Biosimilars

An Overview of U.S. Regulatory Perspectives, Including a Focus on Biosimilars & Interchangeable Insulins 2022

Content

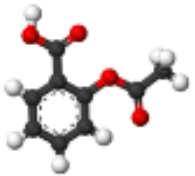
Overview of Biosimilar Products

Biologics Are More Complex Than Small Molecules

Most biological medicines in current clinical use contain active substances made of proteins.[1]

Small chemical molecule[2]

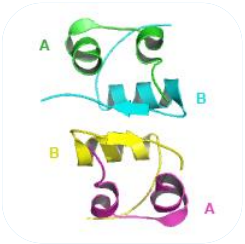
Aspirin



MW = 180 Da
0 amino acids

Biologic[1]

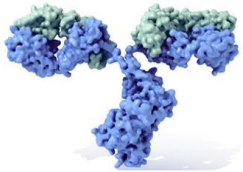
Insulin



MW = ~5800 Da
51 amino acids

Biologic[1,2]

Monoclonal antibody



MW = ~150,000 Da
>1000 amino acids

Complexity

Da = daltons; MW = molecular weight.

1. European Medicines Agency, European Commission. Biosimilars in the EU – Information Guide for Healthcare Professionals. European Medicines Agency. Accessed August 26, 2022. https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guidehealthcare-professionals_en.pdf
2. Food and Drug Administration. Biological Product Definitions. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108557/download

Definitions

Biological Product

A product that is FDA regulated and generally a large, complex molecule produced through biotechnology in a living system that is used to diagnose, prevent, treat, and cure medical conditions

Reference Product

A single biological product, already approved by the FDA, against which a proposed biosimilar product is compared

Biosimilar Product

A biological product that is deemed highly similar to an existing FDA-approved reference product and has no clinically meaningful differences, notwithstanding minor differences in clinically inactive components

Interchangeable Product

A biosimilar product that meets additional FDA requirements. Unless directed by the prescribing HCP to dispense the reference product, an interchangeable product may be substituted for the reference product at the pharmacy without the involvement of the prescriber who has prescribed the reference product (substitution is subject to state pharmacy laws)

FDA = US Food and Drug Administration; HCP = healthcare provider.

Food and Drug Administration. Biological Product Definitions. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108557/download

Difference Between Biosimilars & Generic Drugs

Both biosimilars and generic drugs:

- Are versions of brand name therapeutics
- Offer more affordable treatment options to patients
- Have abbreviated approval processes

	Biosimilar (Biological Products Only)	Generic (Non-Biological)
Active ingredient	Highly similar to reference product	Identical to brand name therapeutic
Manufacturers requirements	No clinically meaningful differences between biosimilar and reference product in terms of safety, purity, and potency	Must demonstrate bioequivalence

Food and Drug Administration. Biosimilar Product Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108621/download

Biosimilar Development Program

To ensure safety and effectiveness, biosimilar medicines are:

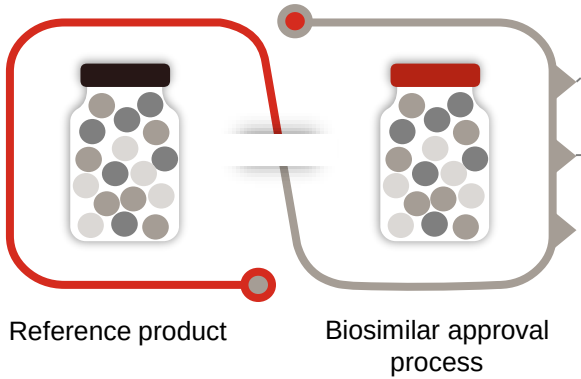
- Regulated by the FDA
- Evaluated through a rigorous process
- Monitored continuously after approval

GOAL

Demonstrate biosimilarity between the proposed biosimilar and its reference product, not to independently establish the safety and effectiveness of the proposed biosimilar

Food and Drug Administration. Biosimilar Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151061/download

Biosimilar Development Program



The abbreviated. pathway involves an extensive structural and functional comparison of the biosimilar and the reference product

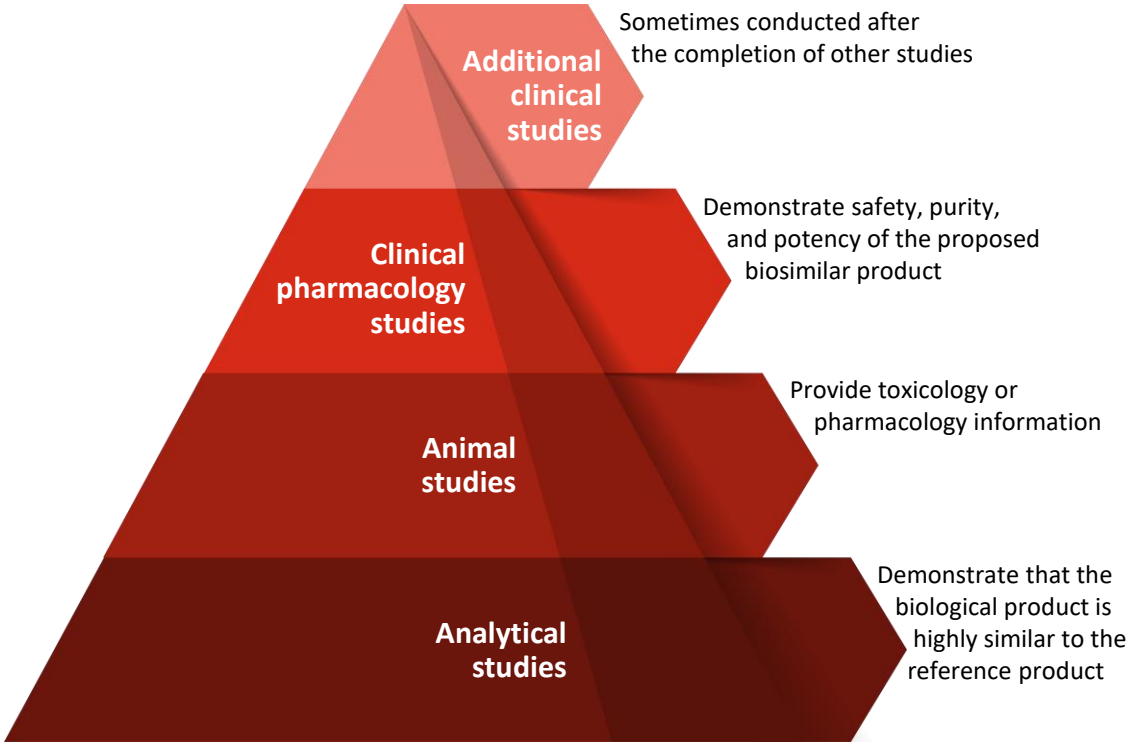
All biologics have variations as part of their manufacturing process. The FDA biologic approval process assesses a manufacturer's strategy to control variation between different batches.

The FDA monitors the safety and effectiveness of all medications after their approval.

Food and Drug Administration. Biosimilar Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151061/download

Regulation of Biosimilar Products in the US

Requirements to Demonstrate Biosimilarity[1,2]



1. *Food and Drug Administration. Biosimilar Product Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108621/download*
2. *Food and Drug Administration. Biosimilar Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151061/download.*

FDA Approach to Biosimilar or Interchangeable Biologics

Section 351 of the PHS Act

Has the following application pathways for biological product licensing:

351(a) BLA: a "stand-alone" application for a reference product; must contain all information and data necessary to demonstrate that the proposed product is safe, pure, and potent.

351(k) BLA: an application for a biosimilar or interchangeable product; must demonstrate that a proposed product is biosimilar to or interchangeable with an FDA-licensed reference product

351(a) BLA may serve as a reference product for a 351(k) biosimilar application

BLA = Biological License Application; PHS = Public Health Service.

Christl L. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Overview-of-theRegulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Productsin-the-US.pdf

FDA Approach to Biosimilar or Interchangeable Biologics

For approval as a biosimilar product under a 351(k) BLA, the following criteria must be met. The biological product:

- Must be highly similar to the reference product notwithstanding minor differences in clinically inactive components
- Has no clinically meaningful differences compared to the reference product in terms of the safety, purity, and potency of the product
- May not be evaluated against more than one reference product

Christl L. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Overview-of-theRegulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Productsin-the-US.pdf

FDA Approach to Interchangeable Biologics

Section 351(k)(4):

Interchangeability Requirements

The biological product:

- Is biosimilar to the reference product
- Is expected to produce the same clinical result as the reference product in any given patient
- Has no increased safety risks or decreased efficacy when alternating use between it and its reference product, compared to only using the reference product without alternation

Christl L. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Overview-of-theRegulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Productsin-the-US.pdf

When Prescribing Biosimilar Products, Remember:

Biosimilar products:

- May be approved for all or a subset of the same indications as the reference product
- Will have no clinically meaningful differences when compared to the reference product
- Can be used both in patients who have and have not previously received the reference product

Food and Drug Administration. Prescribing Biosimilar Products. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108103/download.

Purple Book

- An online database for biological products with reference product, released by FDA
- Contains information about all FDA approved biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products
- Contains information about all FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER)
- Purple book

Food and Drug Administration. Purple Book: Database of Licensed Biological Products. US Dept of Health and Human Services. Accessed August 26, 2022. https://purplebooksearch.fda.gov

Interchangeable Biological Products

What Does It Mean To Be Interchangeable

Pharmacy - level Substitutions

Physician prescribes the reference product

Script goes to the pharmacy

pharmacist substituted the interchangeable for the reference product

Patient receives the interchangeable biosimilar

Note: Not all biosimilars are interchangeable. Additional FDA requirements must be met for an interchangeability determination.[2]

Unless directed by the prescribing HCP to dispense the reference product, an interchangeable product may be substituted for the reference product and vice versa, without consulting the prescriber, depending on state pharmacy laws.

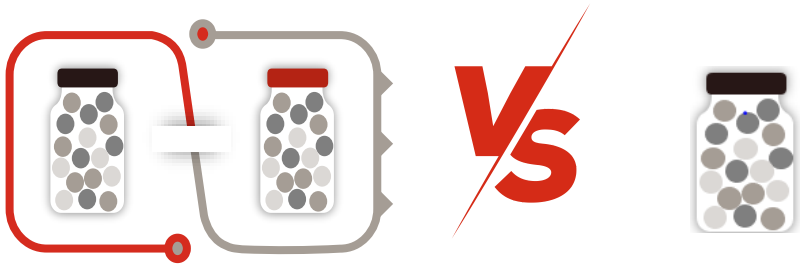
1. Association of Diabetes Care & Education Specialists, The New Frontier of Interchangeable Biosimilar Insulins. Accessed August 26, 2022. https://www.diabeteseducator.org/docs/default-source/practice/educatortools/insulin/new_frontier_of_interchangeable_biosimilar_insulins.pd

2. Food and Drug Administration. Interchangeable Biological Products. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151094/download

Demonstrating Interchangeability

Interchangeable biosimilars are approved through an abbreviated pathway that compares the product to the reference product to show biosimilarity.[1,2]

Studies comparing:



patients switching between the reference product and interchangeable biosimilar

patients on the reference product only

- No decrease in effectiveness or increase in safety risk with switching must be shown.[1,2]
- This does not mean that an interchangeable biosimilar is safer or more effective than other biosimilars.[2]

1. Association of Diabetes Care & Education Specialists, The New Frontier of Interchangeable Biosimilar Insulins. Accessed August 26, 2022. https://www.diabeteseducator.org/docs/default-source/practice/educatortools/insulin/new_frontier_of_interchangeable_biosimilar_insulins.pd
2. Food and Drug Administration. Interchangeable Biological Products. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151094/download

When Prescribing Interchangeable Products, Remember:

Interchangeable products will have the same clinical results as the reference product

Interchangeable products are safe and effective

Interchangeable products have no additional risk or reduced effectiveness when alternating between interchangeable and reference products

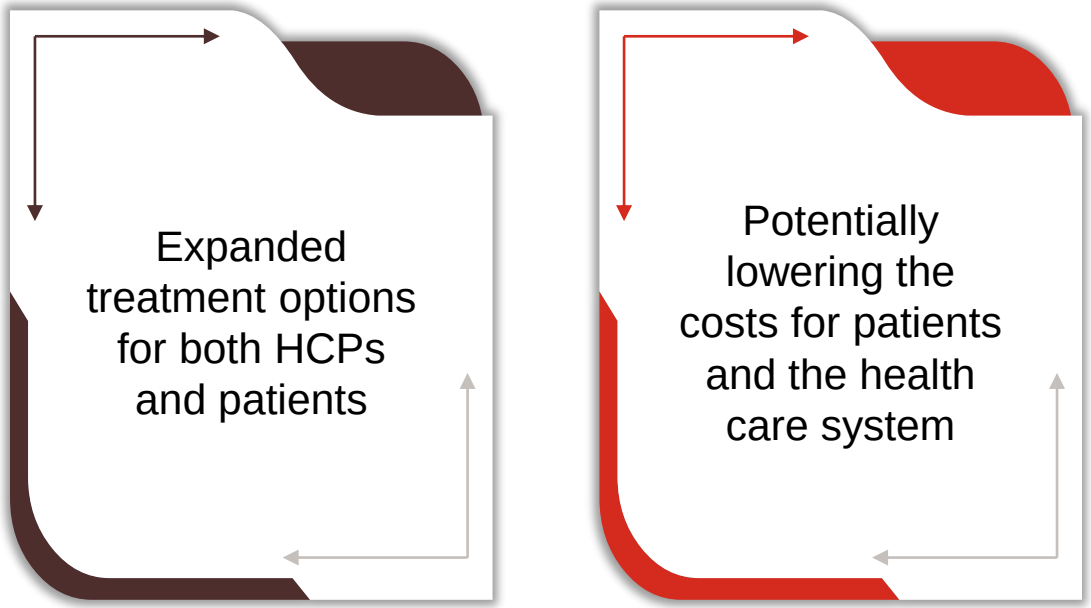
Interchangeable products can be used both in patients who have and have not previously received the reference product

Interchangeable products may have differences that impact personal preference between it and its reference product (eg, specific indication, delivery device)

For information about prescription and substitution laws, check with the state pharmacy board.

Food and Drug Administration. Biological Product Definitions. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108557/download

Benefits of Using Biosimilars & Interchangeable Products



Association of Diabetes Care & Education Specialists, The New Frontier of Interchangeable Biosimilar Insulins. Accessed August 26, 2022. https://www.diabeteseducator.org/docs/default-source/practice/educatortools/insulin/new_frontier_of_interchangeable_biosimilar_insulins.pd

Biosimilar Insulin Products in the US

Biological Products Nomenclature

As per the FDA, the biological products are named as:

- A unique suffix is to be designated for each originator biological product, related biological product, biosimilar product, and interchangeable product.

Franklin J. Biosimilar and Interchangeable Products: The U.S. FDA Perspective. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/112818/download

Approved Insulin Biosimilars

	Semglee® (insulin glargine-yfgn)[1,a]	Rezvoglar® (insulin glargine-aglr)[2,a]
Approval date	July 2021	November 2022
Reference product	Lantus® (insulin glargine)	Lantus® (insulin glargine)
Interchangeable	Yes	Yes
Available as	100 units/mL (U-100) available as: - 10 mL multiple-dose vial - 3 mL single-patient-use prefilled pen	100 units/mL (U-100) available as: - 3 mL single-patient-use prefilled pen

[a]An interchangeable product may be substituted for the reference product without the involvement of the prescriber, depending upon state pharmacy laws.[3]

1. Semglee. Prescribing information. Viatris. 2021.
2. Rezvoglar. Prescribing information. Eli Lilly and Company. 2021.
3. *Food and Drug Administration. Purple Book: Database of Licensed Biological Products. US Dept of Health and Human Services. Accessed August 26, 2022.* https://purplebooksearch.fda.gov

Conclusions

Conclusions

Biological products, including biosimilars, are regulated by the FDA.[1]

Biosimilars are biological products that are similar, but not identical, to a marketed reference product and have no meaningful differences in safety or effectiveness.[1]

An abbreviated approval process for biosimilar and interchangeable products is available in the US.[1,2]

The abbreviated approval process compares the proposed product to the reference product to show biosimilarity.[3]

Biosimilar manufacturing quality matters; processes that may influence quality and/or immunogenicity of biological products include protein production, purification, formulation, and storage & handling.[3]

Biosimilars insulins are an emerging therapeutic option.[4]

1. Food and Drug Administration. Biological Product Definitions. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108557/download.
2. White J, Goldman J. Biosimilar and follow-on insulin: the ins, outs, and interchangeability. J Pharm Technol. 2019;35(1):2-35
3. Food and Drug Administration. Biosimilar Regulatory Review and Approval. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151061/download
4. Davies M, Dahl D, Heise T, Kiljanski J, Mathieu C. Introduction of biosimilar insulins in Europe. Diabet Med. 2017;34:1340-1353

References

1. Association of Diabetes Care & Education Specialists, *The New Frontier of Interchangeable Biosimilar Insulins*. Accessed August 26, 2022. https://www.diabeteseducator.org/docs/default-source/practice/educator-tools/insulin/new_frontier_of_interchangeable_biosimilar_insulins.pdf
2. Christl L. *FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Overview-of-the-Regulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Products-in-the-US.pdf
3. Davies M, Dahl D, Heise T, Kiljanski J, Mathieu C. Introduction of biosimilar insulins in Europe. *Diabet Med*. 2017;34:1340-1353.
4. European Medicines Agency, European Commission. *Biosimilars in the EU – Information Guide for Healthcare Professionals*. European Medicines Agency. Accessed August 26, 2022. https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf
5. Food and Drug Administration. *Biological Product Definitions*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108557/download
6. Food and Drug Administration. *Biosimilar Product Regulatory Review and Approval*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108621/download
7. Food and Drug Administration. *Biosimilar Regulatory Review and Approval*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151061/download
8. Food and Drug Administration. *Interchangeable Biological Products*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/151094/download
9. Food and Drug Administration. *Prescribing Biosimilar Products*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/108103/download
10. Food and Drug Administration. *Purple Book: Database of Licensed Biological Products*. US Dept of Health and Human Services. Accessed August 26, 2022. https://purplebooksearch.fda.gov/
11. Franklin J. *Biosimilar and Interchangeable Products: The U.S. FDA Perspective*. US Dept of Health and Human Services. Accessed August 26, 2022. https://www.fda.gov/media/112818/download
12. Rezvoglar. Prescribing information. Eli Lilly and Company. 2021.
13. Semglee. Prescribing information. Viatris. 2021.
14. White J, Goldman J. Biosimilar and follow-on insulin: the ins, outs, and interchangeability. *J Pharm Technol*. 2019;35(1):2-35.