Facts About Biosimilars

Numerous biosimilars are available in the U.S., and the list is growing. The differences between biosimilars, biologics, interchangeable products, and generics, as well as their various approval processes can be confusing. Biosimilars may be preferred by payers as they are less costly than the reference product (but still expensive). The FAQ below addresses questions that may come up regarding biosimilars, including interchangeability.

Question	Answer/Pertinent Information

What are biological products and biosimilars?	• **Biological products** are generally isolated from living material (human, animal, or microorganism) and may be produced by biotechnology methods or other technologies.[2] They are much larger and more complex molecules or mixture of molecules than a traditional drug.[9]
	  • Examples include monoclonal antibodies (e.g., adalimumab), interferons and other cytokines, growth factors (filgrastim), thrombolytics and other enzymes, and immunomodulators.[5]
	  • In 2020, several hormones (e.g., insulin, human growth hormone), which had historically been FDA-approved as drugs, were reclassified as biologics, allowing for the development of biosimilars and interchangeable products for these meds.[7]
	• **Biosimilars** are biological products that have been shown to be highly similar to an FDA-approved biological product (known as the **reference product**).[5]
	  • Minor differences in clinically inactive components (e.g., stabilizers, buffers) between the biosimilar and reference product are allowed.[5]
	  • There must be no clinically meaningful differences between the biosimilar and reference product in regard to safety, purity, or potency.[5] Dosing and warnings for approved indications (which can be fewer for the biosimilar) are the same.[14,16]

How do biosimilars receive FDA approval?
 	
Continued…
	• Biosimilars are approved through an abbreviated pathway created via the Biologics Price Competition and Innovation Act, that relies on existing safety and efficacy data of the reference product.[1,12]
	  • Biosimilarity must be demonstrated between the reference product and the proposed biosimilar.[1]
	  • The proposed biosimilar product does not need to independently establish safety and effectiveness.[1]
	• A biosimilar product can only be approved by the FDA:
	  • if it has the same mechanism(s) of action, route, dosage form, and strength as the reference product.[13]
	  • for the condition(s) of use that have been approved for the reference product.[13] (Note that the biosimilar can have fewer indications and routes of administration than the reference product).[14]
	  • if the facilities where biosimilars are manufactured meet the FDA's standards.[13]

Question	Answer/Pertinent Information

FDA approval process for biosimilars, continued	• The manufacturer's application for a biosimilar must include, among other things, information demonstrating biosimilarity based upon data from:[1]
	  • analytical studies demonstrating that the biological product is "highly similar" to the reference product, except for minor differences in clinically inactive components
	  • animal studies (including assessment of toxicity)
	  • one or more clinical studies that demonstrates safety, purity, and potency in one or more indications for which the reference product is licensed. This usually includes assessment of immunogenicity, pharmacokinetics, and sometimes pharmacodynamics; and may include a comparative clinical trial.
	  ○ an efficacy study is not required; however, there must be data to support extrapolation of efficacy data from the reference product to the biosimilar.
	• There are additional requirements for **interchangeable** biologics, described later in this document.

Can more than one biologic with the same active ingredient be approved via the new drug pathway?	• Multiple biologics with the same active ingredient can each be approved as **new drugs** (not as biosimilars), for example:
	  • *Granix* contains filgrastim (similar to *Neupogen* and *Zarxio*). *Zarxio* is biosimilar to *Neupogen*; however, *Granix* is **not** biosimilar to *Neupogen*. Instead, *Granix* was approved through the traditional FDA approval pathway for a biologic drug (not the biosimilar pathway).[10]
	  • *Basaglar* contains insulin glargine (similar to *Lantus*). *Basaglar* received approval as a **new drug**, not as a biosimilar to *Lantus*.[10]

How does a biosimilar differ from a generic?	• Biosimilars are not generics. Biosimilars and generics are approved through different abbreviated pathways.[2] • Generic drugs are almost identical to the brand name drug. Small-molecule ("traditional") drugs are made through a predictable set of chemical reactions. However, biologics are made using manufacturing processes (e.g., cell production, purification processes) and living organisms (e.g., cell lines) that are unique to each manufacturer, making it impossible to make an exact copy of a biologic.[11] • FDA-approved generic drugs must contain the same active ingredient(s) as the brand-name/innovator drug (inactive ingredients may vary), be identical in strength, dosage form, and route of administration, have the same indications, and be bioequivalent (i.e., work in the same way and provide the same clinical benefit).[6] • **In some cases, biologics may be approved through the generic drug approval pathway**. • For example, glatiramer is a peptide, a specific type of biologic product. The FDA has tools and guidance to facilitate evaluations of proposed generic peptides.[17] For example, *Glatopa* is a **generic** version of *Copaxone* (glatiramer); it is **not** a biosimilar of *Copaxone*. *Glatopa* was approved as a generic via the abbreviated new drug application (ANDA) pathway.[10] These products are therapeutic equivalents and may be substituted per the generic substitution regulations in your state.[18]

Question	**Answer/Pertinent Information**
Are biosimilars interchangeable with the reference product?	• Biosimilars do not fall under the same rules for generic substitution as traditional drugs. • An **interchangeable** biologic is biosimilar to an FDA-approved reference product **and** meets additional standards for interchangeability.[1] Therefore, not all biosimilars are interchangeable. (See next section for info on identifying interchangeable biologics.) • Federal regulations allow an **interchangeable** biologic to be substituted for the reference product by a pharmacist without the intervention of the prescriber.[5] However, state pharmacy boards may have different regulations.[8,18] To be **interchangeable**, an FDA-approved biosimilar must also prove that:[1] • the proposed interchangeable biological product is expected to produce the same **clinical result** as the reference product in any given patient, (for example, *Semglee* [insulin glargine-yfgn] is an interchangeable biosimilar. *Semglee* has shown similar A1C lowering at six months compared to *Lantus*), **and** • for a product that will be administered more than once to an individual, the risk in regard to safety or diminished effectiveness of switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without switching between products.
How do you find out if a biosimilar and reference product are interchangeable?	• **The Purple Book** (https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm) enables the user to see if a biological product has been determined by the FDA to be interchangeable with the reference biologic.[4] • Biosimilar and interchangeable biologics licensed under section 351(k) of the Public Health Service Act are listed under the reference product to which biosimilarity or interchangeability was demonstrated.[4] • The designation "B" is used if the product is biosimilar. An "I" designation is used if the product is also interchangeable.
How are biosimilars named?	• The FDA's naming convention for all biological products is a "core name" followed by an FDA-designated suffix composed of four lowercase letters attached to the core name with a hyphen.[3] Most of the suffixes are nonsensical.[3] • For example, *Nivestym* is named filgrastim-aafi and *Zarxio* is named filgrastim-sndz. • The suffix format applies to originator biological products as well as biosimilars. Products without suffixes, or with suffixes that do not comply with the guidance, will receive new suffixes over time. The FDA is continuing to consider the appropriate suffix format for interchangeable products.[3]

Question	**Answer/Pertinent Information**

What are some practical prescribing and dispensing implications for biosimilars?	• A biosimilar can be approved only for those indications previously approved for the reference product, but a biosimilar can be approved for **fewer than** all the indications and routes approved for the reference product.[13,14] This could happen if the reference product has an unexpired patent(s) on an indication, the biosimilar manufacturer only applies for certain indications, or the FDA does not allow the indication after reviewing the submitted data.[1,16]
	  • Review the prescribing information to determine the biosimilar's approved indications.[16]
	• **Interchangeable** biosimilars may be substituted by the pharmacist without the intervention of the prescriber (depending on state law).[8,18] (This is analogous to substitution by the pharmacist of an A-rated generic.)
	  • If a specific biologic brand is desired, prescribers can write for that particular brand (e.g., *Neupogen*) and specify "dispense as written" or "brand medically necessary," depending on state law.[15,18]
	• For noninterchangeable products, prescribers should specify the biosimilar's unique name to ensure the desired product is dispensed. For example, if *Zarxio* is desired, write the brand name or specific nonproprietary name (e.g., filgrastim-sndz) instead of just "filgrastim." Be aware that in the hospital setting, a formulary-directed substitution might be made.
	• Pharmacists should be aware of state laws on dispensing biosimilars. Some states may require the prescriber and/or patient to be notified if a substitution is made at the pharmacy.[15,18] Details of individual state regulations around biosimilar interchangeability can be found at https://www.cardinalhealth.com/content/dam/corp/web/documents/publication/Cardinal-Health-Biosimilar-Interchangeability-Laws-by-State.pdf.

Should patients stick with the same biologic?	• An **interchangeable** biological product can be expected to produce the same **clinical result** as the reference product in any given patient.[5,8,16] • Designated **interchangeable** biological products must show that (for products administered more than once to an individual) the risk in regard to safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[1]

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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