, or are set to expire, in the near future. These data suggest that there is a strong demand for increased savings and efficiencies for health care systems. Biosimilars may have the potential to provide value by addressing the high demand for biologics. They may also provide important treatment options, potentially facilitating increased patient access to treatment.

Figure 1. National Health Expenditure as a Percentage of GDP

<table>
<thead>
<tr>
<th>Year</th>
<th>Health Share of GDP</th>
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<tbody>
<tr>
<td>2000</td>
<td>13.2%</td>
</tr>
<tr>
<td>2013</td>
<td>17.4%</td>
</tr>
<tr>
<td>2024</td>
<td>19.6%</td>
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Biosimilars are different from small molecule generics.

Bioequivalent versions of small molecule drugs are called generics. Highly similar versions of biologics are called biosimilars.\textsuperscript{12,13}
Biosimilars are different from small molecule generics. Unlike small molecules, which are chemically synthesized, biologics are created by organic processes that require significant expertise and state-of-the-art technology. Table 1 shows the differences between small molecule drugs and biologics.

Biosimilars are not identical to their reference biologics and are not generics. A generic drug is bioequivalent to the brand-name small molecule drug. A generic medication has to have the same active ingredients, dosage form, safety profile, strength, route of administration, quality, performance characteristics, and intended use as the brand-name drug. In contrast, a biosimilar is a biologic that is highly similar, with no clinically meaningful differences, to an already approved biologic in terms of the safety profile, purity, and potency of the product. There are rigorous regulatory requirements in place to demonstrate biosimilarity.

### Table 1. Differences Between Small Molecule Drugs and Biologics

<table>
<thead>
<tr>
<th></th>
<th>Small Molecule (Chemical)</th>
<th>Biologic (Protein)</th>
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<tbody>
<tr>
<td><strong>Production</strong></td>
<td>Chemical synthesis</td>
<td>Living systems (eg, cultured bacterial, yeast, animal, or plant cells)</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Can be characterized using limited physicochemical methods</td>
<td>Necessary to perform comprehensive structural and functional assessment</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Various routes, including oral, topical, and parenteral (IM, IV, SC)</td>
<td>Parenteral (IM, IV, SC) delivery</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly nonimmunogenic</td>
<td>Potentially immunogenic</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; SC, subcutaneous.
The complexity of biologics

Physically and chemically, biologics are more complex than small molecules. Because biologics are frequently proteins, they must be produced in living systems. The final form of a biologic is not a single entity, but a mix of isoforms. This mixture of isoforms is frequently attributed to "post-translational modifications" due to the fact that they occur after the gene (nucleic acids sequence) has been translated into the corresponding protein sequence (amino acid chain). In addition to the natural variability of biologics within and between production batches, it is important to remember that some additional variation can occur as a result of the manufacturing process. Guidance from the US Food and Drug Administration (FDA) on product comparability has been available since 1996. It explains the steps manufacturers may perform to undergo FDA evaluation to allow them to make manufacturing changes without conducting additional clinical comparability studies to demonstrate safety and efficacy. Thus, manufacturers of biologics perform a variety of comparability studies to help ensure that the new process delivers a product with a comparable benefit/risk and efficacy profile for the pre- and postprocess change biotherapeutic.

Developing a biosimilar is far more complex than manufacturing process changes and establishing comparability. 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. Biosimilar manufacturers must demonstrate a high degree of similarity in analytical and nonclinical studies, and through clinical studies, demonstrate no clinically meaningful differences between the proposed biosimilar and the reference biologic.
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.\textsuperscript{18} 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.\textsuperscript{13}
The introduction of biosimilars into the US health system may potentially broaden the availability of effective biologics.¹
Biosimilars may offer a number of potential benefits to patients, payers, and health care providers. The potential of biosimilars for patients, payers, and providers may include providing additional treatment choices at lower cost to the health care system and increasing access to biologics, which may lead to better health outcomes overall.\textsuperscript{1,19,20} Potentially offering a variety of therapeutic options, biosimilars may also lead to possible savings and efficiencies to the health care system.\textsuperscript{1,19,20}

The rules for development of biosimilars may also foster innovation.\textsuperscript{21} The Biologics Price Competition and Innovation Act (BPCIA) includes provisions to assure 12 years of marketing exclusivity for reference biologics, as well as including mechanisms for patent resolutions to mitigate any potential violations.\textsuperscript{22} These steps may help to encourage development of new biologics with unique or improved mechanisms of action.\textsuperscript{21}
While biosimilars have the potential to provide additional treatment options at lower cost, development of biosimilars requires substantial investment. Development of a biosimilar may take 5 to 9 years at a cost of up to $135 million, not including regulatory fees.\textsuperscript{1,21,23,24} A generic version of a small molecule drug, on the other hand, costs $1 million to $4 million to develop.\textsuperscript{25,26} Because the experience with biosimilars is relatively new, estimates of cost savings may depend on clinical utilization and are quite variable at this juncture (Table 2).\textsuperscript{9,27}

**Table 2. Potential Biosimilar Cost Savings Estimates Are Variable\textsuperscript{9,27}**

<table>
<thead>
<tr>
<th>Source</th>
<th>Examples of Estimated Biosimilar Savings</th>
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<tbody>
<tr>
<td>Express Scripts</td>
<td>$250 billion savings possible during 2014–2024 if 11 likeliest biosimilars enter the United States’ market</td>
</tr>
<tr>
<td>IMS</td>
<td>$54 billion to $108 billion in cumulative savings in the EU5 and United States combined over the next 5 years</td>
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“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.”

—FDA
A known product, a tailored process

With new biologics being approved and the expanding use of existing products, global utilization of innovative biologics will continue to grow.⁹
In 2015, the FDA acknowledged more than 100 therapeutic biologic products, with approval dates ranging as far back as 1965 (collagenase) and covering a range of indications from cosmetics to cancer. Biologics have become an integral part of health care options in the United States and abroad; over 900 vaccines and biologics are currently in clinical development for more than 100 diseases.

In 2015, biologics accounted for more than 25% of all novel drug approvals by the FDA. The number of new biologics being approved has more than doubled between 2005 and 2015 (Figure 2). In 2015, biologics accounted for 7 of the 15 highest-expenditure drugs.

**Figure 2. Growth in US new drug approvals: % biologics**

2005\[=10\%\]

2015\[>25\%\]
According to the Centers for Medicare & Medicaid Services, prescription drug spending growth is projected to average 6.3% annual growth from 2015 through 2024.²
As part of the Affordable Care Act, the BPCIA created the regulatory framework for an abbreviated approval process for biosimilar products. 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. It is estimated that approximately 100 biologics will lose patent or other protections by 2021 (Table 3).

### Table 3. Many Biologic Patents Will Expire in the Coming Years

<table>
<thead>
<tr>
<th>Patent Expiry Year</th>
<th>Number of Products</th>
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<tbody>
<tr>
<td>2012 and earlier</td>
<td>26</td>
</tr>
<tr>
<td>2013</td>
<td>5</td>
</tr>
<tr>
<td>2014</td>
<td>11</td>
</tr>
<tr>
<td>2015</td>
<td>14</td>
</tr>
<tr>
<td>2016</td>
<td>6</td>
</tr>
<tr>
<td>2017</td>
<td>8</td>
</tr>
<tr>
<td>2018</td>
<td>3</td>
</tr>
<tr>
<td>2019</td>
<td>21</td>
</tr>
<tr>
<td>2020</td>
<td>8</td>
</tr>
<tr>
<td>2021</td>
<td>9</td>
</tr>
<tr>
<td>2022 and later</td>
<td>17</td>
</tr>
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</table>
Proving biosimilarity

The approval process for biosimilars in the United States is outlined in Figure 3. The FDA has taken a “totality of evidence” approach to evaluating biosimilar agents. All of the data are generated via a stepwise approach. 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. 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.
In the development of a reference biologic, the greatest contribution to clinical predictability resides at the top of the inverted pyramid (left; Figure 3), 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. 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. For a biosimilar, this molecular characterization will provide the foundation for development, which builds on the clinical experience with the reference biologic. 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.
Common considerations with biosimilars

Manufacturing consistency enables the release of a biosimilar product into the marketplace and clinic with quality attributes similar to those of the original reference product. 38
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. This results in heterogeneity. Potential sources and examples of heterogeneity include glycosylation, methylation, conformation, substitution, and oxidation caused by differences in cell type, culture conditions, and external conditions such as temperature and pH. 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.

FDA guidance on product comparability evaluates the potential significance of changes to biologics, which has been available since 1996. Manufacturing processes of biosimilars are designed, developed, and understood through the science- and risk-based approaches of quality by design. Quality by design uses the full understanding of how product attributes and processes relate to performance. As a result, manufacturing processes can be monitored and strategies can be implemented that help ensure a consistent product is made, with its overall quality and attributes maintained throughout its life cycle.

MANUFACTURING CONSISTENCY

The manufacturing requirements for a biosimilar are equivalent to any new biologic entity, ensuring the production of a consistent, high-quality product. 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. 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. Demonstrating biosimilarity to a reference product requires more data and information than establishing comparability between a post- and premanufacturing change.
EXTRAPOLATION

Extrapolation is a scientific and regulatory principle that refers to the approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with a biosimilar.\textsuperscript{13,38} Once the biosimilar product has met the requirements for approval for a specific indication, FDA guidance has indicated that the potential exists for a biosimilar to be licensed for one or more additional conditions of use for which the reference product is licensed.\textsuperscript{13} The rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency, and to allow resources to be allocated to areas where studies may be more valuable.\textsuperscript{41} Extrapolation to each additional indication will require compelling evidence.\textsuperscript{13} Extrapolation is evaluated based on sufficient scientific justification.\textsuperscript{13} Aspects that may be considered for extrapolation may include mechanism of action in each condition, PK and biodistribution, expected toxicities, and any other factor (such as comorbidities). Thus, extrapolation is not automatic and is considered only after biosimilarity is established based on the totality of evidence.\textsuperscript{13}

Figure 4. Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied\textsuperscript{13,42,43}

**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.\(^{13,44}\) However, there is the potential for these antibodies to have clinical consequences.\(^{13,44}\) This reaction can result in the production of ADA, including neutralizing antibodies, which can lead to decreased efficacy\(^{13,44}\), ADA may also result in general immune effects, including allergy, “serum sickness,” or anaphylaxis.\(^{13,44}\) 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.\(^{13,44}\)

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 as compared with the reference product.\(^{13}\)

**INTERCHANGEABILITY AND SUBSTITUTION**

The FDA mandates that for a biosimilar to be considered interchangeable with a reference product it must be able to produce the same clinical result in any given patient and, if the product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and reference product is not greater than with continued treatment with the reference product alone.\(^{45}\) Even though the FDA has indicated that interchangeability is possible, as of November 2016 it has not yet provided detailed guidance on approval requirements. The designation of interchangeability will require a higher standard than biosimilarity alone. *Substitution* is a practice by which an “interchangeable” biologic is dispensed by a pharmacist to the patient without the prior informed consent of the treating physician.\(^{46}\) In the United States, while the FDA defines interchangeability, each state governs its regulation of substitution; details regarding substitution legislation differ from state to state.\(^{47}\)
What's in a name?

A biosimilar obviously cannot carry the same proprietary brand name as the reference product. However, the FDA has indicated that it also is not appropriate for biosimilar and reference products to share the same nonproprietary name. Rather, biosimilars should include an FDA-designated suffix. There is a need to clearly identify and distinguish biological products that have not been determined to be interchangeable, for the purposes of safe use and to improve pharmacovigilance. Approved biosimilars, therefore, should have both names and labels that are readily distinguishable from the reference product and reflect their unique manufacturing processes and origins.

The FDA recommends use of a brand name in the label, where feasible and appropriate, in order to make distinctions between products as clear as possible. In addition to this, a clearly distinguishable nonproprietary name is necessary to track adverse events related to the specific biosimilar or reference product, to help ensure appropriate prescribing and dispensing, and to allow prescriber choice in health care systems where the nonproprietary name is typically used.
Introducing biosimilars into clinical practice
Approved biosimilars should be a potential consideration for all patients who receive treatment with biologic medications for eligible indications.\textsuperscript{41} Acceptance by physicians that all qualifying patients can be treated with biosimilars may potentially facilitate increased access to biologic therapies for all patients.\textsuperscript{41}

**AT THE PHARMACY LEVEL**

In the United States, while the FDA defines interchangeability, the states regulate substitution.\textsuperscript{47} Many states have considered legislation governing the substitution of biosimilars. While details vary from state to state, laws generally have a number of things in common\textsuperscript{47}:

- Substitution is permitted only if the biosimilar has been designated as interchangeable
- Substitution may be prohibited if the prescribing physician has indicated a preference for the reference product
- The prescriber must be notified of any substitution made by the pharmacy

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**Where do we go from here?**

Since their introduction more than 30 years ago, biologics have had a meaningful impact on patient management in multiple disease states.\textsuperscript{5-8} As demonstrated by their growth in share of total pharmaceutical sales, there is a strong demand for patient access to innovative biologic therapies.\textsuperscript{9}

Biosimilars are highly similar versions of existing biologic drugs.\textsuperscript{13} The introduction of these agents into a variety of markets around the world may fulfill the promise of providing effective biologics to previously underserved and undertreated patients, leading to better overall health outcomes.\textsuperscript{1} With a heritage of bringing innovation to health care, Pfizer is positioned to help integrate biosimilar medicines into clinical practice. Leveraging developmental and clinical expertise, Pfizer Biosimilars has 3 marketed biosimilars outside the United States,\textsuperscript{50-52} 4 monoclonal antibodies in late-stage clinical development, and 1 approved biosimilar in the United States. Pfizer strives to extend its legacy of quality treatment options to patients in need.\textsuperscript{53-55}
**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.\(^3\)

**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.\(^3\)

**Biosimilar:** Biosimilars are similar to the original biologics. Although it is impossible to produce an identical copy of any biologic medicine, a biosimilar must be proven to show no clinically meaningful differences from an originator medicine.\(^3\)

**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.\(^3\)

**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 assure 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.¹²

**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).⁵⁶

**Interchangeability:** 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.⁴⁵

**Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.⁵⁶

**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.¹³

**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.⁵⁷
References


