Sandoz
Biopharmaceuticals

From concept to reality

Sandoz Biosimilars

SANDOZ A Novartis Division

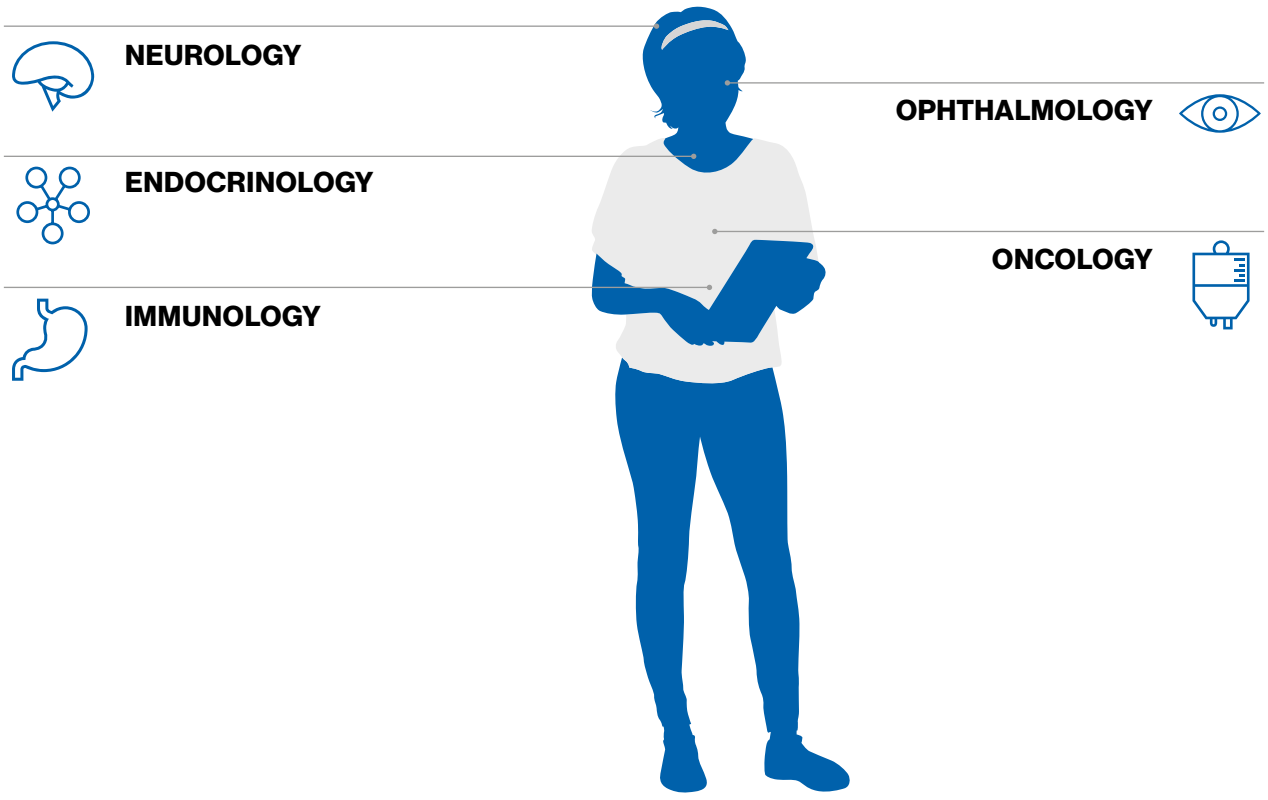
The basics of biosimilars

Biosimilars explained

Biologic medicines are developed using a complex process, as they are made by or extracted from living organisms, tissues, or cells.[1]

These medicines have revolutionized the treatment and prevention of many disabling and life-threatening diseases.[1]

A biosimilar is a successor to a biological medicine (also known as 'reference medicine') for which the patent has expired, and exclusivity has been lost. Biosimilars match the reference medicines in terms of quality, safety and efficacy.[2,3]



Did you know?

Innovation in scientific discovery and detection processes have enabled greater precision and sensitivity — for example, sensitivity for detection of peptides with mass spectrometry increased by 10 million-fold between 1990 and 2011 alone. Today's mass spectrometry capabilities enable complete amino acid sequencing of a monoclonal antibody preparation by one laboratory within days. These advancements have made it possible to develop biosimilars with identical amino acid sequences as the reference medicine at a more rapid rate.

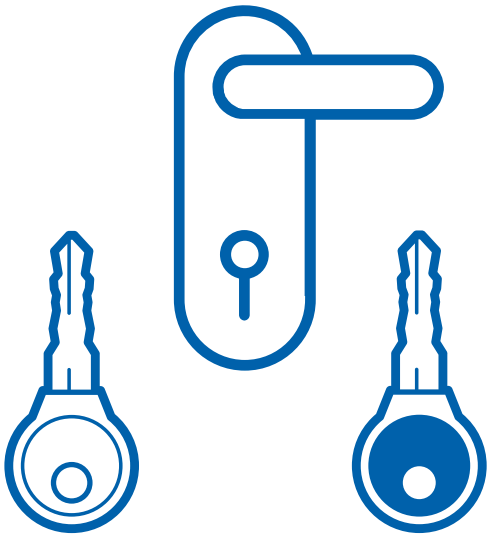
References:
1. European Medicines Agency and European Commission. Biosimilars in the EU: Information guide for healthcare professionals. 2019. Available from: Biosimilars in the EU – Information guide for healthcare professionals (europa.eu) [Accessed October 2022].
2. Weise M, *et al.* Biosimilars: what clinicians should know. *Blood* 2012;120:5111-7.
3. Kay J. A 'Wind of change' to biosimilars: the NOR-SWITCH trial and its extension. J Intern Med. 2019;285:693-5.

Biologics: reference medicines and biosimilars

Indistinguishable structure, same outcome

To be approved for use, a biosimilar must have equivalent efficacy and comparable safety and immunogenicity in patients as the reference medicine. Therefore, physicians and patients can expect the same clinical outcome.[1]

Biosimilars are approved via stringent regulatory pathways by the same regulatory authorities, such as the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) that approve reference medicines. They are manufactured with the same quality standards that are used for reference medicines.[2,3]



An original and a duplicate key – the same lock and door

Think of a reference biologic and a biosimilar like an original key and another version that a locksmith makes. Both keys produce the same result, both will fit the same lock and open the same door, even if there are slight differences between the original key and the new key. In the same way, an approved biosimilar can be expected to have the same safety and clinical outcome in patients as the reference medicine.[1,4,5]

References:
1. Kay, JA. A 'wind of change' to biosimilars: The NOR-SWITCH trial and its extension. Journal of Internal Medicine. 2019;285(6):693-5.
2. Food and Drug Administration. Information on Biosimilars. Available from: Slide 1 (fda.gov) [Accessed October 2022]
3. European Medicines Agency. Biosimilar medicines: Overview. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview [Accessed October 2022]
4. Kurki P et al. Interchangeability of biosimilars: A European perspective. BioDrugs. 2017;31(2):83-91
5. Barbier L., et al. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clinical Pharmacology and Therapeutics. 2020; 108(4):734-755.

Understanding biosimilar development

Variability of biologics

All biologics, whether reference medicine or biosimilar, are produced in living organisms. As a result of this and the complex manufacturing process, all biologics have a certain degree of inherent variability — no two batches are ever 100% identical.[1]

To manage this, any variation has to stay within precise ranges to maintain clinical safety and efficacy. These ranges are set and tightly controlled by both the regulatory authorities and the pharmaceutical company to ensure that all batches of any one biologic are delivering the same clinical outcome.[2,6]

Regulatory bodies such as the EMA and the US FDA will only approve a biosimilar if it is demonstrated that the biosimilar matches the reference medicine in terms of quality, safety and efficacy and that there are no clinically meaningful differences.[3,4]

EMA

"Comparable safety and efficacy of a biosimilar to its reference product has to be demonstrated or otherwise justified in accordance with the data requirements laid down in Directive 2001/83/EC"[5]

US FDA

"All FDA-approved biologics undergo a rigorous evaluation to ensure their safety, effectiveness, and quality."

"The approval process provides assurance that biosimilars provide the same treatment benefits as their respective reference products."[6]

Did you know?

Biologics may slightly change over time due to modifications made to the manufacturing process, as long as those changes do not affect clinical safety or efficacy. All biologics, whether reference medicines or biosimilars, are required to go through similarity testing whenever there is such a change in the manufacturing process to ensure that the new process yields a product that falls within the acceptable range of variability.[7]

References:
1. Weise M, *et al.* Blood. 2012; 120(26):5111-1117
2. European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available from: biosimilars_report_en.pdf (medicinesforeurope.com) [Accessed October 2022]
3. Food and Drug Administration. Information on Biosimilars. Available from: Biosimilar Product Regulatory Review and Approval (fda.gov) [Accessed October 2022]
4. European Medicines Agency. Biosimilar medicines: Overview. Available from: Biosimilar medicines: Overview | European Medicines Agency (europa.eu) [Accessed October 2022]
5. European Medicines Agency. Guideline on similar biological medicinal products. Available from: Guideline on similar biological medicinal products containing biotechnology-derived protiens as active substance (europa.eu) [Accessed October 2022]
6. Food and Drug Administration. Overview of Biosimilar Products. Available from: https://www.fda.gov/media/151058/download [Accessed October 2022]
7. Schiestl *et al.* Nature Biotechnol. 2011; 29:310

Robust development process

Demonstrating biosimilarity

The main goal in biosimilar development is to confirm biosimilarity, which means to confirm that the proposed biosimilar is therapeutically equivalent to its reference medicine.[1]

Therefore, analytical, functional and clinical studies are performed to demonstrate that the **biosimilar medicine** matches the reference medicine in terms of quality, safety and efficacy.

The stages of biosimilar development generate the totality of evidence, tailored to each molecule:

This is different to the development of reference medicines which focuses on establishing and proving clinical benefit.
Both approaches provide the same level of confidence with regard to safety and efficacy of the biologic.

Did you know?

A biosimilar has an identical amino acid sequence to the reference medicine.

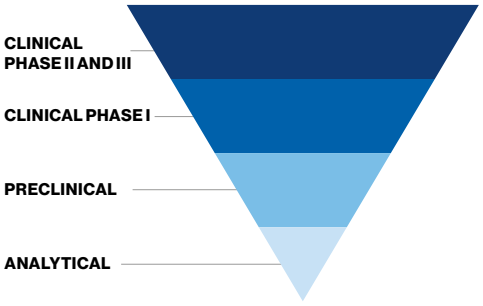
Stages of the biosimilar development program[1,2]:

Analytical
Extensive physicochemical characterization to establish 'sameness' of the biosimilar to the reference molecule e.g. in terms of molecular structure.

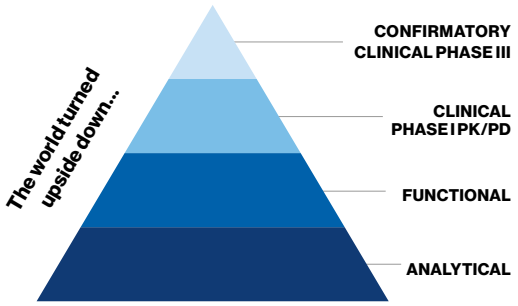
Functional
Extensive in vitro (cell culture) testing and biological characterization to demonstrate functional comparability of the biosimilar with the reference molecule.

Clinical PK/PD
Robust, comparative Clinical Phase I PK/PD studies in humans to determine bioequivalence i.e. that the biosimilar and the reference medicine will work in the body the same way.

Clinical Phase III
Clinical Phase III confirmatory safety and efficacy study conducted in a sensitive patient population to confirm that the safety and efficacy of the biosimilar matches the reference medicine.



REFERENCE MEDICINE DEVELOPMENT
Main goal is to determine the clinical benefit for each indication



BIOSIMILAR DEVELOPMENT
Main goal is to establish similarity to the reference medicine

References:
1. Weise M, et al. Biosimilars: What clinicians should know. Blood 2012;120:5111-1117
2. Kurki P. et al. Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience. Biodrugs 2022 36:359–371

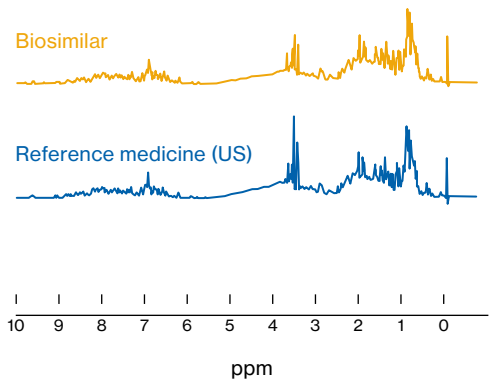
Totality of evidence

Completeness in data generated through biosimilar development

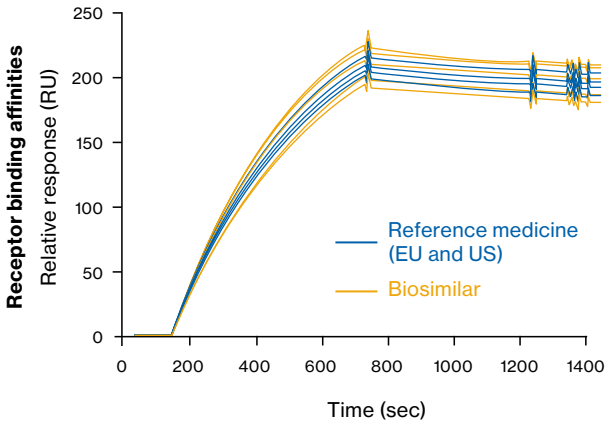
The totality of evidence is the data package generated from the biosimilar development program to show that the biosimilar matches the reference medicine in terms of structure, function, PK/PD profile, efficacy and safety.[1,2]

Totality of the evidence: Required to conclude whether a proposed biosimilar is approvable as a biosimilar

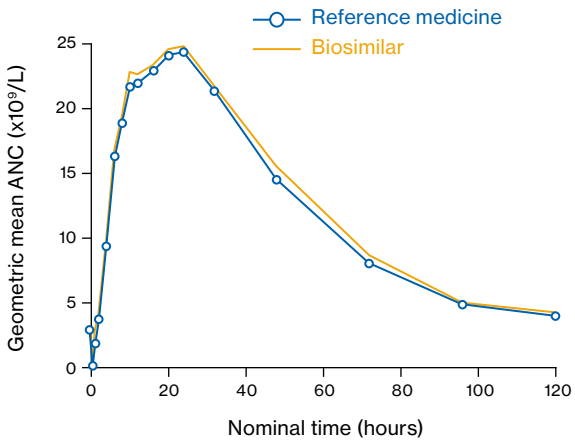
PRIMARY STRUCTURE[3]
(Magnetic resonance spectra)



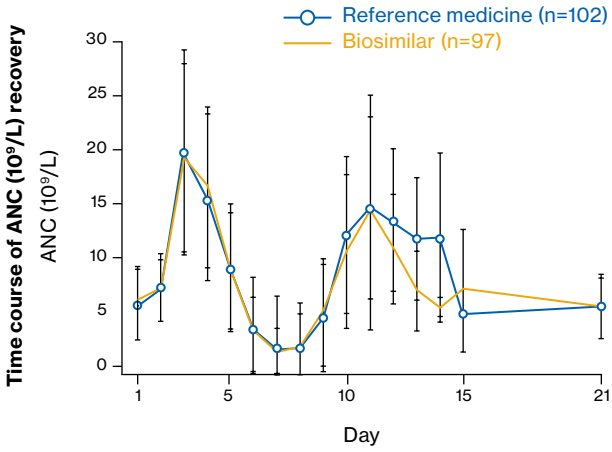
FUNCTION[3]



PHARMACODYNAMIC (PD)[3]



EFFICACY & SAFETY[4]



Schematic diagram showing the different levels of comparison of biosimilar and reference medicine, which form the 'totality of the evidence'. The examples shown here are from the development of biosimilar filgrastim. ANC, absolute neutrophil count; ppm, parts per million; RU, resonance units.

References:
1. Weise M, *et al.* Blood. 2012; 120(26):5111-1117
2. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. 2015. Available from: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry (fda.gov) [Accessed October 2022]
3. Sorgel F, et al. BioDrugs. 2015; 29:123-131
4. Blackwell K, et al. Ann Onc. 2015; 26:1948-1953

Extrapolation

A well-established scientific principle

Extrapolation is the scientific and regulatory process of granting a clinical indication to a medicine without conducting a clinical safety and efficacy study to support that indication.[1-3] It is regularly applied to maintain approval after major changes in the manufacturing process for any biologic or to introduce and approve new formulations.

From molecule to molecule

- Through its development program, the safety and efficacy of the reference medicine is assessed in every indication for which it is subsequently approved.[1]
- The biosimilar molecule matches the reference molecule. This is demonstrated through all the information generated in the biosimilar development program i.e. the totality of evidence.[4,5]
- Therefore, the biosimilar molecule can be expected to behave the same way as the reference molecule in all indications and patient populations that the reference medicine is approved in.[1]

Basic principle of extrapolation – The same molecule will behave the same way in all indications

Did you know?

Extrapolation to all approved indications of the reference medicine became typically a default characteristic of biosimilar medicines, based on the experiences in Europe and US.[4,5]

References:
1. European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available from: biosimilars_report_en.pdf (medicinesforeurope.com) [Accessed October 2022]
2. European Medicines Agency and European Commission. Biosimilars in the EU: Information guide for healthcare professionals. 2019. Available from: Biosimilars in the EU – Information guide for healthcare professionals (europa.eu) [Accessed October 2022].
3. Weise M et al. Biosimilars: The science of extrapolation, Blood VOLUME 124, NUMBER 22, 2014.
4. Food & Drug Administration. Biosimilar Development Process. Available from: Biosimilar Development Process (fda.gov) [Accessed October 2022]
5. EPAR Reports. Available from: Download medicine data | European Medicines Agency (europa.eu) [Accessed October 2022]

Real-world evidence

Biosimilars have consistently shown to work as expected

Over 2 billion patient days
of experience in Europe alone.[1]

More than
30 biosimilars approved in the US.[2]
80 biosimilars approved in Europe.[3]

The EMA's Information Guide for Healthcare Professionals states:[4]

"Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines."

All studies have shown that there is no increase in immunogenicity of biosimilars when compared to their reference medicines.[5,6]

References:
1. Medicines for Europe. Available from: The total clinical experience with biosimilar medicines exceeds 2 billion patient treatment days | Medicines for Europe [Accessed October 2022]
2. U.S. Food & Drug (FDA). Biosimilar Product Information. Available from: Biosimilar Product Information | FDA [Accessed October 2022]
3. GABI. Biosimilars approved in Europe. Available from: https://www.gabionline.net/biosimilars/general/biosimilars-approved-in-europe. [Accessed October 2022]
4. European Medicines Agency and European Commission. Biosimilars in the EU: Information guide for healthcare professionals. 2019. Available from: Biosimilars in the EU – Information guide for healthcare professionals (europa.eu) [Accessed October 2022]
5. McCamish M and Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther. 2012;91:405-17.
6. Kurki P, et al. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31:83-91

Realizing the potential

Biosimilars benefit patients, payors and healthcare professionals

Biologics have revolutionized the treatment of many serious, life-threatening, and chronic diseases; however their high costs place a significant burden on healthcare systems and sometimes hinder patient access.[1]

Biosimilar medicines have the potential to improve access for patients, contribute to healthcare systems sustainability, increase treatment options for healthcare professionals and stimulate innovation in development of next-generation biologics.

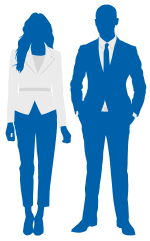
The benefits biosimilars can bring to healthcare systems depend on policies and systems implemented by countries' healthcare authorities.

Benefit to patients

The introduction of affordable, high-quality biosimilars can expand access to potentially life-changing medicines for patients worldwide.[2]

Innovation

Biosimilars introduce competition, which leads to innovation such as enhancements of existing medicines and development of new treatments.[3]



Benefit to payors

Biosimilars introduce competition, increasing affordability of biologics which delivers savings for healthcare systems, helping to liberate resources that can be used to improve care and fund next-generation medicines.

Up to $215 billion savings

Estimated to lead to cumulative savings over five years (2021-2026) worldwide.[4]

Benefit to HCPs

Introduction of biosimilars drives competition, resulting in increased treatment options and value-added services to support patient care and the healthcare community.[5]

120 new substances

Between 2021 and 2029, more than 120 biologic medicines will lose exclusivity—twice the number of biologics that have come off patent over the past decade.[6]

References:
1. Dutta, B., et al. Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price! BioDrugs (2019)
2. National Institute for Health and Care Excellence. NICE recommends several treatment options to help thousands with moderate rheumatoid arthritis. June 2021. Available from: NICE recommends several treatment options to help thousands with moderate rheumatoid arthritis | News and features | News | NICE [Accessed October 2022]
3. Vulto AG, et al. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020 Oct; 108(4): 734-755
4. IQVIA Institute for Human Data Science. Global Use of Medicines 2022. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/library/publications/the-global-use-of-medicines-2022.pdf. [Accessed October 2022]
5. Winegarden, W. Falling Prices: Biosimilar competition has saved billions of dollars, but policy changes can incentivize billions more. Pacific Research Institute, 2022.
6. IQVIA Institute for Human Data Science. The Impact of Biosimilar Competition in Europe. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/emea/the impact-of-biosimilar-competition-in-europe-iqvia.pdf [Accessed October 2022]

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