Demystifying the language of biologic and biosimilar medicines: A glossary

Index

SANDOZ

Demystifying the language of biologic and biosimilar medicines: A glossary

A Analytical and functional characterization

Analytical and functional characterization is a technical process that enables the detailed identification of a molecule's most basic structural features.[1]

When developing a new reference biologic medicine, analytical and functional characterization is used to provide data for the first time on how the new medicine is chemically structured and may interact with body cells.[2]

For a biosimilar medicine, analytical and functional characterization is instead used to show that the biosimilar matches the chemical structure of the reference biologic; this includes proving that the biosimilar and its reference medicine have an identical amino acid sequence and indistinguishable three-dimensional shape (namely, how the protein folds).[3,4]

Additional note: Analytical and functional characterization of biosimilar medicines is done using state-of-the-art techniques that are able to detect very small structural differences between a biosimilar and its reference medicine[1]

B Biologic medicine

Biologic medicines are medicines in which the active component, i.e. the part of the medicine that has a therapeutic effect in the body, is made from bacteria or yeast, or from living mammalian or plant cells.[5]

Biologic medicines can be antibodies, such as monoclonal antibodies, or complex proteins, such as cytokines and growth hormones.[5]

Additional note: Examples of biologic medicines used in the treatment of multiple sclerosis include alemtuzumab, ocrelizumab, and natalizumab[6]

Additional note: Due to the natural variability of living cells, slight structural differences naturally exist between batches of biologic medicines during their manufacture, a property known as 'inherent variability' (see **'Variability'**)[3,4]

B Biosimilarity

Biosimilarity is a term used to describe that a biosimilar medicine (see '**Biosimilar medicine**') matches its reference medicine (see '**Reference medicine**') and that there are no clinically meaningful differences between them in terms of safety, efficacy, and immunogenicity.

Additional note: Biosimilarity is established using a collection of analytical, preclinical, and clinical data (see **'Totality of Evidence'**)[3,4]

B Biosimilar medicine

A biosimilar medicine is a biologic medicine and a successor to a biologic 'reference' medicine for which the patent and exclusive marketing rights have expired.[3,4] To be approved for use, a biosimilar must have equivalent efficacy and comparable safety and immunogenicity in patients to the reference medicine. Therefore, physicians and patients can expect the same clinical outcome.[3,7]

It is important to note that, while biosimilar medicines are developed to match their reference medicine, slight structural differences naturally exist between batches of biologic medicines, due to the natural variability of living cells.[3,4]

Synonyms: Successor biologic; Follow-on biologic

Additional note: The terms 'successor' and 'follow-on' can be used in relation to a biosimilar medicine and also when referring to generic medicines, e.g. 'a successor small molecule medicine'; 'a follow-on non-biological complex medicine'

Additional note: An example of an approved biosimilar medicine used in the treatment of multiple sclerosis is biosimilar natalizumab[8,9]

Demystifying the language of biologic and biosimilar medicines: A glossary

E Extrapolation

If biosimilarity between a biosimilar medicine and its reference medicine has been proved in one indication through the Totality of Evidence approach (see **'Totality of Evidence'**), then approval of that biosimilar medicine can be extended to other indications the reference medicine is approved in, without the need for additional specific studies in those other indications. This scientific and regulatory process is called extrapolation.[3,4]

G Generic medicine

A generic medicine is a small molecule or non-biological complex medicine that is developed as a successor to a reference small molecule or non-biological complex drug for which the patent and exclusive market rights have expired. The generic medicine must have the same clinical benefit, safety profile, and work in the body in the same way as the reference medicine.[6,10,11]

Synonyms: Successor small molecule medicine/non-biological complex drug; Follow-on small molecule medicine/non-biological complex drug

Additional note: Examples of small molecule medicines with generic options used in the treatment of multiple sclerosis include fingolimod and dimethyl fumarate. Glatiramer acetate is an example of a non-biological complex drug with a generic option for the treatment of multiple sclerosis (see **'Non-biological complex drugs'**)[6]

I Immunogenicity

Immunogenicity can be described as the ability of a molecule to induce an immune response after it is introduced to the body. This is the body's defensive mechanism to respond to and destroy a substance that can seem foreign and harmful, for example bacteria, a virus, or a medicine that is used to target the body's immune system.[12]

Additional note: Immunogenicity is a principal concern for all therapeutic proteins, whether it is a reference biologic or a biosimilar. All biologics have the potential to elicit an immune response, including both reference medicines and biosimilars[3,4,13]

N Nocebo

Patients can sometimes experience the 'nocebo effect', considered as the opposite of a placebo effect. 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 are not related to the treatment itself.[14]

Additional note: The nocebo effect is quite common in healthcare, and despite being difficult to quantify, it can be minimized through education. For example, in the context of biosimilars, educating patients on how the same clinical outcomes can be expected with both reference and biosimilar medicines empowers patients about their treatment decision and might help mitigate the nocebo effect[14]

Demystifying the language of biologic and biosimilar medicines: A glossary

N Non-biological complex drugs

Non-biological complex drugs are medicines that have many characteristics in common with biologic medicines but that are manufactured synthetically (while biologics are made from living cells). The active component of a non-biological complex drug contains many molecules of different sizes which cannot be fully characterized. For this reason, the manufacturing process for these medicines is strictly regulated.[15]

Additional note: Non-biological complex drugs can sometimes be confused with biologic medicines. An example of this is glatiramer acetate, which is a non-biological complex drug but is often misdescribed as a biologic medicine. Likewise, successor/follow-on glatiramer acetate is not a biosimilar medicine but a generic non-biological complex drug[6,7]

P Pharmacodynamics

This term comes from two ancient Greek words: 'drug' (pharmakon) and 'power' (dynamikos). It means the study of the molecular, biochemical, and physiologic effect that a medicine has when interacting with its molecular target; in other words, what does the medicine do to the body?[16]

P Pharmacokinetics

This term comes from two ancient Greek words: 'drug' (pharmakon) and 'relating to motion' (kinētikos). It means the study of the body's response to a molecule moving across it, namely the absorption, distribution, metabolism, and excretion of the molecule; in other words, what does the body do to the medicine?[17]

P Phase I study

While a Phase I study for a reference medicine is done to establish the pharmacokinetic and pharmacodynamic aspects of the medicine, a Phase I study for a biosimilar medicine is performed to show the biosimilar medicine has a matching pharmacokinetic and pharmacodynamic profile to its reference medicine.[3,4,18]

Additional note: Pharmacokinetic and pharmacodynamic parameters are usually considered more relevant than clinical efficacy endpoints when investigating a biosimilar medicine[3,4]

P Phase II study

A Phase II study for a reference medicine is performed to determine whether the medicine is sufficiently effective in a small population of patients in order to be tested in a larger population during a Phase III study (see **'Phase III study'**). Phase II studies usually also help establish the optimal dose a medicine should be given at and how frequently.[18]

For biosimilar medicines, a Phase II study is usually not required because the effectiveness and therapeutic dose have already been established for the reference medicine. Therefore, once the biosimilar medicine has been proven to match the structure and pharmacokinetic/pharmacodynamic profile of the reference biologic medicine via analytical and functional characterization and a Phase I study (see **'Analytical and functional characterization'** and **'Phase I study'**), the biosimilar medicine can directly be tested in a Phase III study in the relevant patient population if applicable.[3,4,6]

Demystifying the language of biologic and biosimilar medicines: A glossary

P Phase III study

A Phase III study for a reference medicine is designed to establish that the medicine is safe and efficacious in a very large sample of the patient population it is intended for.[18] A Phase III study for a biosimilar medicine is instead designed to show that the biosimilar medicine has the same effect on patients as the reference medicine. This is done by proving that the biosimilar medicine matches its reference medicine when it comes to efficacy, safety, and immunogenicity in the studied population.[3,4]

Additional note: Unlike reference medicines, only one indication of the new biosimilar medicine needs to be studied, and approval can be 'extrapolated' (see **'Extrapolation'**) to any other indications treated by the reference medicine[3,4]

R Reference medicine

A reference medicine is the name given to a medicine that has already been approved by the European and/or US regulatory agencies for which a biosimilar or generic medicine is being developed.[3]

Synonyms: Originator; Original-brand; Existing

S Switching

Switching describes a change in therapy from one treatment to another that has the same therapeutic intent.[3,4]
Switching can happen:

1. Between two different treatments, for example when the person being treated is experiencing side effects or a lack of effectiveness with the current medicine.[18]
2. Between two versions of the same treatment, as can be done between a reference and biosimilar medicine. In this case, the goal may be to decrease treatment costs and improve patient access while maintaining treatment efficacy.[3,7,19]

Additional note: In therapeutic areas such as some cancers, psoriasis, inflammatory bowel disease, and rheumatoid arthritis, switching between a reference and a biosimilar medicine is an established process and it has been shown to have no impact on treatment outcomes via extensive experience[20]

T Totality of Evidence

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, pharmacokinetic/pharmacodynamic profile, efficacy and safety. This comprehensive data package is required by health authorities to grant approval of a biosimilar medicine.[3,4]

Demystifying the language of biologic and biosimilar medicines: A glossary

V Variability

All biologics, whether reference medicine or biosimilar, are produced in living organisms.[3] As a result of this and the complex manufacturing process, all biologics have a certain degree of inherent variability.[3,21,22]

This means that there may be some small differences between different batches of the same biologic reference medicine, between a biosimilar medicine and its reference, and between different batches of the same biologic biosimilar medicine — no two batches are ever 100% identical. These minor differences are not clinically meaningful, and strict controls are used to make sure they do not affect the way the medicine works or its safety.[3,22]

Additional note: Interestingly, because the characteristic of variability belongs to all biologic medicines, it can be said that with time, as more batches of a biologic 'reference' medicine are produced, the reference medicine becomes a biosimilar of itself

MS, multiple sclerosis; US, United States.

1. Kirchhoff C, et al. Biotechnology and Bioengineering 2017;114(12):2696–2705; **2.** Horien C and Yuan P. Yale J Biol Med 2017;90(1):1–3; **3.** EMA. Guide to biosimilars for healthcare professionals. Available at: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Accessed March 2023; **4.** US FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Available at: https://www.fda.gov/media/82647/download. Accessed March 2023; **5.** Zhao L, et al. Acta Pharmacol Sin 2012;33(11):1339–1347; **6.** Greenberg B, Giovannoni G. Mult Scler Relat Disord 2023;77:104841. **7.** US FDA. Information on Biosimilars. Available at: https://www.fda.gov/drugs/biosimilars/review-and-approval. Accessed March 2023; **8.** Sandoz Inc. Tyruko® (Natalizumab-sztn). Prescribing Information, 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761322s000lbl.pdf. Accessed October 2023; **9.** Sandoz GmbH. Tyruko® (natalizumab). Summary of product characteristics, 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/tyruko-epar-product-information_en.pdf. Accessed October 2023; **10.** EMA. Generic and hybrid medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines. Accessed March 2023; **11.** US FDA. Generic drugs: Questions & Answers. Available at: https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers. Accessed March 2023; **12.** Mahanty S, et al. BMC Immunol 2015;16(31):1–6; **13.** Shakhnovich V, et al. Clin Transl Sci 2020;13(2):219–223; **14.** Spanou I, et al. Front Pharmacol 2019;10:809; **15.** Crommelin DJA, et al. Eur J Pharm Sci 2015;76:10–17; **16.** Marino M, et al. Pharmacodynamics. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing, 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507791/. Accessed March 2023; **17.** Saghir SA and Ansari RA. Pharmacokinetics. In: Reference module in Biomedical Sciencies. Elsevier, 2018. Available at: https://www.sciencedirect.com/science/article/pii/B9780128012383621542. Accessed March 2023; **18.** Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development. Development of New Therapeutic Drugs and Biologics for Rare Diseases; In: Field MJ and Boat TF (eds). Rare Diseases and Orphan Products: Accelerating Research and Development. National Academies Press (US), 2010. ISBN-13:978-0-309-15806-0; **19.** Mysler E, et al. Drugs 2021;81(16):1859–1879; **20.** Cohen HP, et al. Drugs 2018;78(4):463–478; **21.** Vezér B, et al. Curr Med Res Opin 2016;32(5):829–834; **22.** Weise M, et al. Blood 2012;120:5111–5117

The contents of this training were co-created and approved by an international advisory committee of experts in MS nursing and nurse education, and sponsored by Sandoz.

MLR ID: 316061 | Date of preparation: February 2024

SANDOZ

Index