How biosimilars are developed

The approval and manufacture of biosimilars in Europe and the US is strictly regulated[1–6]

Regulatory Health Authority approval of a biosimilar:

This is based on confirmation of comparable quality, safety and efficacy of the biosimilar to its reference biologic[1–3]

US FDA[2]

"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."

EMA[3]

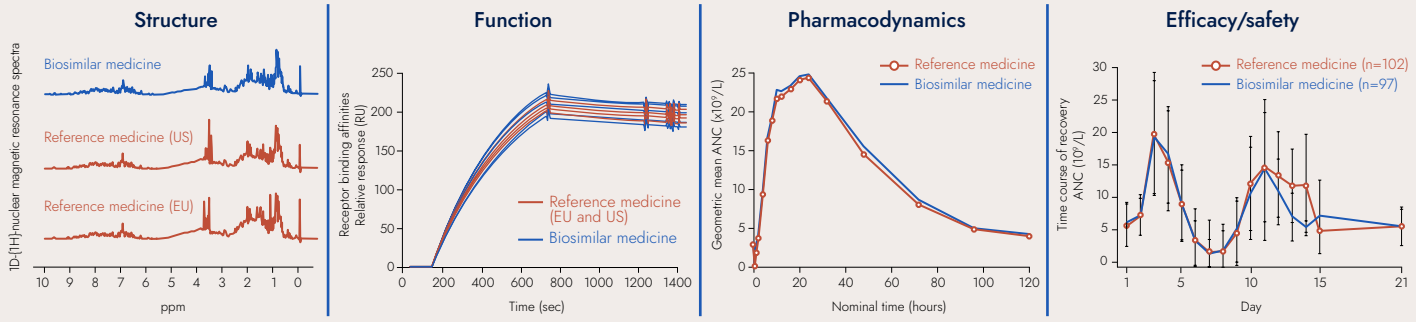
"Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU.

The aim of biosimilar development is to demonstrate biosimilarity – high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile."

Demonstrating biosimilarity:

A robust development process

Biosimilar approval is based on a robust stepwise structural and functional **comparability assessment** of the proposed biosimilar to the reference biologic.[2,3,6] The data collected are known as the **totality of evidence**; this demonstrates biosimilarity between the proposed biosimilar and its reference biologic in terms of **quality, safety, and efficacy.**[3,4,7] Therefore, physicians and patients can expect the **same clinical outcome.**[1,3,7]



Figures reproduced from: Sorgel F, et al. BioDrugs 2015;29(2):123–131; Blackwell K, et al. Ann Onc 2015;26(9):1948–1953.

Totality of Evidence

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

Figures adapted from: Chang S, Hanauer S. Curr Treat Options Gastroenterol 2017;15(1):53–70; McCamish M and Woollett G. Clin Pharmacol Ther 2012;91(3):405–417.

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Extrapolation:

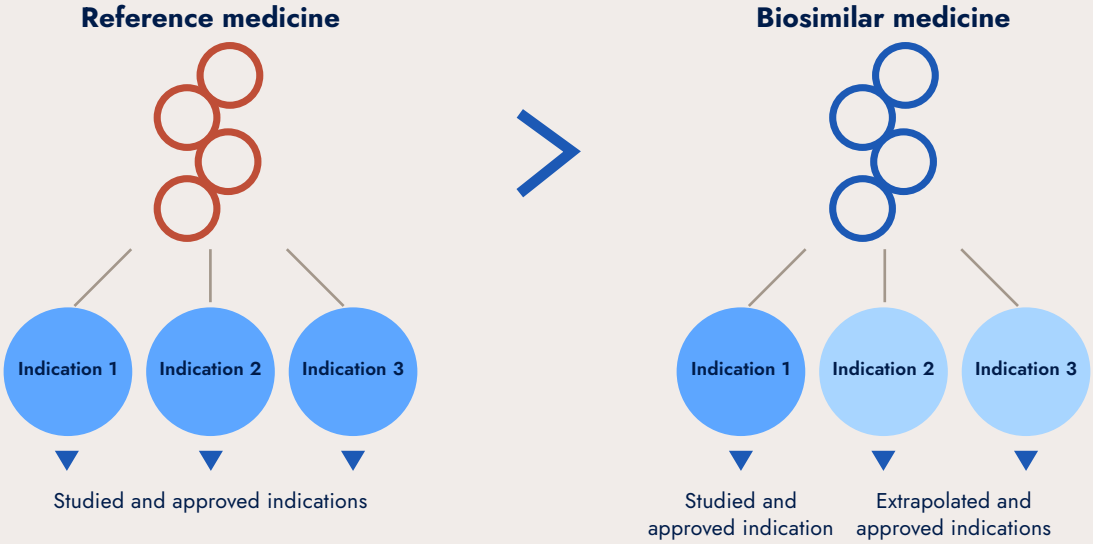
A well-established scientific principle[3]

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.[3,6–8]

A reference biologic may be approved in several indications and must show **clinical benefit** in every therapeutic indication.[6]

However, if a **biosimilar** shows **comparable totality of evidence** to its **reference medicine** for **one indication...**

...the **totality of evidence** may be used to **support approval of the biosimilar,** without direct study, for **other indications** in which the **reference medicine is approved.**[3,7–9]



The biosimilar molecule can be expected to behave the same way as the reference molecule in all indications and patient populations that the reference biologic is approved in.[10]

Manufacturing rigor:

Biosimilars are manufactured using the same quality standards used for the reference biologic, in accordance with **Current Good Manufacturing Practice** requirements.[1,3,5,6]

This includes strict controls around methods, facilities, manufacturing, processing and storage that ensures quality of biosimilar and reference biologic medicines.[5]

ANC, absolute neutrophil count; EMA, European Medicines Agency; US FDA, US Food and Drug Administration; PD, pharmacodynamics; PK, pharmacokinetics; ppm, parts per million.

1. Weise M, et al. Blood 2012;120(26):5111–5117. **2.** FDA. Overview of Biosimilar Products. Available at: https://www.fda.gov/media/151058/download. Accessed May 11 2022. **3.** EMA. Biosimilars in the EU. Available at: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Accessed May 11 2022. **4.** Strand V, et al. Curr Med Res Opin 2017;33(6):993–1003. **5.** FDA. CGMP regulations. Available at: https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations. Accessed May 11 2022. **6.** FDA. Guidance document, 2015. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product. Accessed May 11 2022. **7.** FDA. Biosimilar development, review and approval. Available at: https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Accessed May 11 2022. **8.** Weise M, et al. Blood 2014;124(22):3191–3196. **9.** Chang S, Hanauer S. Curr Treat Options Gastroenterol 2017;15(1):53–70. **10.** European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2016/03/biosimilars_report_en.pdf. Accessed May 11 2022.

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