Facts About Biosimilars

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Numerous biosimilars are available in the US and Canada, 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). This FAQ addresses questions that may come up regarding biosimilars, including interchangeability.

Question	Answer/Pertinent Information

What are biological products (biologic drugs) and biosimilars?	• **Biological products** (Canada: biologic drugs) are usually large complex molecules manufactured in living material (e.g., animal, plant, microorganism) using biotechnology methods.[2,21] 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 (e.g., filgrastim), thrombolytics and other enzymes, and immunomodulators.
	  ○ In the US, 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 (Canada: biologic drugs) that have been shown to be highly similar to an approved biological product (Canada: biologic drug), known as the **reference product** (Canada: reference biologic drug).[13,22]
	  • In Canada, biosimilars were previously referred to as subsequent entry biologics (SEBs).[22]

How do biosimilars receive approval?	• Biosimilars are approved through an abbreviated pathway (in the US, created via the Biologics Price Competition and Innovation Act), that relies on existing safety and efficacy data of the reference product (Canada: reference biologic drug).[1,12,22]
	• Biosimilarity must be demonstrated between the reference product and the proposed biosimilar.[1,22]
	• The proposed biosimilar product does not need to independently establish safety and effectiveness.[1,22]
	• A biosimilar product can only be approved:
	  ○ if it has the same dosage form, route of administration, strength, and mechanism (for the desired indication[s]) as the reference product.[13,22] (US: minor differences in clinically inactive components [e.g., stabilizers, buffers] between the biosimilar and reference product are allowed.[2,22])
	  ○ for the condition(s) of use that have been approved for the reference product.[13,22] (Note that the biosimilar can have fewer indications and routes of administration than the reference product).[14,22]

Question	Answer/Pertinent Information
Continued… How biosimilars are approved, continued	• The manufacturer's application for a biosimilar must include, among other things, information demonstrating no clinically meaningful differences from the reference product in regard to safety, efficacy, potency, and purity based upon data from:[1,22] o analytical studies demonstrating that the biological product is "highly similar" to the reference product (US: except for minor differences in clinically inactive components).[1,22] o animal studies, if necessary.[1,22] o 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.[1,22] ▪ An efficacy study is not required if there is sufficient information to support extrapolation of efficacy data from the reference product to the biosimilar.[1,22] ▪ In Canada, manufacturers must include a Risk Management Plan which explains how immunogenicity and other safety signals will be monitored post-marketing.[21] Biosimilar manufacturers must also keep abreast of post-marketing safety information for the reference biologic drug.[21] • In the US, there are additional requirements for **interchangeable** biologics, described later in this FAQ. • The majority of the product labeling for the biosimilar (dosing, administration, and warnings) will be the same as the reference biologic drug.[14,21] However, the biosimilar may be approved for fewer indications than the reference biologic drug and labeling will reflect this difference.[14,16,21] • Biosimilars cannot enter the market until the reference biologic drug patents for the desired indication(s) have expired or litigated.[9,21]
In the **US**, 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) via the biologics license application (BLA) pathway, for example: o *Granix*, *Neupogen*, *Nivestym*, *Nypozi*, *Releuko*, and *Zarxio* are all filgrastim products. But *Granix* is **not** biosimilar to *Neupogen* (reference product).[19] Instead, *Granix* was approved through the traditional FDA approval pathway for a biologic drug (not the biosimilar pathway).[10] o There are multiple insulin glargine formulations on the market. *Basaglar* was approved after *Lantus*; however, it was approved as a **new biologic**, not as a biosimilar to *Lantus*.[19]
How does a biosimilar differ from a generic? *Continued…*	• 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]

Question	Answer/Pertinent Information
Biosimilar vs generic, continued	• **In the US**, in some cases, biologics may be approved through the generic drug approval pathway. • For example, glatiramer is a peptide, a specific type of biological 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.[20] These products are therapeutic equivalents and may be substituted per the generic substitution regulations in your state.[18]

Are biosimilars interchangeable with the reference product/reference biologic drug?	• Biosimilars do not fall under the same rules for generic substitution as traditional drugs.
	United States
	• 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.[2] However, state pharmacy boards may have different regulations.[8,18]
	• To be **interchangeable**, an FDA-approved biosimilar must also prove that:[1]
	  o 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**
	  o 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.
	Canada
	• Each province and territory in Canada determines the interchangeability of biosimilars, not Health Canada.[21]

How do you find out if a biosimilar and reference product/reference biologic drug are interchangeable?	**United States** • **The Purple Book** (https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or) 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] **Canada** • Drugs designated as interchangeable may be denoted as such on your provincial Drug Benefit List.[5]

Question	Answer/Pertinent Information
How are biosimilars named?	**United States** • 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] o For example, *Nivestym* is named filgrastim-aafi. • 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] **Canada** • Biologic drugs should be identified by both their brand name and their non-proprietary or common name (e.g., "filgrastim [*Grastofil*]"). Each biologic drug has its own Drug Identification Number (DIN). Unlike in the US, a suffix is not used.[15]

What are some practical prescribing and dispensing implications for biosimilars?	• Review the prescribing information to determine the biosimilar's approved indications.[16]
	  o A biosimilar may have **fewer** indications and routes approved than the reference product.[13,14,21] 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/Health Canada does not allow the indication after reviewing the submitted data.[1,21]
	• Check carefully for important differences between biosimilars and the reference product (US)/reference biologic drug (Canada). There may be differences in **storage** requirements; shelf life; available dosages, strengths or concentrations; or inactive ingredients (e.g., **latex**, citrate).
	• **In the US**, 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.[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 (US only [e.g., filgrastim-sndz]) instead of just "filgrastim." Be aware that:
	  o in the hospital setting, a formulary-directed substitution might be made.
	  o coverage through a third-party payer/provincial plan may not be available for that brand.
	• Pharmacists should be aware of state/provincial laws on dispensing biosimilars. Some states may require the prescriber and/or patient to be notified if a substitution is made at the pharmacy.[18] Details of individual state regulations around biosimilar interchangeability can be found at https://www.cardinalhealth.com/en/product-solutions/pharmaceutical-products/biosimilars/state-regulations-for-biosimilar.html.
	• Keep in mind that patients enrolled in patient assistance programs for a reference biologic will need a new enrollment if they are switching to a biosimilar.
	• Ensure patient med lists accurately reflect the specific biosimilar that they are using (e.g., the brand name, suffix [US]).

Question	Answer/Pertinent Information
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.[5,8,16,21] o Designated **interchangeable** biological products (US) 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] • Reassure patients that it is ok to start or switch to a biosimilar. Even a biosimilar that is not designated as interchangeable is highly similar to, and has no clinically meaningful differences from, the reference product.[5]

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.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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