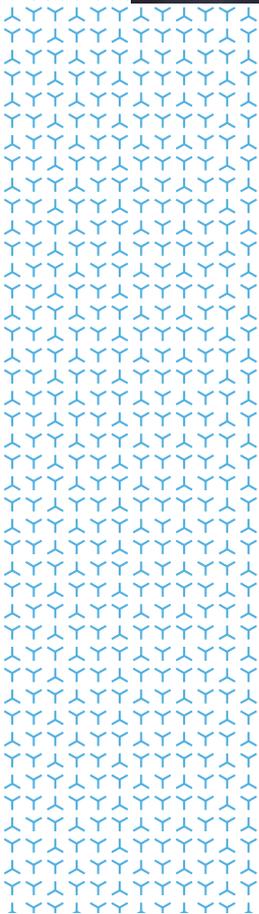


Sandoz
Biopharmaceuticals



From concept to reality

Sandoz Biosimilars



SANDOZ A Novartis
Division

The basics of biosimilars

Biosimilars explained

Biologic medicines are produced by a complex process involving living organisms¹.

These medicines have revolutionized the treatment and prevention of many disabling and life-threatening diseases¹.

A biosimilar is a follow-on medicine of an existing biologic (also known as 'reference medicines') when the patent has expired^{1,2}.

**GROWTH
DISORDERS**

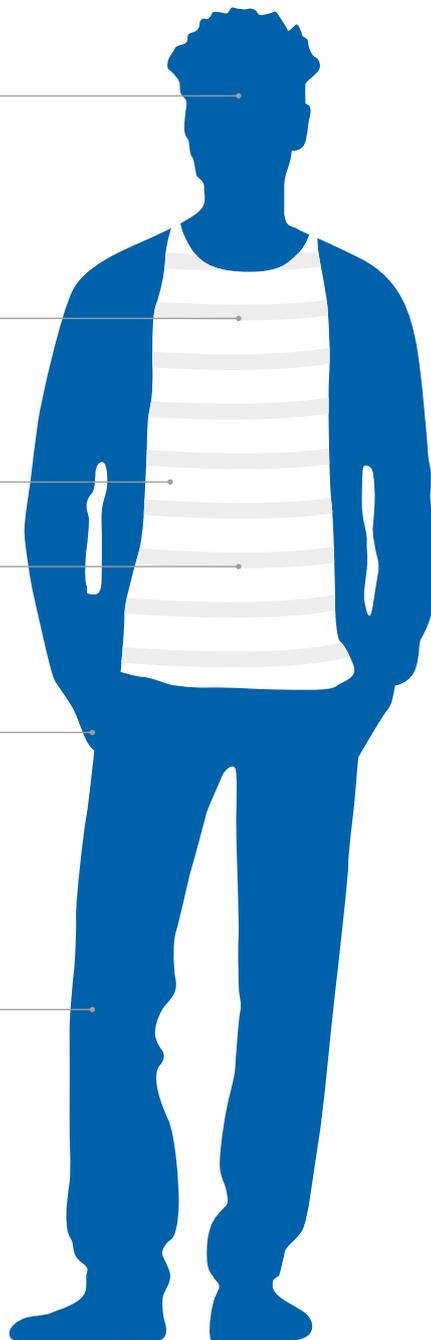
CANCER

DIABETES

**INFLAMMATORY
DIGESTIVE
DISEASES**

PSORIASIS

ARTHRITIS



References:

1. European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available from: <http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native> [Accessed July 2020]
2. Weise M, et al. Biosimilars: what clinicians should know. *Blood* 2012;120:5111-7

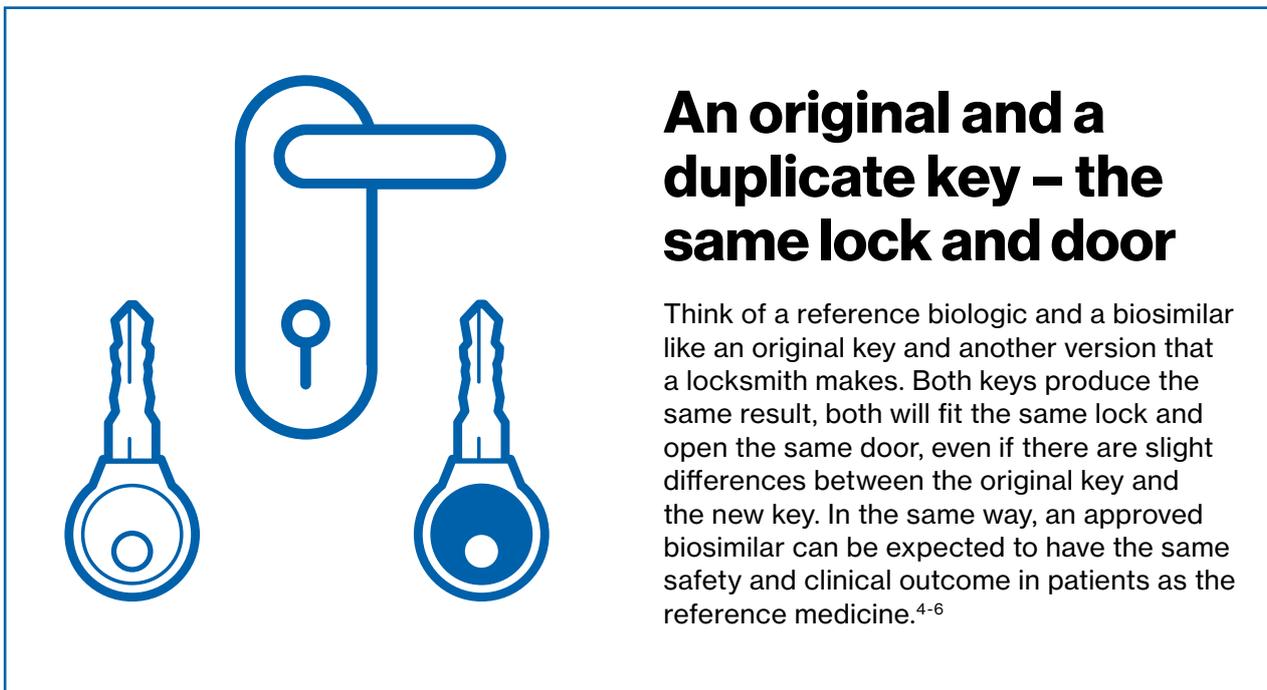
Biologics: reference medicines and biosimilars

Indistinguishable structure, same outcome

To be approved for use, a biosimilar has to match the reference medicine in terms of safety and efficacy in patients, demonstrating no clinically meaningful differences. This is done using advanced analytical, preclinical and clinical studies^{1,2}.

Biosimilars are approved via stringent regulatory pathways by the same regulatory

authorities, such as the European Medicines Agency (EMA) or the 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}.



References:

1. European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available from: <http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native> [Accessed July 2020]
2. Information on Biosimilars. FDA. Available from: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/> [Accessed July 2020]
3. European Medicines Agency. Biosimilar medicines: overview. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview> [Accessed July 2020]
4. Kurki P et al. Interchangeability of biosimilars: a European perspective. *BioDrugs*. 2017;31(2):83-91
5. Cohen HP et al. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs*. 2018;78(4):463-78.
6. Kay JA 'wind of change' to biosimilars: the NOR-SWITCH trial and its extension. *J Intern Med*. 2019;285(6):693-5

Understanding biosimilar development

Variability of biologics

All biologics, whether reference medicine or biosimilar, are produced from living organisms. As a result of this and the complex manufacturing process, they have a certain degree of inherent variability – no two batches are ever the same¹.

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 similar².

Regulatory bodies such as the EMA and the FDA will only approve a biosimilar if it demonstrated to have no clinically meaningful differences compared to the reference biologic, and therefore it can be expected to have the same safety and clinical outcome in the patient.^{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”

EMA, 2014⁵

FDA

“[Biosimilars can only be approved by the FDA if] there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”

US law (BPCIA)⁶

Did you know?

Biologics may slightly change over time due to modifications made to the manufacturing process. All biologics, whether reference medicines or biosimilars, are required to go through similarity testing whenever there is a change in the manufacturing process to ensure that the new process yields a product that falls within the acceptable range of variability⁷.

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: <http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native> [Accessed July 2020]
3. Information on Biosimilars. FDA. Available from: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/> [Accessed July 2020]
4. European Medicines Agency. Biosimilar medicines: overview. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview> [Accessed July 2020]
5. European Medicines Agency (EMA). Guideline on similar biological medicinal products. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf [Accessed July 2020]
6. Food and Drug Administration (FDA). Patient protection and affordable care act. Available from: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> [Accessed July 2020]
7. Schiestl et al. *Nature Biotechnol.* 2011; 29:310

Robust development process

Demonstrating biosimilarity

Analytical, preclinical and clinical pharmacokinetic/pharmacodynamic (PK/PD) studies demonstrate that the active substance in the biosimilar medicine matches the reference medicine. Final confirmation of biosimilarity requires a clinical Phase III confirmatory safety and efficacy study in a sensitive indication^{1,2}.

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 program²:

Analytical

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

Preclinical

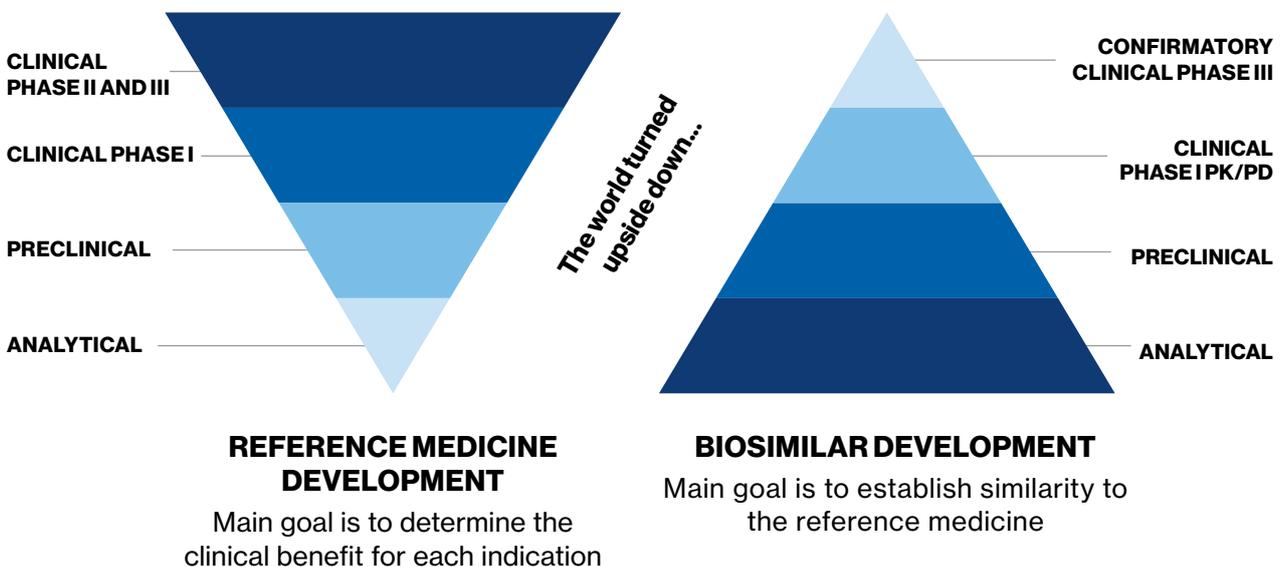
Functional studies to confirm biological function, for example mode-of-action, between the biosimilar and the reference molecule.

Clinical PK/PD

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.



References:

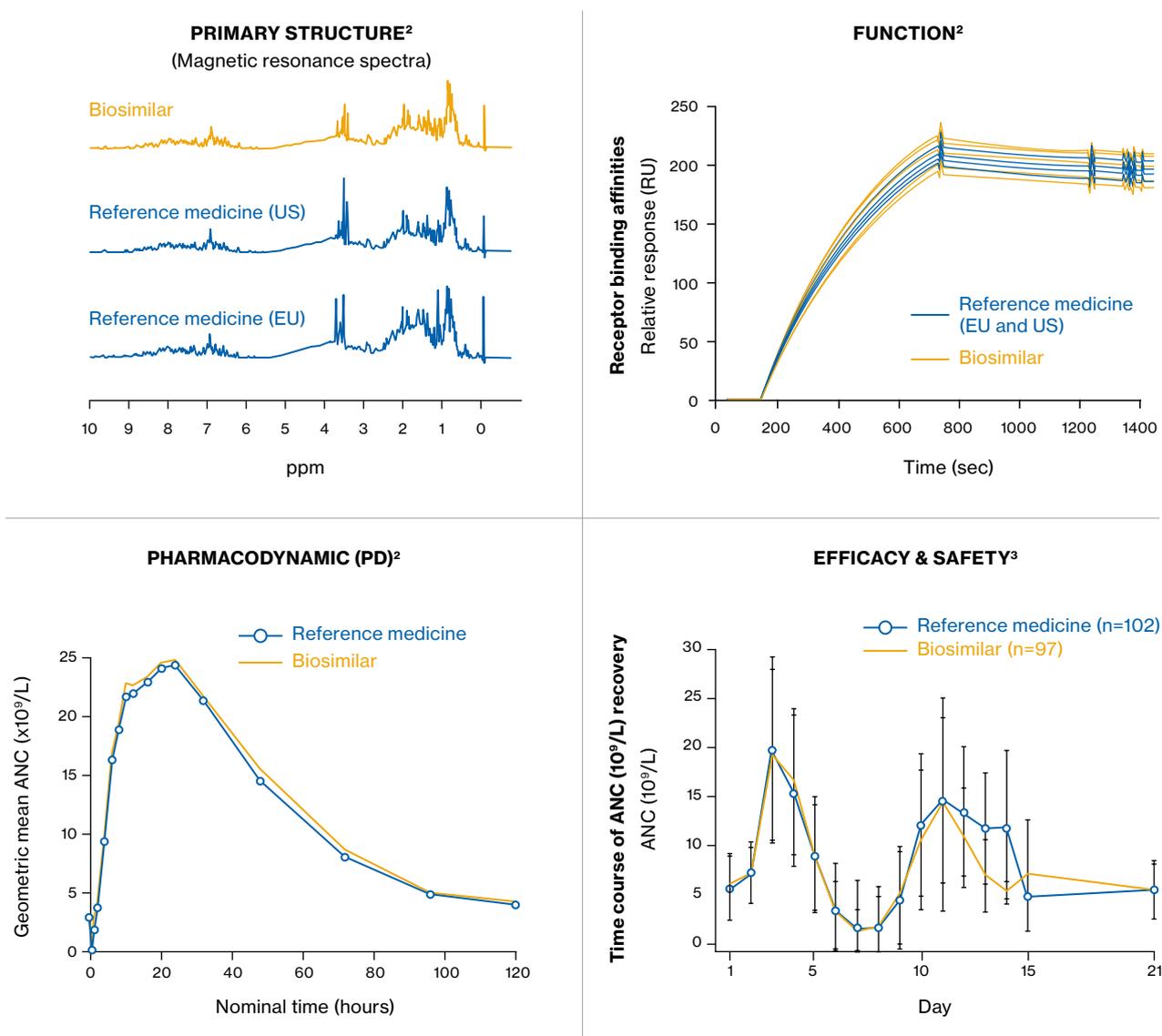
1. Lemery SJ, et al. *Clin Cancer Res.* 2010; 16(17):4331-4338
2. McCamish, M and Woollett, G. *Clin Pharmacol Ther.* 2012; 91(3):405-417

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 safety¹.

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



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. Strand *et al. Curr. Med. Res. Opin.* 2017; 33(6):993-1003
2. Sorgel F, *et al. BioDrugs.* 2015; 29:123-131
3. Blackwell K, *et al. Ann Onc.* 2015; 26:1948-1953

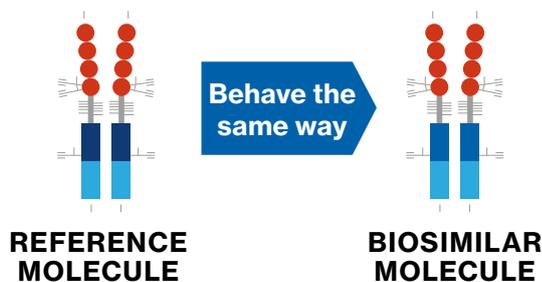
Extrapolation

From molecule to molecule

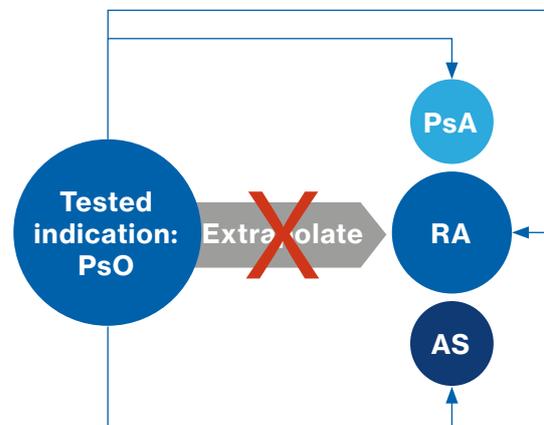
Extrapolation is the scientific and regulatory process of granting a clinical indication to a medicine without conducting a separate clinical efficacy and safety study to support that indication¹⁻³:

- Through its development program, the safety and efficacy of a reference medicine is assessed in every indication for which it is subsequently approved¹.
- 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^{1,2}.
- 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 medicines is approved in¹.

Extrapolation is from reference molecule to biosimilar molecule...



Extrapolation is not from indication to indication³.



Psoriasis (PsO)
 Psoriatic arthritis (PsA)
 Rheumatoid arthritis (RA)
 Ankylosing spondylitis (AS)

References:

1. European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available: <http://www.ec.europa.eu/DocsRoom/documents/8242>. [Accessed July 2020]
2. European Medicines Agency and the European Commission. Biosimilars in the EU: Information guide for healthcare professionals. April 2017. Available: <http://ec.europa.eu/DocsRoom/documents/22924>. [Accessed July 2020]
3. Weise M et al. Biosimilars: The science of extrapolation, Blood VOLUME 124, NUMBER 22, 2014

Realizing the potential

Biosimilars benefit patients, payors and healthcare professionals

Biologics have been developed for some of the most serious, life-threatening, and chronic diseases, however their high costs places a significant burden on the healthcare system and sometimes hinders patient access¹.

Biosimilar medicines have the potential to improve access challenges faced by patients, generate cost savings for healthcare communities and increase treatment options for healthcare professionals (HCPs), depending on policies and systems implemented by countries' healthcare authorities.



Benefit to patients

The introduction of affordable, high-quality biosimilars improves access to life-changing medicines for patients worldwide

100% increase ▲

The EU saw a 100% increase in use of biologic treatments after the introduction of biosimilars in the EU²



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

€49 - 98 billion savings

Cumulative savings over the next five years (2016-2021) in the EU5* and the US combined could range from 49 billion EUR to 98 billion EUR²



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

270 new substances

Between 2019 and 2023, 270 new active substances are set to come to market worldwide, with 35% expected to be biologics³

*EU5 countries include France, Germany, Italy, Spain and the United Kingdom

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. M. Aitken, Delivering on the Potential of Biosimilar Medicines report. IMS Institute Report. March 2016
3. IQVIA Institute for Human Data Science. The Global Use of Medicine in 2019 and Outlook to 2023. Published January 2019. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf?_=1590749942116. [Accessed July 2020]