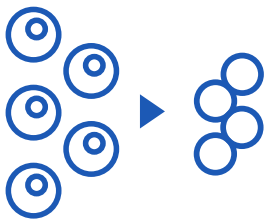
# Exploring biologic and biosimilar medicines and how they differ from other medicine groups

## Biologics: Reference and biosimilar medicines

### Biologic medicines are large, complex molecules whose active component is derived from bacteria or yeast, or from living mammalian or plant cells[1–3]

The active component of biologic medicines is made to **interact exactly with a specific target** in the human body[4]



**Living cells are naturally variable**; for this reason, the active component of all **biologic medicines** can have a degree of **inherent variability**[3,5]

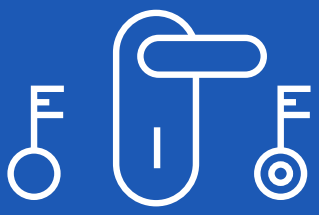
As a result of this variability, **there can be structural differences between batches** and no two batches of any biologic medicine are ever 100% identical[3–5] Therefore, minor variability is normal, expected and tightly controlled[3,5]

**Reference biologic medicine**

A **biosimilar medicine is a biologic medicine** and a **successor to a reference** ('originator' or 'original-brand') **biologic medicine** for which the patent and exclusive marketing rights have expired[3,6]

**Biosimilar medicine**

A biosimilar medicine matches its reference medicine, and has **no clinically meaningful differences in terms of purity, safety, and effectiveness** to an existing US FDA- or EMA-approved reference biologic medicine[3,6]



Similar to the original key and a replica of the key that a locksmith can make, an approved biosimilar and its reference biologic medicine can be expected to have the **same safety and clinical outcome in patients**[3,7]

Biosimilar approval is based on a robust structural and functional comparability assessment of the proposed biosimilar medicine to its reference biologic medicine[4,7]

The data collected are known as the totality of evidence; this demonstrates biosimilarity between the biosimilar medicine and its reference biologic medicine in terms of safety, efficacy, and immunogenicity[3,6]

As for all biologic medicines, once biosimilars are approved by regulatory agencies and enter the market, their safety profile continues to be monitored throughout the medicine's life cycle.[3,6]

### Because of inherent variability, strict manufacturing processes for all biologic medicines (be it the reference or biosimilar biologic medicine), ensure that:[3,5,8]

**Efficacy, safety and quality** are maintained

There is **consistency** across batches

The treatment **works the same way** each time

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# A closer look at different medicine groups

## Small molecule medicine[1,3,9,10]

**Example: Teriflunomide[11]**

- **Production:** Chemical synthesis
- **Molecular composition:** Single well-defined molecule
- **Successor:** Generic small molecule medicine
  - A generic small molecule medicine is a copy of a reference small molecule medicine that is made once the patent has run out on the reference. Identical copies can be made due to the simple chemical composition of small molecule medicines[11]
  - Example: Generic teriflunomide[11]

## Non-biological complex drug (NBCD)[1,3,9]

**Example: Glatiramer acetate[11]**

- **Production:** Chemical synthesis
- **Molecular composition:** Multiple molecules of different sizes
- **Successor:** Generic NBCD
  - A generic NBCD is a successor to a reference NBCD for which the patent has run out. A generic NBCD will not be identical to its reference NBCD due to its complex chemical composition[11]
  - Example: Generic glatiramer acetate[11]

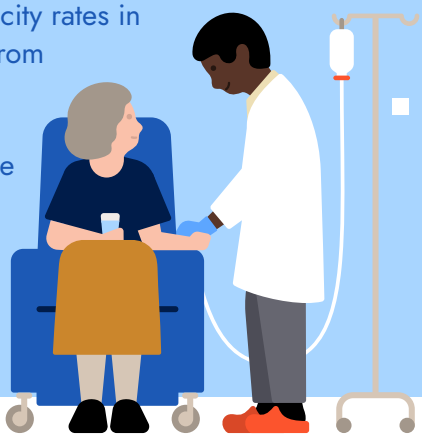
## Biologic medicine[1,3,9,10]

**Example: Natalizumab[11]**

- **Production:** Living cells or organisms
- **Molecular composition:** Complex and large composition made of single/multiple active substance(s)
- **Successor:** Biosimilar medicine
  - Because of the inherent variability of all biologics, it is not possible to create an identical version of a biologic medicine, even between reference medicine batches. Successors to reference biologic medicines are called 'biosimilars' that match their reference medicine in terms of safety and efficacy[11]
  - Example: Biosimilar natalizumab[11]

## Switching and biosimilars

- The term 'switching' can be used to describe the process by which a prescriber decides to exchange one medicine for another medicine with the same therapeutic intent[3,12]
- An extensive systematic review and meta-analysis of 31 studies for 21 biosimilars (N=5,252) by the FDA found no difference in safety or immunogenicity rates in patients switched to or from a biosimilar medicine, compared to those remaining on a reference or biosimilar medicine across various biosimilars and therapeutic areas[13]



## The nocebo effect

- Patients can sometimes experience the 'nocebo effect', considered as the opposite of placebo effect[14,15]
- The nocebo effect occurs when a negative context surrounding a treatment (e.g. a person's negative expectations or anxiety) can lead to unwanted side effects which may not be related to the therapy itself[14,15]
- In the context of biosimilars, educating patients on how the same clinical outcomes can be expected with both reference biologic and biosimilar medicines, empowers patients about their treatment decision and might help mitigate the nocebo effect[16]

EMA, European Medicines Agency; MS, multiple sclerosis; NBCD, non-biological complex drug; US FDA, US Food and Drug Administration.

**1.** Zhao L, et al. Acta Pharmacol Sin 2012;33(11):1339–1347; **2.** World Health Organization. Biologicals. Available at: https://www.who.int/health-topics/biologicals#tab=tab_1. Accessed June 2024; **3.** EMA and EC Biosimilars in the EU. 2019. Available at: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Accessed June 2024; **4.** European Commission. What you need to know about biosimilar medicinal products. 2013. Available at: https://ec.europa.eu/docsroom/documents/8242. Accessed June 2024; **5.** US FDA. Biological Product Definitions. Available at: https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf. Accessed June 2024; **6.** US FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Available at: https://www.fda.gov/media/82647/download. Accessed June 2024; **7.** Webster CJ, et al. BioDrugs 2019;33(6):603–611; **8.** Research Advocacy Network. Available at: https://researchadvocacy.org/sites/default/files/resources/Biosimilar%20Medicines6_4Final.pdf. Accessed June 2024; **9.** Crommelin DJA, et al. Eur J Pharm Sci 2015;76:10–17; **10.** Declerck PJ. GaBI Journal 2012;1(1):13–16; **11.** Greenberg B, Giovannoni G. Mult Scler Relat Disord 2023;77:104841; **12.** Mysler E, et al. Drugs 2021;81(16):1859–1879; **13.** Herndorn TM, et al. PloS One 2023; 3;18(10):e0292231; **14.** Weissenfeld J, et al. Die Pharmazie - An International Journal of Pharmaceutical Sciences 2010;65(7):451–456; **15.** Faasse K, et al. Front Psychiatry 2019;10:396; **16.** Pouillon L, et al. Expert Rev Clin Immunol 2018;14(9):739–749.

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