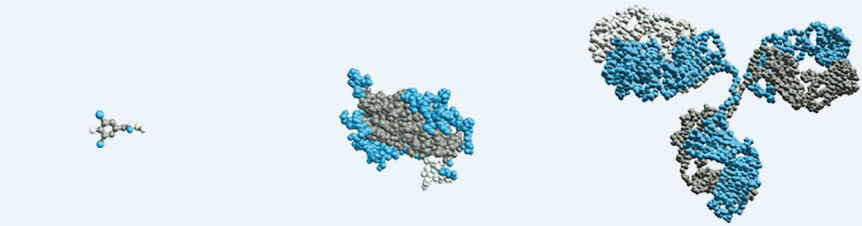
Important Facts

Health Care Professionals Should Know About Biosimilars

Biosimilars: Defining Characteristics

Biosimilars are highly similar versions of reference biologics, with no clinically meaningful differences in terms of safety, purity, and potency.[1]

Biologics, including biosimilars, are more complex than small molecules.[2-5]

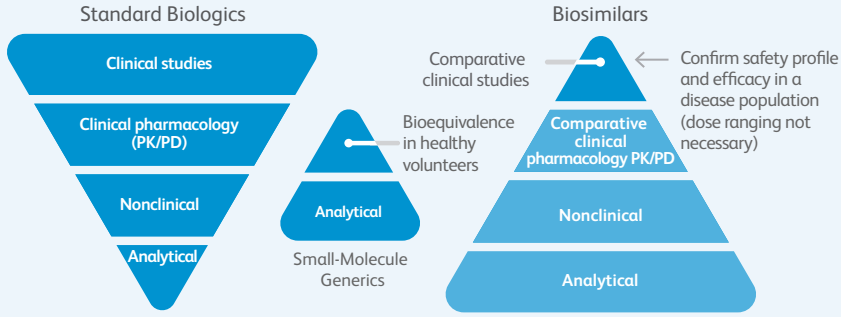


While small-molecule generics are chemically synthesized, biosimilars (and reference biologics) are created in living cells and require significant expertise and state-of-the-art technology to manufacture and produce.[3,6]

Development of Biosimilars

Providing a change in thinking from how reference biologics are evaluated, the US Food and Drug Administration (FDA) evaluates biosimilars based on a totality-of-evidence approach.[1,7,8]

DEVELOPMENTAL PATHWAYS[1,7-11]



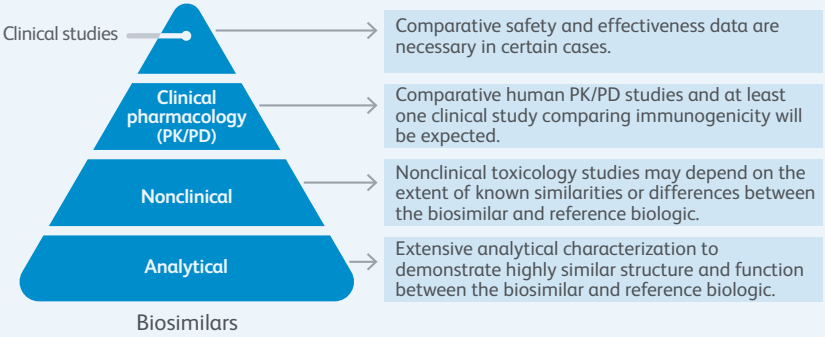
PK, pharmacokinetic; PD, pharmacodynamic.

The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences between the proposed biosimilar and the reference biologic—not to reestablish the clinical benefit of the reference biologic.[1]

The Totality of Evidence

The FDA approval process evaluates the totality of evidence to ensure biosimilar quality, efficacy, and safety.[1]

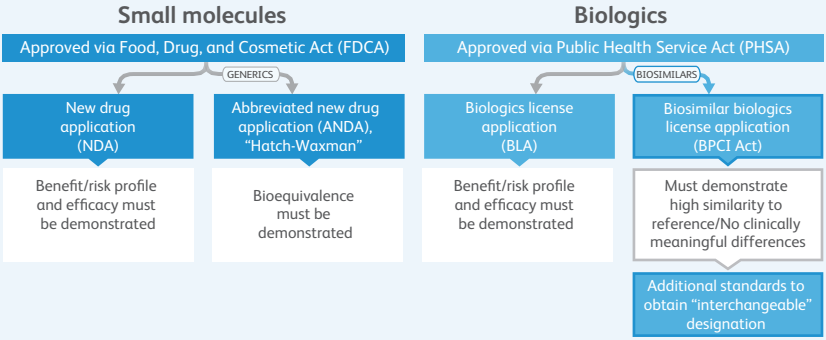
THE TOTALITY OF EVIDENCE: A STEPWISE APPROACH[1]



Approval Pathway for Biosimilars

Biosimilars may be approved through an abbreviated licensure pathway if high similarity with a reference product is established.[1]

STANDARD AND ABBREVIATED PATHWAYS FOR DRUG APPROVAL IN THE UNITED STATES[1,12-16]



Development of a biosimilar requires substantial time and financial investment.[17]

A biosimilar may involve a time investment of 5 to 9 years or more and cost more than $100 million to develop (not including regulatory fees),[17,18] whereas development of a small-molecule generic may take up to 2 years and cost $1 million to $4 million.[19,20]

Extrapolation: A Scientific and Regulatory Principle

After biosimilarity is determined, extrapolation enables potential licensure of a biosimilar across indications approved for the reference biologic.[1,21-23]

SCIENTIFIC JUSTIFICATION IS REQUIRED IN EACH INDICATION NOT STUDIED CLINICALLY[1,24-26]

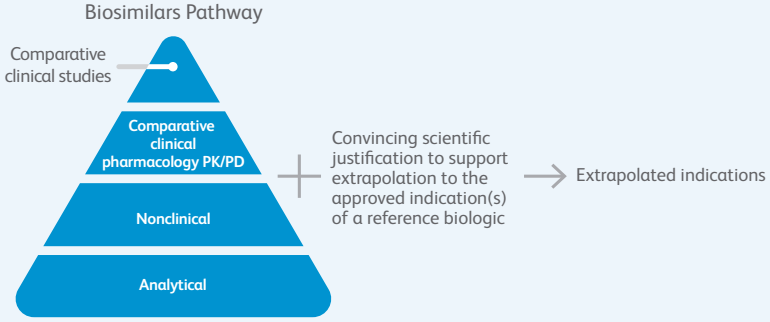


Image adapted from FDA Overview of Regulatory Guidance for Biosimilars 2019.

> Biosimilar extrapolation occurs from the reference biologic to the biosimilar, when scientifically justified, based on all available data—not from the indication(s) studied with the biosimilar to other indications[25]

Extrapolation is not automatic—scientific justification in each indication not clinically studied is organized around 4 key aspects that are considered by the FDA.[1]

KEY FDA CONSIDERATIONS FOR EXTRAPOLATION[1]

MECHANISM OF ACTION
- Experience with the reference biologic can help define the mechanism of action (MOA) and functional moieties in each indication

PK AND BIODISTRIBUTION
- PD measures may provide important MOA information

IMMUNOGENICITY
- Differences that may exist in each patient population

EXPECTED TOXICITIES
- Differences that may exist in each indication and patient population

Scientific justification combines experience with the reference biologic and the totality of evidence.[1,27-29]

SCIENTIFIC JUSTIFICATION FOR EXTRAPOLATION[1,27-29]

EXPERIENCE WITH THE REFERENCE BIOLOGIC

- **Building on the high structural similarity** between the 2 products, **experience with the reference biologic** helps provide an understanding of the 4 key FDA considerations

SUPPORT FROM THE TOTALITY OF EVIDENCE

- **Structural studies and in vitro models** demonstrating **functional similarity across potential MOAs**
- Clinical data that **address differences between indications**
- Clinical data that may be compared to **existing evidence with the reference biologic**

The rationale for extrapolation is to[21,24,30]

- Avoid unnecessary clinical studies
- Reduce development costs
- Allow for reallocation of resources

An Interchangeability Designation Requires a Biosimilar to Meet Additional Standards[15,31]

According to the FDA, products designated interchangeable may be substituted at the pharmacy level for the reference biologic without the intervention of the prescribing health care provider.[15,31]

To be designated interchangeable, the biologic product[15,31]

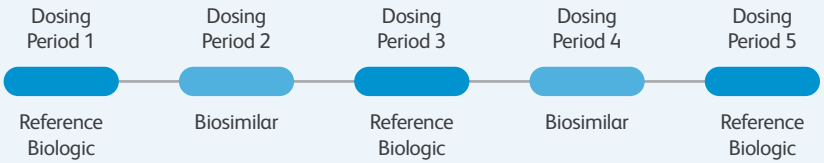
- Must be biosimilar to the reference biologic
- Must be expected to produce the same clinical result as the reference biologic in any given patient

For a biological product administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference biologic is not greater than the risk of using the reference biologic without such alternation or switch.

The interchangeability designation

An interchangeability designation considers the potential for alternation (multiple switches) between a biosimilar and reference biologic without physician intervention.[15,31]

ALTERNATION



As of December 2019, no biosimilar has been designated interchangeable by the FDA

Potential Value of Biosimilars

Biologics have been used successfully to treat many life-threatening and chronic diseases. Between 2008 and 2018, biologics have grown from 13 % to 25 % of new FDA approvals.[32,33]

The potential cost savings from biosimilars to health care systems may be substantial.[34]

ESTIMATED REDUCTION IN DIRECT SPENDING ON BIOLOGIC DRUGS IN THE UNITED STATES BETWEEN 2017 AND 2026 (RAND CORPORATION)[34,a,b]

Up to $150 billion

Biosimilars may provide multiple benefits to the US health care system.[35-37]

POTENTIAL OF BIOSIMILARS FOR PATIENTS, PAYERS, AND PROVIDERS[35-37]

- Additional treatment choices at potentially lower cost to the health care system
- Offer a variety of therapeutic options
- Possible savings and efficiencies to the health care system

Biosimilars may provide potential financial flexibility to practices[34,38]

- Reduced drug spend on biologics may lead to potential cost savings
- Savings may provide reallocation of funds for other important projects
- Helps meet cost targets

How Biosimilars May Help Bring Value to Patients[39,40]

Biosimilars may help reduce the out-of-pocket costs of biologic medicines. One of the main reasons biosimilars were introduced in the United States was to potentially lower health care costs. Thus, it is expected that health care providers, such as clinics or hospitals, will be able to acquire biosimilars at a lower wholesale cost than their reference products. Because of this, biosimilars may have the potential to lower out-of-pocket costs for patients with cost-sharing requirements, such as coinsurance and copayments. For example, patients who may pay less in the form of coinsurance include:

Patients with Medicare Part B who don't have supplemental coverage and typically pay 20% of the Medicare-approved amount for most outpatient therapies[41,42]

Patients with private insurance required to pay coinsurance for specialty drugs, including biologics[39,43]

Even patients who don't have a cost-sharing requirement may benefit from biosimilars, as savings to the health care system could potentially be reinvested in other areas of patient care[39,44]

[a]Based on an assumption of constant reference biologic prices, a biosimilar market share of 50%, and biosimilar prices that are 50% of the reference biologic.
[b]Savings realized by patients may depend on various factors, including changes in copays, coinsurance, etc, which may be more apparent in the future.[39]

References

1. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations Demonstrating Biosimilarity to a Reference Product*. Silver Spring, MD: FDA; 2015. **2.** Ryan AM. Frontiers in nonclinical drug development. *Biosimilars Vet Pathol*. 2015;52(2):419-426. **3.** Huml RA, Chance K, Baum AR, Provost E. Investment decisions based on biosimilar programs. https://www.raps.org/regulatory-focus/news-articles/2013/8/investment-decisions-based-on-biosimilar-programs,-part-1. Accessed December 11, 2019. **4.** Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. *N Engl J Med*. 2011;365(5):385-388. **5.** National Center for Biotechnology Information. Structure Summary MMDB. http://www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?uid=49463. Accessed December 9, 2019. **6.** Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol*. 2008;19(3):411-419. **7.** McCamish M. EBG's perspective on the draft guidance on the non-clinical/clinical issues. https://www.ema.europa.eu/en/documents/presentation/presentation-ebgs-perspective-draft-guideline-non-clinical/clinical-issues-mark-mccamish_en.pdf. Accessed December 11, 2019. **8.** Berghout A. Clinical programs in the development of similar biotherapeutic products: rationale and general principles. *Biologicals*. 2011;39(5):293-296. **9.** Schneider CK, Vleminckx C, Gravanis I, et al. Setting the stage for biosimilar monoclonal antibodies. *Nat Biotechnol*. 2012;30(12):1179-1185. **10.** Noaisieh G, Moreland L. Current and future biosimilars: potential practical applications in rheumatology. *Biosimilars*. 2013;3:27-33. **11.** US Food and Drug Administration. Abbreviated New Drug Applications (ANDA): Generics. Last updated May 22, 2019. https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda. Accessed December 11, 2019. **12.** US Congress. Drug Price Competition and Patent Term Restoration Act of 1984. Title I, 98 Stat 1585, Public Law 98-417. **13.** Patient Protection and Affordable Care Act, March 2010. **14.** US Congress. United States Public Health Services Act. Sec 262 Regulation of Biological Products. 42USC262. https://www.govinfo.gov/content/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapII-partF-subpart1.pdf. Accessed December 11, 2019. **15.** US Food and Drug Administration. *Guidance for Industry: New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*. Silver Spring, MD: FDA; 2019. **16.** US Food and Drug Administration. New Drug Application (NDA). https://www.fda.gov/drugs/types-applications/new-drug-application-nda. Last updated June 10, 2019. Accessed December 11, 2019. **17.** Blackstone EA, Fuhr JP. The economics of biosimilars. *Am Health Drug Benefits*. 2013;6(8):469-478. **18.** Generics and Biosimilars Initiative. GaBI Online. Development of biosimilars. http://www.gabionline.net/Biosimilars/Research/Development-of-biosimilars. Posted July 1, 2011. Accessed December 9, 2019. **19.** Grabowski H, Cockburn I, Long G. The market for follow-on biologics: how will it evolve? *Health Aff (Milwood)*. 2006;25(1):1291-1301. **20.** IMS Health. Shaping the biosimilars opportunity: a global perspective on the evolving biosimilars landscape. London, UK: IMS Health Inc; December 2011. **21.** European Medicines Agency. Concept Paper on Extrapolation of Efficacy and Safety Profile in Medicine Development [final]. London, UK; March 19, 2013. **22.** Windisch J. Biosimilars versus originators: similarities and differences from development to approval. *Int J Clin Rheumatol*. 2015;10(6):1-10. **23.** US Food and Drug Administration. Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US. Arthritis Advisory Committee; February 9, 2016. **24.** Weise M, Bielsky MC, De Smet K, et al. Biosimilars: what clinicians should know. *Blood*. 2012;120(26):5111-5117. **25.** FDA Webinars, Presentations, and Articles. https://www.fda.gov/drugs/biosimilars/webinars-presentations-and-articles. Accessed December 11, 2019. **26.** US Food and Drug Administration. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. Presentation by Leah Christl, PhD. https://www.fda.gov/media/90496/download. Accessed December 11, 2019. **27.** Weise M, Pekka K, Wolf-Holz E, Bielsky MC, Schneider C. Biosimilars: the science of extrapolation. *Blood*. 2014;124(22):3191-3196. **28.** US Food and Drug Administration. FDA Briefing Document. Arthritis Advisory Committee Meeting; BLA 125544. February 9, 2016. **29.** US Food and Drug Administration. FDA Briefing Document. Arthritis Advisory Committee Meeting; BLA 761024. July 12, 2016. **30.** European Medicines Agency. Gaucher Disease: Strategic Collaborative Approach From EMA and FDA. London, UK; May 12, 2014. **31.** US Food and Drug Administration. *Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product*. Silver Spring, MD: FDA; 2019. **32.** Morrison C. Fresh from the biotech pipeline-2017. *Nat Biotechnol*. 2018;36:131-136. **33.** Morrison C. Fresh from the biotech pipeline-2018. *Nat Biotechnol*. 2019;37(2):118-123. **34.** Mulcahy AW, Hlávka JP, Case SR. Biosimilar Cost Savings in the United States. Santa Monica, CA: RAND Corporation; 2017. **35.** Strober BE, Armour K, Romiti R, et al. Biopharmaceuticals and biosimilars in psoriasis: what the dermatologist needs to know. *J Am Acad Dermatol*. 2012;66(2):317-322. **36.** Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—"O brave new world." *Nat Rev Rheumatol*. 2012;8(7):430-436. **37.** Henry D, Taylor C. Pharmacoeconomics of cancer therapies: considerations with the introduction of biosimilars. *Semin Oncol*. 2014;41(suppl 3):S13-S20. **38.** Congressional Budget Office Cost Estimate. S. 1695. Biologics Price Competition and Innovation Act of 2007. https://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/94xx/doc9496/s1695.pdf. **39.** Mulcahy AW, Predmore Z, Mattke S. The Cost Savings Potential of Biosimilar Drugs in the United States. Santa Monica, CA: RAND Corporation; 2014. **40.** US Food and Drug Administration. Biosimilar development, review, and approval. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Accessed December 9, 2019. **41.** Medicare.gov. Medicare costs at a glance. https://www.medicare.gov/your-medicare-costs/medicare-costs-at-a-glance. Accessed December 9, 2019. **42.** Kaiser Family Foundation. An overview of Medicare. February 13, 2019. https://www.kff.org/medicare/issue-brief/an-overview-of-medicare/. Accessed December 9, 2019. **43.** Magellan Rx Management Medical Pharmacy Trend Report™. 2016 7th ed. https://www1.magellanrx.com/publications/medical-pharmacy-trend-report/. Accessed December 9, 2019. **44.** IMS Institute for Healthcare Informatics. Delivering on the potential of biosimilar medicines. The role of functioning competitive markets. Parsippany, NJ: IMS Health Incorporated; March 2016.

Visit **PfizerBiosimilars.com** to learn more about biosimilars.