Provisional Translation (as of May 2026) *

Considerations for Determining the Necessity of Comparative Efficacy Studies in Demonstrating Biosimilarity between Biosimilars and Reference Products (Early Consideration)

May 18, 2026

Pharmaceuticals and Medical Devices Agency
Office of Cellular and Tissue-based Products

1. Introduction

In the development of biosimilars, comparative efficacy studies (CESs) have traditionally been conducted to demonstrate biosimilarity to the reference product, in addition to comparative quality studies and pharmacokinetic (PK) studies.

In recent years, advances in analytical technologies in the field of biotechnology have improved both the comprehensiveness and performance of analytical methods used to characterize biological products. Under these circumstances, it has been suggested that CESs are less sensitive than comparative quality studies in detecting differences between a biosimilar and its reference product [1)].

Furthermore, with the accumulation of experience in the development and approval review of biosimilars, it has been recognized that, in certain cases, biosimilarity between a biosimilar and its reference product can be adequately established without conducting a CES [2–6)]. In addition, there has been growing international discussion regarding the circumstances under which a CES may be considered unnecessary in the development of biosimilars [7, 8)].

Against this background, in Japan, it has been clarified that, under certain circumstances, a CES may be considered unnecessary through the issuance of "Questions and Answers (Q&A) on Guidelines for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Part 2)" (Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), Administrative Notice, May 12, 2026). In the administrative notice, applicants are encouraged to consult the Pharmaceuticals and Medical Devices Agency (PMDA) on a case-by-case basis, including through face-to-face consultation meetings, regarding the necessity of conducting a CES [9)].

The purpose of this document is to supplement the content presented in the aforementioned administrative notice with respect to the considerations for determining the necessity of a CES in the demonstration of biosimilarity between a biosimilar and its reference product, and to more clearly present the current regulatory perspective.

2. Scope of Application

This document applies to medicinal products that fall within the scope of "Guidelines for Ensuring the Quality, Safety, and Efficacy of Biosimilars" (Pharmaceutical Evaluation Division, Pharmaceutical

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Safety and Environmental Health Bureau Notification No. 0204, MHLW, dated February 4, 2020).

3. Basic Principles

In the development of biosimilars, it is necessary to clarify the extent of similarity in quality attributes though comparative quality studies with the reference product based on a scientifically justified selection of relevant quality attributes, including physicochemical, structural and functional attributes. It is also necessary to demonstrate that any differences identified in quality attributes do not have an impact on efficacy, safety, and immunogenicity.

When it is demonstrated, based on the results of comparative quality studies, comparative PK studies (or comparative PK/pharmacodynamic (PD) studies), and an adequate understanding of the product characteristics, that differences in quality attributes do not affect efficacy, safety, and immunogenicity, and that biosimilarity to the reference product can be established, a CES may be considered unnecessary.

4. Considerations for Determining the Necessity of a CES

When, through a face-to-face consultation meeting with the PMDA, discussing whether a CES is necessary, applicants should clearly explain the rationale for considering that biosimilarity between a biosimilar and its reference product can be established without conducting a CES.

The items to be included in the consultation materials are outlined below.

(1) Quality-Related Data

(i) Information on the mechanism of action (MoA) of the biosimilar under consultation

For the indications approved for the reference product, at least those intended to be included in the initial marketing authorization application of the biosimilar under consultation, an explanation should be provided as to whether there are similarities and differences in the MoA among the indications.

(ii) Available information on the relationship between the quality attributes (including physicochemical, structural and functional attributes) of the biosimilar under consultation and its PK, efficacy, safety, and immunogenicity

(iii) An overview of the analytical methods used for the assessment of each quality attribute

(iv) Information on similarities or differences in the cell substrates used for the biosimilar under consultation and the reference product

(v) Plan or results of comparative quality studies

Based on the information described in items (i) to (iv) above, applicants should explain the appropriateness of the selected test items, the number of lots, and the evaluation methods, including the results of risk assessments for each quality attribute. Where results of comparative quality studies, including results from preliminary comparative quality studies, are available, such results should be

presented. The potential impact, if any, of differences identified in quality attributes on efficacy, safety, and immunogenicity should be explained with appropriate scientific justification.

(2) Clinical Study-Related Data

(i) Study protocol or results

In addition to an overview of the comparative PK study (including the study population, dosage and administration, evaluation endpoints, methods for equivalence assessment, and number of subjects), an explanation should be provided regarding the conduct and appropriateness of safety evaluation, immunogenicity assessment, and, if applicable, PD evaluation in the comparative PK study.

(ii) Clinical data package

(iii) Rationale for the extrapolation of indications

For the indications approved for the reference product, at least those intended to be included in the initial application for marketing authorization of the biosimilar under consultation, the rationale for considering that such indications can be obtained should be explained.

(3) Other consideration

Where the target disease is a rare disease and the conduct of a CES is difficult, the grounds for this difficulty, including information on the number of patients with the target disease, should be clearly explained.

5. References

1) Cohen, H.P., Turner, M., McCabe, D., et al. Future Evolution of Biosimilar Development by Application of Current Science and Available Evidence: The Developer's Perspective. BioDrugs. 2023; 37(5): 583–93. https://doi.org/10.1007/s40259-023-00619-0
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5) Ji, P., Schrieber, S. J., Glaser, R., et al. A Meta-Analysis of the Safety and Immunogenicity of

Pharmacokinetic Similarity Studies and Comparative Clinical Studies. The Journal of Clinical Pharmacology. 2025, 65(4): 499-507. https://doi.org/10.1002/jcph.6165

6) Schiestl, M., Roy, N., Trieb, M., et al. Analytical Data and Single-Dose PK are Sufficient to Conclude Comparable Immunogenicity for Biosimilars: An Ustekinumab Case Study. BioDrugs. 2025, 39(5): 769-76. https://doi.org/10.1007/s40259-025-00733-1

7) IPRP BWG Workshop Summary Report: Increasing the Efficiency of Biosimilar Development Programs—Reevaluating the Need for Comparative Efficacy Studies. 6 May 2024. https://admin.iprp.global/sites/default/files/2024-07/IPRP_BWG_Final%20IPRP%20Scientific%20Workshop%20Summary%20Report_2024_0506.pdf

8) Final Concept Paper; M18: Framework for Determining the Utility of Comparative Efficacy Studies in Biosimilar Development Programs. https://database.ich.org/sites/default/files/ICH_M18_Final_Concept_Paper_MCEndorsed_2025_1119.pdf

9) Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Part 2) (Administrative Notice dated May 12, 2026) https://www.pmda.go.jp/files/000280738.pdf