

Streamlining the Development of Biosimilar Medicines

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Abstract

Biologic drugs have been marketed globally for over 50 years. During that time, regulators and industry have developed experience with originator biologics and biosimilars and with the modern analytical techniques used to characterize them that we now know can reliably identify clinically meaningful differences between a biosimilar and its reference product. The development paradigm for biosimilars must be updated to account for scientific advances to allow for the elimination of unnecessary regulatory requirements, such as clinical efficacy studies, when data have already demonstrated there are no clinically meaningful differences between the biosimilar and its reference product. Removing regulatory barriers will bring more affordable treatments to the market more quickly for patients across the United States and globally.

I. Introduction

A. Biosimilars Generally

Biosimilars – biologic medicines that are highly similar to and have no clinically meaningful differences from previously approved biologics currently on the market (known as “reference products”) – are derived from living cells and used to treat a variety of diseases like cancer, rheumatoid arthritis, and inflammatory bowel disease. Biosimilars provide competition in the market and expand patient access to critical medicines.

In 2010, Congress passed the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”) as part of the Patient Protection and Affordable Care Act.¹ The BPCIA created an abbreviated licensure pathway for biosimilar products in the United States to open biologics markets to competition and lower the price of these expensive and increasingly important pharmaceuticals. FDA approved its first biosimilar medicine in 2015.² Since that time, biosimilars have saved about \$24 billion for U.S. patients and the U.S. healthcare system and have been used in over 694 million days of patient therapy, including nearly 344 million days of patient therapy that would not have been otherwise provided in the United States.³ It has been estimated that switching all patients on just one biologic, adalimumab, to biosimilars would save patients, employers and health plans in the United States up to \$6 billion per year.⁴ Biosimilars have expanded access to more affordable treatments in the United States and across the globe and have proven to be as safe and effective as their reference biologics.

B. FDA Requirements for Biosimilar Approval

The Public Health Service Act, as amended by the BPCIA, provides that a biosimilar application must include 1) data derived from analytical studies demonstrating that the biosimilar is highly similar to the reference product

1 Pub. L. No. 111-148, §§ 7001 through 7003, which amended section 351 of the Public Health Service Act, 42 U.S.C. § 262.

2 U.S. Food and Drug Administration, Biosimilar Product Information, <https://www.fda.gov/drugs/biosimilars/biosimilar-product-information>. Accessed May 5, 2024.

3 Association for Accessible Medicines, The U.S. Generic & Biosimilar Medicines Savings Report, <https://accessiblemeds.org/sites/default/files/2023-09/AAM-2023-Generic-Biosimilar-Medicines-Savings-Report-web.pdf> Accessed May 06, 2024.

4 IQVIA (2024). Adalimumab Biosimilar Tracking, Q1 Readout, Prepared for Biosimilars Council at 3. https://biosimilarscouncil.org/wp-content/uploads/2024/04/04022024_IQVIA-Humira-Tracking-Executive-Summary.pdf. Accessed May 5, 2024.

notwithstanding minor differences in clinically inactive components, 2) an assessment of toxicity, and 3) a clinical study or studies that are sufficient to demonstrate safety, purity, and potency,⁵ unless FDA determines that any such element is unnecessary.⁶ Historically, FDA has taken a conservative approach when considering what scientific evidence is necessary to establish biosimilarity. In addition to analytical studies to support the structural and functional similarity of a proposed product to its reference product and, until recently, nonclinical animal studies to provide toxicology or pharmacology information,⁷ FDA generally requires comparative pharmacokinetic (“PK”) clinical data or, where applicable, comparative pharmacodynamic (“PD”) clinical data, a clinical immunogenicity assessment, and usually, a comparative clinical efficacy study to evaluate whether there are clinically meaningful differences in safety, purity, and potency between the proposed biosimilar and the reference product.⁸ In guidance issued in 2015, FDA took the following position:

As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there is residual uncertainty about whether there are clinically meaningful differences between the proposed product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.⁹

Most of the fifty¹⁰ FDA biosimilar approvals since 2015 have included comparative human clinical studies comparing the reference product and proposed biosimilar.¹¹ Many of these studies have also included a transition arm with a single cross-over step in which patients treated with the reference product were switched to the proposed biosimilar and were compared (1) to the patient responses prior to the switch and (2) to patients treated continuously with the proposed biosimilar. Furthermore, when a sponsor has sought to use a reference product sourced from Europe (“EU”) instead of the United States in a comparative clinical efficacy trial, the sponsor’s PK (and, if applicable, PD) study has included a three-way PK/PD comparison of EU-sourced reference product, U.S.-sourced reference product, and the proposed biosimilar. FDA has concluded that a comparative clinical efficacy study using conventional clinical endpoints was not needed in a handful of instances for some biosimilars such as filgrastim, pegfilgrastim, and insulin for which a PD study could be done instead.¹² However, this option is available only for a minority of biological products for which quantitative PD markers have been identified, and in any event, PD markers, like conventional clinical endpoints, are far less sensitive for detecting differences than physicochemical and functional assays.¹³

The absence of regulatory clarity about what, if any, clinical efficacy studies will be required, combined with this previous experience, means that sponsors generally plan to conduct comparative clinical efficacy studies as part of their development programs regardless of their scientific utility. Some companies may decide to forego biosimilar development programs because of the projected expense, reducing patient access to these important, safe and effective, more affordable medications.

5 See 42 U.S.C. § 262(k)(2)(A)(i)(I).

6 42 U.S.C. § 262(k)(2)(A)(ii).

7 Although the statute originally mandated animal studies, Congress subsequently removed that requirement. See Food and Drug Omnibus Reform Act of 2022, Pub. L. 117-328, § 3209(b), which amended 42 U.S.C. §262(k)(2)(A)(i)(I)(bb) to state that the assessment of toxicology may consist of the analytical and clinical studies already required under the statute.

8 U.S. Food and Drug Administration (2015). Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry (“Biosimilarity Guidance”) at 8. <https://www.fda.gov/media/82647/download>. Accessed May 5, 2024. See also, U.S. Food and Drug Administration. Biosimilars Info Sheet, Level 2: Regulatory and Scientific Concepts, <https://www.fda.gov/media/154916/download?attachment>. Accessed May 5, 2024.

9 Biosimilarity Guidance at 18.

10 As of May 6, 2024. U.S. Food and Drug Administration. Biosimilar Product Information, <https://www.fda.gov/drugs/biosimilars/biosimilar-product-information>.

11 U.S. Food and Drug Administration. Biosimilar Product Information. Accessed May 6, 2024. See also, Moore, T.J., Mouslim, M.C., Blunt, J.L., Alexander, G.C. & Shermock, K.M. (2021). Assessment of Availability, Clinical Testing, and US Food and Drug Administration Review of Biosimilar Biologic Products. *JAMA Intern Med.* 181(1):52–60 at 55. <https://doi.org/10.1001/jamainternmed.2020.3997>. Accessed May 5, 2024.

12 Cohen, H.P., Turner, M., McCabe, D., & Woollett, G.R. (2023). Future Evolution of Biosimilar Development by Application of Current Science and Available Evidence: The Developer’s Perspective. *BioDrugs.* 37(5):583-593. <https://doi.org/10.1007/s40259-023-00619-0>. Accessed May 5, 2024.

13 *Id.*

II. Scientific Advances and Regulatory Discretion Can Help Streamline Development

A. Comparative Efficacy Studies Are Usually Unnecessary

Analytical methods have advanced so they are now sensitive enough to detect small differences, including those that would be considered clinically meaningful between a biosimilar and a reference product, differences that previously might have created sufficient residual uncertainty for FDA to require comparative clinical studies. Clinical efficacy studies using conventional clinical endpoints or PD endpoints generally are not sensitive enough to detect differences between a biosimilar and the reference product that were not observed in early analytical testing or PK studies.¹⁴ Therefore, in most cases, additional comparative clinical efficacy studies offer no meaningful, new, or actionable information for the regulatory decision-making process and should not be required.¹⁵ FDA retains the ability and flexibility to request additional evidence (e.g., a comparative clinical efficacy study) before approval, but it should only do so when scientifically justified and unique risk-based considerations are identified considering, for example, the mechanism of action, the complexity of the product, or the delivery mechanism. Such requests should be the exception rather than a generally applied rule, and FDA should discourage the conduct of comparative efficacy studies when analytical, functional, and PK methodologies are sufficient to detect clinically meaningful differences.

B. Three-way PK Comparisons Are Usually Unnecessary

If a sponsor seeks to use data comparing a proposed product with a non-U.S.-approved comparator product to support a demonstration of biosimilarity, FDA expects the sponsor to provide adequate data or information to establish an acceptable bridge to the U.S.-licensed reference product.¹⁶ For example, typically, FDA requires PK studies that include the biosimilar and both the FDA-licensed and EU-approved reference biologics.¹⁷ Inclusion of both the FDA-licensed and EU-approved reference products in PK studies is usually unnecessary if the versions of biologics licensed in different jurisdictions with similar scientific and regulatory standards share the same development data, for example the same pivotal clinical studies, and manufacturing changes have been justified by a rigorous comparability process. In such a case, a global comparator can be established eliminating the need for duplicative testing of multiple reference products to support the requirements of various health regulatory authorities.¹⁸ Establishment of a global comparator in the United States and other jurisdictions is well-supported scientifically and in practice and would help to make high quality biosimilars available for patients more quickly and at lower cost without any compromise of safety or effectiveness.

III. Streamlining Development Can Reduce Costs, Spur Competition, and Increase Patient Access

Bringing a biosimilar product to market is estimated to cost \$100-300 million, and a biosimilar's clinical efficacy studies typically account for half its research and development costs.¹⁹ Unnecessary clinical efficacy studies demand critical resources, delay competition and deter investment in lower cost biologic alternatives without improving the quality, safety, or efficacy of the treatments ultimately approved. Furthermore, this high expense

14 *Id.*

15 Schiestl, M. et al. (2020). The Path Towards a Tailored Clinical Biosimilar Development. *BioDrugs* 34:297–306. <https://doi.org/10.1007/s40259-020-00422-1>. Accessed May 5, 2024.

16 Biosimilarity Guidance at 6.

17 U.S. Food and Drug Administration, Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry (2021) at 7–8.

18 Webster, C.J. & Woollett, G.R. (2017). A 'Global Reference' Comparator for Biosimilar Development, *BioDrugs* 31:279–286. <https://link.springer.com/content/pdf/10.1007/s40259-017-0227-4.pdf>. Accessed May 5, 2024. See also, World Health Organization (WHO) Guidelines on evaluation of biosimilars, Replacement of Annex 2 of WHO Technical Report Series, No. 977 (2022). Section 6, [https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-\(ecbs\)/annex-3---who-guidelines-on-evaluation-of-biosimilars_22-apr-2022.pdf](https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/annex-3---who-guidelines-on-evaluation-of-biosimilars_22-apr-2022.pdf) and International Generic and Biosimilar Medicines Association (IGBA) (2022). Embracing Science with Confidence: Adopting the Revised 2022 WHO Biosimilars Guideline at 11 <https://www.igbamedicines.org/doc/Embracing-Science-with-Confidence-9-11-2022.pdf>, both accessed May 5, 2024.

19 Fontanillo, M., Kors, B. & Monnard, A. (2020). Three imperatives for R&D in biosimilars, McKinsey & Company. <https://www.mckinsey.com/industries/life-sciences/our-insights/three-imperatives-for-r-and-d-in%20biosimilars>. Accessed May 5, 2024.

reduces the number of biosimilars any given company can develop, leaving many originator biologics to dominate the market with no competition. In particular, for biological products with smaller markets, development costs are a significant barrier to developing less expensive biosimilars. It is currently estimated that ~50% of originator biologics facing loss of exclusivity within the next 10 years do not have biosimilars in development.²⁰ Development costs are a significant reason for the lack of investment in such products.

The development of new biological treatments for serious diseases is expanding rapidly, but under the current regulatory framework, development of biosimilars for newly approved biologic medicines will be very costly. The primary contributor to these costs is the expense of conducting comparative clinical efficacy studies, which, as described by one publication, appeared to be as rigorous as and often larger, longer and more costly than pivotal trials for new molecular entities.²¹ Unnecessary, duplicative PK testing of multiple reference products to support the requirements of various health authorities also contributes to the high cost of developing a biosimilar.

Many patients in the United States and globally will continue to be deprived of access to modern biologics because of high development costs unless the regulatory paradigm for developing biosimilar medicines changes, and development costs are reduced through the elimination of unnecessary comparative clinical efficacy studies and the establishment of global comparators for PK studies.

A. Conclusions and Recommendations

To fulfill the promise of the BPCIA to open biologic markets to competition and lower the price of these medicines, the U.S. development paradigm for biosimilars must be updated and streamlined. The updated paradigm must account for scientific advances that allow for the elimination of unnecessary regulatory requirements, such as clinical efficacy studies, when data from analytic and PK studies have already demonstrated there are no clinically meaningful differences between the biosimilar and its reference product. Analytic methods are now sensitive enough to detect small differences between a biosimilar and a reference product, differences that previously might have created sufficient residual uncertainty for FDA to request comparative clinical studies.

The Biosimilars Council makes the following recommendations for FDA:

- **Eliminate unnecessary clinical efficacy studies**

To reduce the costs and risks of biosimilar development and encourage industry investment in biosimilars, FDA should clarify in regulations and/or guidance that requests for clinical efficacy studies should be the exception rather than a generally applied rule and explain the limited circumstances in which they might be scientifically justified. FDA should discourage the conduct of comparative efficacy studies when analytical, functional, and PK methodologies are sufficient to detect clinically meaningful differences.

- **Establish global regulatory comparators to support demonstration of biosimilarity.**

FDA should work with other regulatory authorities to establish global comparators that would eliminate the need for duplicative PK testing of reference products from different regions of the world to support the requirements of various health regulatory authorities when sponsors seek to use data comparing a proposed product with a non-U.S.-approved comparator product to support a demonstration of biosimilarity.

The recommended streamlining will not lower safety, efficacy, or quality standards, nor will it involve an extensive revision of the regulatory framework for biosimilars. It does not seek to eliminate clinical efficacy studies altogether. Rather, it preserves FDA's authority to request additional evidence in exceptional circumstances when scientifically justified, unique risk-based considerations are identified.

20 IQVIA Institute for Human Data Science (2023). Biosimilars in the United States 2023-2027. <https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027>. Accessed May 5, 2024.

21 Moore, T.J., Mouslim, M.C., Blunt, J.L., Alexander, G.C. & Shermock, K.M. (2021). Assessment of Availability, Clinical Testing, and US Food and Drug Administration Review of Biosimilar Biologic Products. *JAMA Intern Med.* 181(1):52–60 at 53. <https://doi.org/10.1001/jamainternmed.2020.3997>. Accessed May 5, 2024.

Streamlining the biosimilar program using robust scientific tools and advanced analytical methodology will help to make high quality biosimilars available for patients more quickly and at a lower cost, without any difference in safety or effectiveness. Eliminating unnecessary clinical studies will reduce patient exposure to clinical studies that do not contribute to regulatory decision-making. Streamlining can improve the predictability of requirements and shorten the timelines to approval for biosimilar manufacturers, reducing development costs and permitting research and development dollars to go farther for broader biosimilar development enhancing competition. Streamlining will improve the efficiency of FDA reviews and its interactions with industry, saving resources that can be devoted to other priorities.

The time is now to update and streamline the current regulatory paradigm for biosimilars in the United States and pave the way for the next generation of these critical, lower-cost medications.

The Biosimilars Council works to increase patient access to lifesaving, affordable biosimilar medicines. The Council is a division of the Association for Accessible Medicines, an organization dedicated to improving access to safe, quality, effective medicine. The Biosimilars Council strives to create a positive regulatory, reimbursement, political and policy environment to assure biosimilars thrive, providing billions in savings to patients and the health care system. In fact, the use of biosimilars has saved nearly \$24 billion for patients and taxpayers since 2015. Our members include biosimilar manufacturers and stakeholders working to promote biosimilar products.

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Advantages of Streamlining Regulatory Requirements for Biosimilars

For patients:

- Increases availability of high quality biosimilar treatment options that are safe and effective and more cost-effective
- Reduces patient exposure to clinical studies that will not contribute to regulatory decision-making

For Industry:

- Improves the predictability of requirements and shortens timelines for biosimilar approvals
- Reduces costs, enabling research and development dollars to go farther for broader biosimilar development

Streamlining of Biosimilar Development – What It Is and What It Isn't

What Streamlining Is:

- A way to get safe and effective biosimilar medicines to patients more quickly using robust scientific tools and advanced analytical methodology to identify clinically meaningful differences if they exist - instead of relying on studies that are less discriminating
- A way to eliminate duplicative, unnecessary, costly and time-consuming studies

What Streamlining Is NOT:

- Does not lower biosimilar safety, efficacy, or quality standards
- Does not seek to eliminate all clinical efficacy studies; preserves FDA's authority to request additional evidence in exceptional circumstances when scientifically justified, unique risk-based considerations are identified