Frequently Asked Questions

Biosimilars
FORUM

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About the Biosimilars Forum

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ABOUT THE BIOSIMILARS FORUM

The Biosimilars Forum was incorporated in Washington, DC, as a nonprofit organization to advance biosimilars in the United States with the intent of expanding access and availability of biological medicines, and improving health care. The Biosimilars Forum will provide evidence-based information to inform and support public policies that encourage awareness, access, and adoption of biosimilars.

The introduction of biosimilars in the United States may help expand access to high-quality treatment options for clinicians and patients as well as potentially reduce costs to families, caregivers, payers, and the entire health care system. Using state-of-the-art technology, biosimilars are manufactured using the same with the same high-quality systems and processes as existing biological medicines.

The founding members of the Biosimilars Forum represent the majority of companies with the most significant U.S. biosimilars development portfolios, including: Amgen, Boehringer Ingelheim, Coherus BioSciences, EMD Serono, Merck, Pfizer, Samsung Bioepis, Sandoz, and Teva.

The FDA approval of the first biosimilar in the United States and the ongoing development and production of other biosimilars serve as important milestones. The founding members and key stakeholders recognize there is a need for a sustained and unbiased biosimilars education and advocacy program in the U.S.

To this end, the development of an independent non-profit forum to raise awareness of biosimilars and serve as a credible resource for information is timely. The Biosimilars Forum will provide an opportunity for companies developing biosimilars for the U.S. to work together and with other key stakeholders on topics instrumental to biosimilars and patient care.

Learn more about biosimilars, the Forum, and how to get involved, visit BiosimilarsForum.org, @USBiosimilars, or go to facebook/USBiosimilars to follow related conversations and join the dialogue.

BIOSIMILARS FAQS

Here are answers to some of the most common questions people have about biosimilars and how they'll be used and regulated in the U.S. If you don't find the information you are seeking, please contact us.

What is a biologic medicine?

Biological medicines, also known as biological therapies or "biologics," are medicines that are produced by living organisms, including human, animal, or microorganism cells. Today, they are commonly produced through biotechnology. Biologics are very large, complex molecules or mixtures of molecules and can be proteins, sugars, and nucleic acids, as well as living entities such as cells and tissues.

Biologics are different than most drugs used today because most drugs are made by synthetic chemical processes and are much smaller molecules than biologics.

Biologics work within a patient's body by supplementing or interrupting natural pathways, processes, and signals in order to treat a specific disease or disorder.

All biological medicines vary to a degree from one batch to the next even when the same manufacturing process is used. This is normal and expected. Strong manufacturing controls are put in place to ensure that all variability stays within pre-specified and pre-approved ranges.

What is a biosimilar medicine?

A biosimilar medicine is a biologic that is approved based on a demonstration that it is highly similar to an FDA-approved biological medicine, known as a reference product. A biosimilar must be determined by the FDA to (1) be highly similar to the reference product notwithstanding minor differences in clinically inactive components and (2) have no clinically meaningful differences compared to the reference product in terms of safety, purity, and potency. Patients and their health care providers can expect that biosimilars will have the same safety and effectiveness as the corresponding reference product.

Biosimilars are neither required nor expected to be "identical" to the reference biologic, which itself has some degree of inherent variability because they are produced in living cells. Nonetheless, it is important to know that biosimilars are

highly similar to the reference product, and any differences that may exist are expected to not have an impact on safety or effectiveness.

What does interchangeable mean?

When applied to biological drugs, the term "interchangeable" or "interchangeability," means that a biosimilar drug may be substituted by a pharmacist for the reference product without first getting permission from the health care provider who wrote the prescription. This is different from substitution by the health care provider, which is a common medical process whereby that provider can write a prescription for one drug in place of another.

According to U.S. law, an interchangeable biologic is a distinct category of biosimilar and is not a different product. To obtain an FDA designation of “interchangeability,” the sponsor of a biosimilar typically must conduct a clinical study with multiple switches back and forth between the biosimilar and reference product. This clinical study must prove that for a product administered to an individual more than once, the risk in terms of safety or diminished efficacy of switching back and forth between the interchangeable biologic and its reference product is not greater than the risk of using the reference product by itself, without switching. The manufacturer of the interchangeable biologic must establish that the interchangeable biologic can be expected to have the same clinical result in all patients and indications for which the reference product is approved.

There is no legal or regulatory requirement that suggests or requires that a biosimilar meet the statutory definition of interchangeability as a prerequisite for a *physician* to switch a patient from a reference biologic to a biosimilar. Physicians always have the freedom to prescribe whatever drug they believe is appropriate for their patients.

There are no additional quality requirements to establish interchangeability, as the additional data required is clinical in nature. In fact, the interchangeable biologic molecule is exactly the same as the biosimilar that was initially approved from that sponsor, — the difference being that additional clinical data was provided in order to gain the interchangeability designation from the FDA. This clinical data is used to support the requirement that an interchangeable biologic can be expected to produce the same clinical effect in any given patient for which the reference product is approved and that there is no additional risk as a result of switching repeatedly between the reference product and the interchangeable biosimilar.

While the FDA will designate biologic interchangeability nationally, individual states regulate the practice of pharmacy, including laws describing how and when a pharmacist can substitute one drug for another. Since state substitution laws were originally written based on generic drugs, the laws in each state are being updated to permit pharmacy-level substitution of an interchangeable biologic for a reference product. Many states have either passed or are considering legislation, but the enabling legislation is not yet in place in all states. The status of state-by-state substitution laws can be located here.

What are the benefits of biosimilars?

Some of the most difficult-to-treat diseases, such as cancer, anemia, and autoimmune disorders (e.g., multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease) may be treated or managed with biologics. Some biologic treatments are delivered in a health care setting in the form of an injectable or a solution to be administered intravenously. While biologics make up a small percentage of the total number of drugs on the market, they can be very expensive to the patients who rely on them, and are a significant cost to the U.S. health care system. Since their origins in the 1980s, biologics have grown to be a $179 billion market in 2014 (EvaluatePharma World Preview 2015, Outlook to 2020. 8th Edition – June 2015), and the overall market for biologics is expected to continue growing due to the number of new biologic drugs currently under development. The RAND Corporation has projected that the introduction and growth of biosimilar medicines in the U.S. will reduce direct spending on biologics by $44.2 billion from 2014 to 2024.

The introduction of biosimilars is anticipated to help lower the cost burden of biologics on the U.S. health care system, and may help expand access to biological medicines. Expiring patents for several biological medicines in the coming years will create an opportunity to develop biosimilars to these products.

What are the benefits to providers?

The growth of the biosimilar market will provide multiple sourcing options for health care professionals and may provide broader and earlier patient access to these important treatment options. This has been observed in some European markets where the number of patients being treated with a given biologic (combined originator and biosimilar) has increased since the introduction of biosimilars in Europe more than ten years ago.

What are the benefits to patients?

The availability of biosimilars introduces competition, which provides more treatment options and may help to bring down prices. The availability of affordable biosimilars may improve access, and enable more patients to be treated with these therapies. Data have shown that in some indications for which biologics may be used, the use of biologics earlier in a treatment regimen (e.g. by lessening or eliminating step therapy) may improve individual patient outcomes when compared to patients not treated with biologics until later in the treatment cycle.

What is the benefit to payers and health care systems?

The introduction of biosimilars on the market means more treatment options and increased competition. This competition may lead to high-value therapies at reduced prices. Industry experts have suggested the savings obtained with biosimilars could free up health care funding for coverage of new medicines or other societal needs.

Do biosimilars work in the same way as their biological reference products?

Yes. There are no clinically meaningful differences in terms of safety, purity, and potency between an FDA-approved biosimilar and its reference product. A biosimilar must have the same mechanism(s) of action as its reference product to the extent they are known, which means it will work in the same way. The FDA will only approve a biosimilar if:

- Convincing data is provided to demonstrate that it is highly similar to the reference product.
- It utilizes the same mechanism(s) of action for the condition or conditions of use prescribed (to the extent they are known for the reference product).
- Condition(s) of use have been previously approved for the reference product. Route of administration, dosage form, and the strength of the biological product are the same as those of the reference product.
- The facility in which the biosimilar is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Biosimilars work in the same way as their biological reference product; biosimilars have no clinically meaningful differences in safety and efficacy compared to their reference products.

How are biosimilars prescribed?

A biosimilar may be prescribed by a physician for patients newly diagnosed with a disease, or at the discretion of the physician, for patients who may already have been treated with the reference product. A provider must write the specific name of the biosimilar on the prescription or order. A pharmacist must dispense the biologic specified, or must obtain permission in advance from the prescribing physician to dispense a different biologic in place of the product identified on the prescription order.

Once a biosimilar is approved by the FDA as an interchangeable biologic it may be substituted by a pharmacist for the prescribed reference product without first getting permission from of the prescribing physician, subject to the appropriate state laws governing the practice of pharmacy.

Are biosimilars generic versions of their reference biological products?

No. Biosimilars are not like generic drugs because most generic drugs are chemically synthesized while biosimilars are manufactured using living systems. Generic drugs are identical copies of brand-name drugs, and sponsors must demonstrate that generic drug levels in the body are the same over time as their respective reference drugs. This means they have the same active ingredient and are identical in terms of dose form, safety, strength, administration, quality, performance characteristics, and intended use.

In contrast to generics, biosimilars are derived from living systems and are commonly more complex than generic drugs. Biosimilars are highly similar to their respective reference product, notwithstanding minor differences in clinically inactive components. Manufacturers must demonstrate that there are no clinically meaningful differences between a biosimilar and reference product in terms of safety, purity, and potency.

How are biosimilars approved?

Biosimilars are approved by the FDA using a new regulatory pathway that focuses heavily on structural analysis, although some clinical studies are often required. The heavy focus on structural and analytical testing is appropriate because analytics are often more sensitive and have a greater capability to detect differences than would be apparent in a clinical study.

Biosimilars are approved using data obtained in a stepwise fashion. The data are evaluated at each step of development to influence subsequent steps, and are used to provide extensive, head-to-head comparisons of the biosimilar and reference product at many levels, which may include:

1. Structural and functional comparisons, which are the foundation of biosimilarity. High similarity must be established at this step before further development can proceed.
2. Testing of toxicity in animals.
3. Human pharmacokinetic comparisons (what happens to a drug in the body).
4. Human pharmacodynamic comparisons (what happens to the body in the presence of a drug), where a relevant pharmacodynamic marker exists.
5. Human clinical studies to confirm that there are no clinically meaningful differences in safety and efficacy.
6. Comparison of the immunogenicity of the biosimilar and reference product.

These data, taken together, form the "totality of evidence" that the FDA examines when considering approval of a biosimilar, although the FDA has the discretion to decide that certain types data may not be needed for a particular biosimilar.

Once satisfied that the totality of evidence is both substantial and sensitive enough to detect potential differences and to address residual uncertainty that may exist, the FDA could approve the biosimilar. The biosimilar regulatory pathway specifies that a biosimilar can be approved for use in one or more indications of use on the basis of the biosimilar being highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

What is "extrapolation?"

A biosimilar may be approved for one or more conditions of use (known as "indications and usage") for which its reference biological product is licensed but for

which there was no head-to-head clinical comparison. This approval is based on extrapolating the totality of evidence obtained with the biosimilar in direct comparison to the reference product when we know (to the extent possible) that the molecule works in the same way in both the studied and extrapolated indication (known as the "mechanism of action").

The FDA examines requests for extrapolation on a case-by-case and indication-by-indication basis. Every indication for which extrapolation is sought must be scientifically justified by the company seeking extrapolation for their product. Approval of an additional indication through scientifically valid extrapolation expedites the development of biosimilars and eliminates unnecessary clinical studies, thereby increasing patient access to important therapies.

What is "non-medical switching" and does it apply to biosimilars?

Non-medical switching is the switching of a medication from one molecule in a therapeutic class to a separate and *structurally different* molecule in the same class for reasons other than medical need, with the goal of having the same clinical outcome (defined by the by the American College of Clinical Pharmacologists as "therapeutic interchange" and by the American Medical Association as "substitution of therapeutic alternates"). The concept of non-medical switching does not apply to biosimilars and interchangeable biologics because the switch from a reference product to a biosimilar is a switch between two medicinal products that are confirmed by FDA to be structurally highly similar.

Classes of medicine in which non-medical switches could occur due to the availability of multiple medicines in the class include blood pressure medications, cholesterol lowering drugs (statins), anti-TNF inhibitors for treatment of arthritis, psoriasis or GI indications, and NSAIDs for treatment of pain. All of these are examples of different drug structures that have the same effect in people.

As part of the FDA approval process, biosimilars must be proven to have a "primary structure" (sequence of amino acids) that is identical to the reference biological product. In addition, the biosimilar must have a three-dimensional shape that is indistinguishable from the reference product. Only minor differences are permitted, which is why the term "highly similar" is used.

Biosimilars are approved based on a stringent review by FDA to assess their safety and efficacy. Patients, prescribers, and pharmacists can be confident that approved biosimilars are as safe and effective as the reference biologic product.