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Recent Regulatory Trends for Biosimilars in Japan

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Reviewer
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The views expressed in this presentation are those of the author and do not necessarily reflect the official views of PMDA.

Outline

- Current Status of Biosimilars in Japan
- Regulatory Trends in Japan
- International Regulatory Trends
- Implications and Future Directions

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Outline

- **Current Status of Biosimilars in Japan**
- Regulatory Trends in Japan
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Definition of Biosimilar in Japan

- A biosimilar is a product comparable with regard to quality, safety, and efficacy to a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients (original biopharmaceutical), which is developed by a different marketing authorization holder.

Scope of application

- Proteins and peptides produced from recombinant expression systems
- Proteins and peptides highly purified and well characterized

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars (PSEHD/PED Notification No.0204-1, February 4, 2020)

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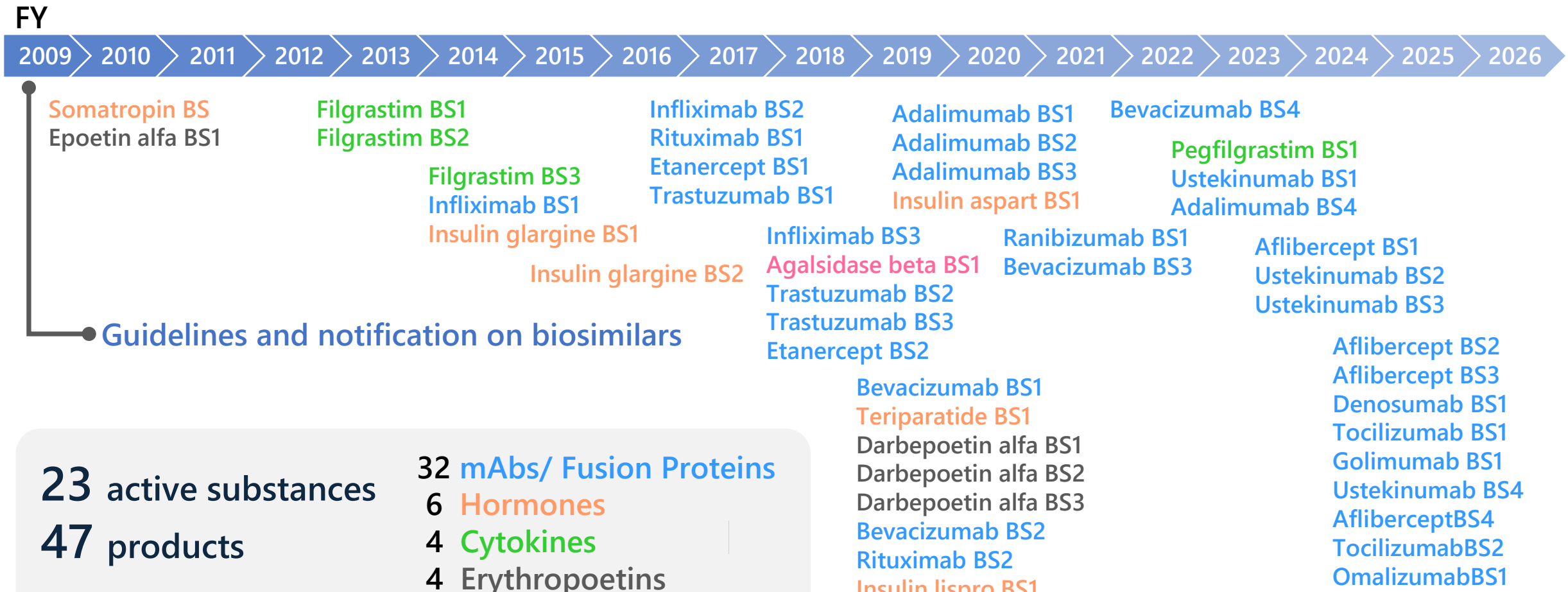
Overview of the biosimilars approved in Japan



23 active substances

47 products

FY 2009-2025

32 mAbs/ Fusion Proteins
6 Hormones
4 Cytokines
4 Erythropoetins
1 Enzyme

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Consultation for biosimilar in Japan

- Consultations with PMDA can be conducted for each comparative assessment, as needed.

★ Quality Comparative Studies

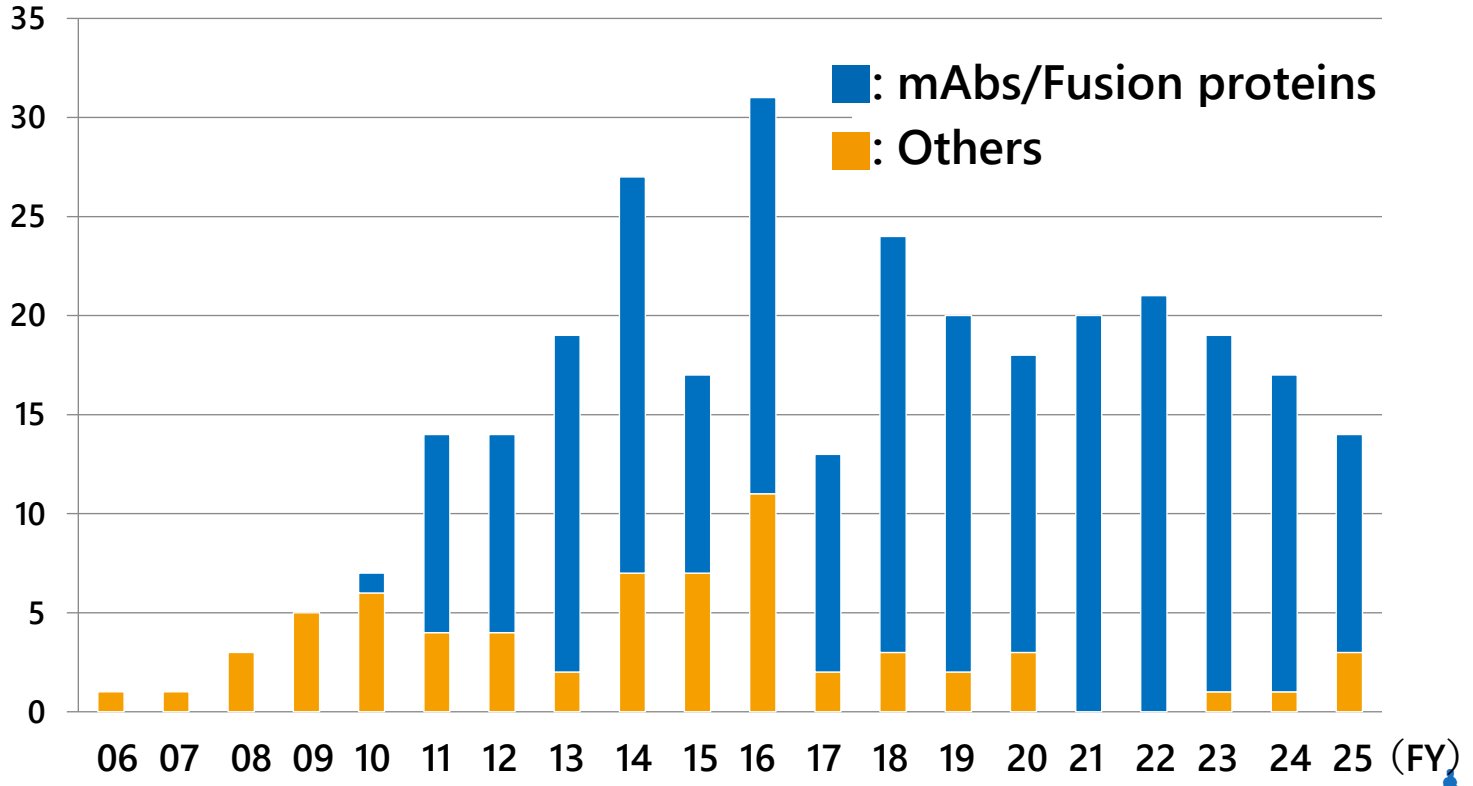
★ Non-clinical Comparative Studies

★ PK (/PD) Comparative Studies

★ Efficacy Comparative Studies

- Number of consultation

>250: Consultations, >75%: mAbs/Fusion proteins



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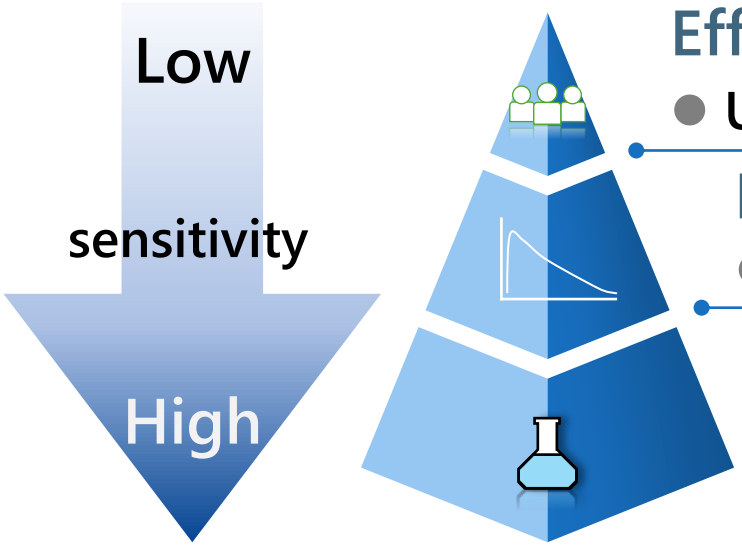
Reweighting evidence by analytical sensitivity

- Comparative Efficacy Studies(CES) were historically used as confirmatory evidence for biosimilarity and require substantial time and resources.
  →Biosimilar developments are generally more costly and time-consuming than generic drug developments.
- However, the discriminatory value of CES may be limited in certain cases.
- Advances in analytical characterization now allow highly sensitive detection of physicochemical, structural and functional differences.



Efficacy Comparative Studies(CES)

- Used to resolve residual uncertainty when needed.

PK (/PD) Comparative Studies

- Characterizes exposure similarity and biological behavior.

Quality Comparative Studies

- Detecting physicochemical, structural and functional differences.

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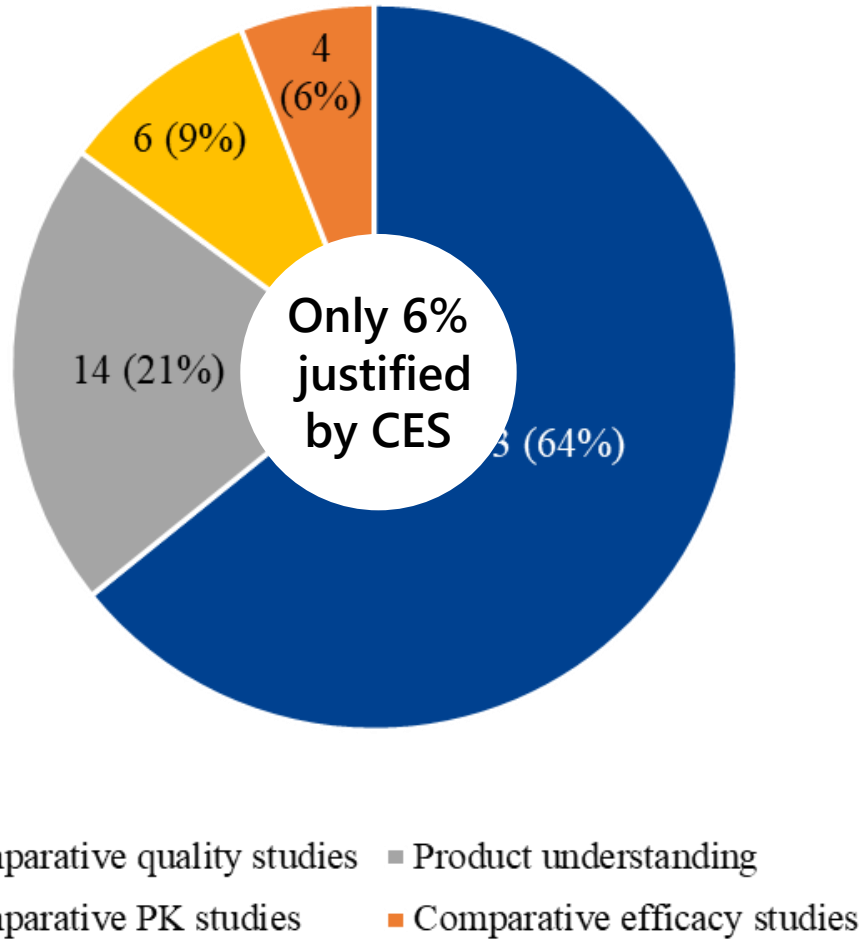
Analysis of the Evidence Supporting Identified Differences in Quality Attributes

- Although CES were conducted for all products, only 6% of the identified differences in quality attributes were ultimately justified through CES.
- Growing scientific knowledge has strengthened the understanding of the relationships between quality attributes and PK and clinical outcomes.
- Taken together, these findings suggest that CES contribute only marginally to biosimilarity assessment and that the need for such studies should be determined on the basis of the clinical significance of any observed differences in quality attributes.



Goto K. et al. Pharmaceut Med. 39(6), 477-491 (2025) https://doi.org/10.1007/s40290-025-00583-w

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Recent Key Regulatory Milestones in Japan

Before 2024 — Procedural requirements predominated

- Japanese subject data were generally required in key clinical studies
- CES were commonly expected as confirmatory evidence

Jan 2024 — Revision of requirements for Japanese subject data

- Non-Japanese data may be acceptable when ethnic factors are not expected to affect PK, efficacy, safety, and immunogenicity

Revision of Questions & Answers on Guideline

May 2026 — Clarification of the role of CES

- CES may not be required when analytical, PK or PK/PD, and product-specific understanding are sufficient

Revision of Questions & Answers on Guideline (Part2)

Early Consideration

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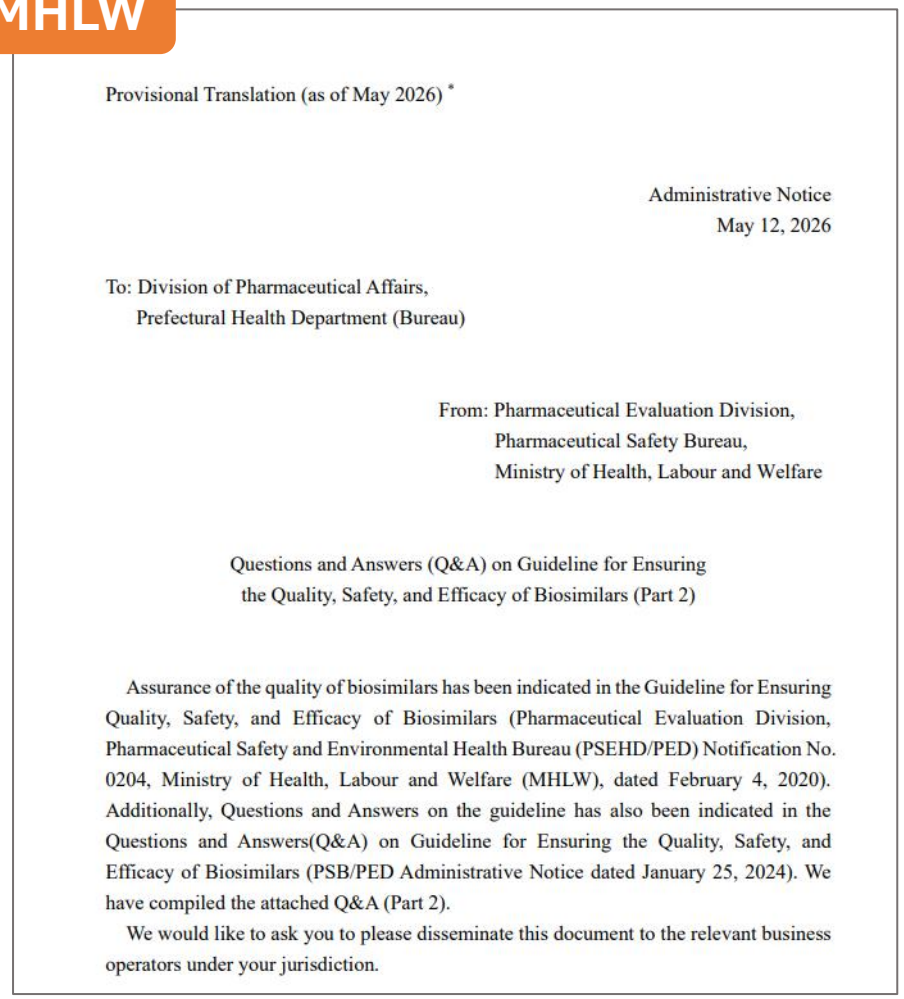
Clarification of the role of CES

MHLW



Provisional Translation (as of May 2026) *

Administrative Notice
May 12, 2026

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on Guideline for Ensuring
the Quality, Safety, and Efficacy of Biosimilars (Part 2)

Assurance of the quality of biosimilars has been indicated in the Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars (Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (PSEHD/PED) Notification No. 0204, Ministry of Health, Labour and Welfare (MHLW), dated February 4, 2020). Additionally, Questions and Answers on the guideline has also been indicated in the Questions and Answers(Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (PSB/PED Administrative Notice dated January 25, 2024). We have compiled the attached Q&A (Part 2).

We would like to ask you to please disseminate this document to the relevant business operators under your jurisdiction.

① Revision of Questions & Answers on Guideline

Basic Concept:

- When sufficient data ensure biosimilarity through quality studies, PK or PD studies, CES may be omitted

- Clarification that CES is not mandatory
- Recommendation to consult PMDA regarding whether CES can be omitted

Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Part 2) (PSB/PED Administrative Notice, May 12, 2026)

Clarification of the role of CES

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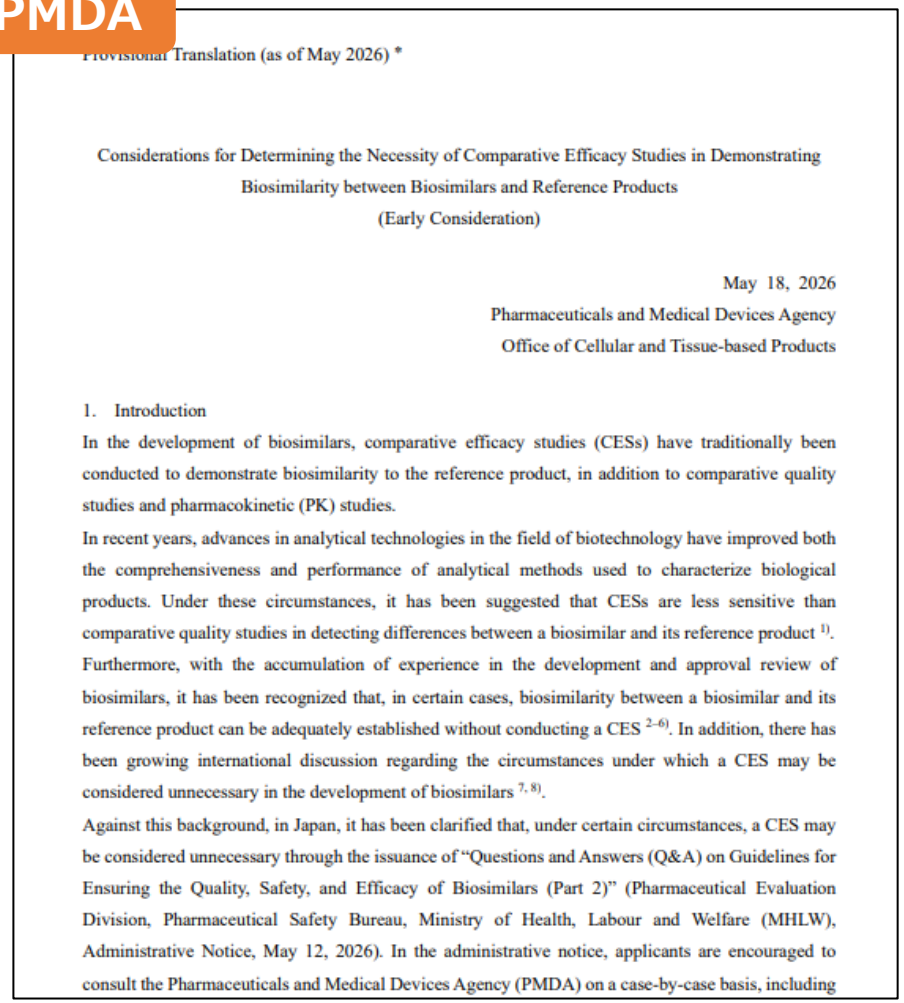

Provisional Translation (as of May 2026) *

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

② Early Consideration

Basic Concept:

- When quality differences do not affect efficacy, safety, and immunogenicity through comparative studies and product understanding, CES may be unnecessary

Considerations for Determining the Necessity of Comparative Efficacy Studies in Demonstrating Biosimilarity between Biosimilars and Reference Products (Early Consideration)(May 18, 2026)

Clarification of the role of CES

PMDA

Provisional Translation (as of May 2026) *

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Consultation Focus:

<Quality>

- Knowledge of mechanism of action
- Quality attributes relationship to PK, efficacy, safety, and immunogenicity
- Analytical methods for quality evaluation
- Scientific justification for the use of different cell substrates
- Quality comparative study plan or results

<Clinical>

- Study implementation plan or results
- Clinical data package
- Rationale for reference biologic indications

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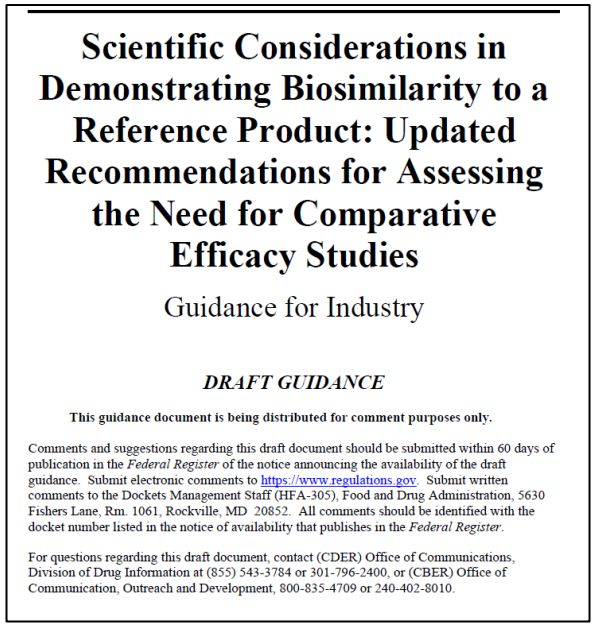
Global Movement Toward Streamlined Biosimilar Development

- A global consensus is emerging that CES may be waived in biosimilar development if specific conditions are satisfied.

FDA Draft Guidance Oct 2025[1]



Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at (855) 543-3784 or 301-796-2400, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

EMA Reflection Paper Mar 2026[2]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

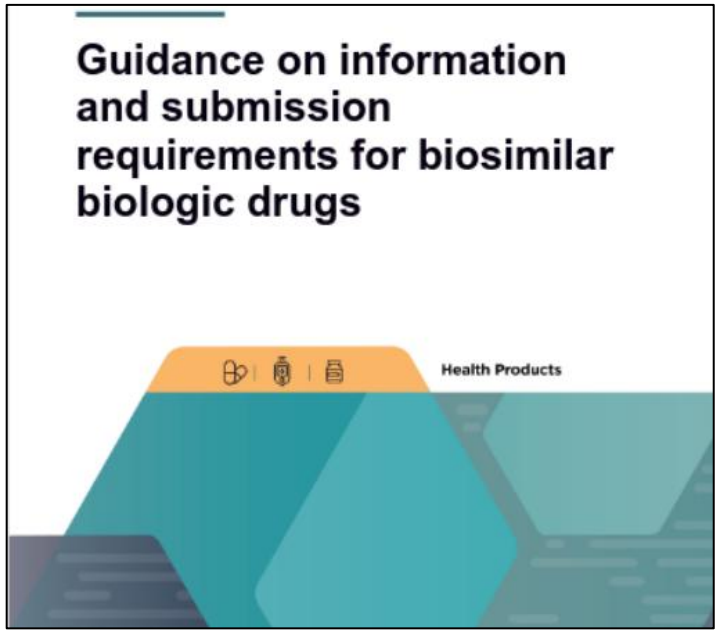
16 March 2026
EMA/CHMP/BMWP/60916/2025
Committee for Medicinal Products for Human Use (CHMP)
Biosimilar Medicinal Products Working Party (BMWP)

Reflection paper on a tailored clinical approach in biosimilar development

Draft for internal consultation agreed by Biosimilar Medicines Working Party	21 October 2024
Consultation with MWP, BWP and SAWP	17 January 2025
Draft agreed by Biosimilar Medicinal Products Working Party	12 February 2025
Adopted by CHMP for release for consultation	17 March 2025
Start of public consultation	27 March 2025
End of consultation (deadline for comments)	30 September 2025
Agreed by Biosimilar Medicinal Products Working Party	02 March 2026
Adopted by CHMP	16 March 2026

Keywords	**Reflection Paper, Biosimilar, Comparative Efficacy Study, Tailored clinical approach**

Health Canada Guidance May 2026[3]



Guidance on information and submission requirements for biosimilar biologic drugs

Health Products

1 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product-updated-recommendations
2 https://www.ema.europa.eu/en/documents/other/reflection-paper-tailored-clinical-approach-biosimilar-development_en.pdf-0
3 https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs.html

ICH M18 Activities

ICH harmonisation for better health

Final Concept Paper

M18: Framework for Determining the Utility of Comparative Efficacy Studies in Biosimilar Development Programs
November 2025

Endorsed by the MC on 19 November 2025

Type of Harmonisation Action Proposed

This proposed new multidisciplinary guideline will outline the factors to consider when determining the utility of comparative efficacy studies (CES) in biosimilar development programs intended to support regulatory approval. It will also describe the conditions under which similar efficacy and safety and an acceptable immunogenicity profile can be ensured should such trials be deemed unnecessary. The guideline will describe how these factors may be applied in determining the utility of CES and provide guidance for tailored biosimilar development programs (without CES), to facilitate consistent global expectations early in biosimilar development when planning for CES typically occur.

Background to the proposal and Statement of the Perceived Problem

Historically, CES have been a default expectation as part of a biosimilarity assessment to support regulatory approval of biosimilars. As experience with the development and approval of biosimilars has grown, there has been increasing recognition that CES lack the sensitivity required to differentiate between products with differences in quality attributes, including physicochemical, structural and functional attributes. Additionally, modern analytical technologies have the sensitivity to discriminate differences between biosimilars and their reference products, providing assurance about their clinical performance thereby leaving little residual uncertainty. Therefore, CES may not provide useful information, yet require substantial time and resources in biosimilar development programs.

Over time, this has led to increasing calls from industry, academia, and regulators in support of streamlining biosimilar development by eliminating the default expectation for CES. For example, multiple publications of accrued clinical study data have shown that CES results were consistent with analytical similarity data, did not inform approvability, and required extensive resources to conduct. [Refs 1, 2, 5, 6, 8, 9]. Additionally, an increasing number of regulatory health authorities have issued updated guidelines to reflect the position that CES are not generally necessary [Refs 3, 4, 5, 11, 14, 15, 17, 18, 19].

The performance of CES that are not scientifically warranted involves the use of valuable resources, including clinical trial participants for studies that do not provide additional information, and potentially discourages biosimilar development.

ICH M18
“Framework for Determining the Utility of Comparative Efficacy Studies in Biosimilar Development Programs”

- Development of criteria for determining the need for CES
- Establishing a scientifically robust framework to ensure comparable efficacy, safety, and immunogenicity when CES are waived

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Expected Impact

Improved Development Efficiency	Enables a more targeted use of CES, potentially shortening timelines and lowering costs.
Enhanced Market Competition	Lowers barriers to entry, particularly for products with small markets or rare-disease indications.
Expanded Patient Access	Supports timely availability of high-quality, affordable biologic therapies.
Health System Sustainability	Contributes to containment of biologic expenditure and strengthens health insurance resilience.
Global Regulatory Convergence	Aligns with the emerging shift at the FDA, EMA, and ICH toward evidence-proportionate evaluation.

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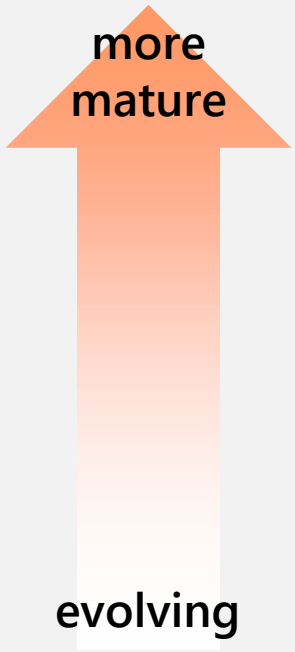
Future Perspectives

- Continued accumulation of consultation, development, and review experience regarding CES waivers.
- Increasing role of analytical characterization in biosimilar development.
- Emerging use of AI and machine learning to support analytical comparability and manufacturing optimization.
- Greater emphasis on early quality-focused development and risk management.
- Continued importance of communication with healthcare professionals, and post-marketing surveillance.

Emerging Role of AI in Biosimilar Development

- Less reliance on CES may increase the importance of advanced analytical science, including AI-supported data analysis.
- AI is not expected to replace scientific assessment but may support data-driven analytical comparability and quality-focused development.

Potential applications across the lifecycle



Manufacturing	Process optimization
Quality / CMC	Glycan, spectral and chromatographic data analysis
Comparability	AI-assisted similarity assessment
Clinical	Prediction of response or PK/PD patterns
Post-marketing	Signal detection and real-world evidence

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Summary

- Biosimilar regulation is undergoing a global transition.
- Long-standing default requirements, particularly CES, are being re-examined.
- Japan's recent regulatory reforms reflect a shift toward evidence-proportionate and science-based regulation.

By the end of FY2029, MHLW aims for biosimilars to achieve more than 80% market share in 60% of biologic product categories.

MHLW (Ministry of Health, Labour and Welfare)
https://www.mhlw.go.jp/content/12401000/001309914.pdf (Japanese only)

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Introduction about our Website

Home > Reviews and Related Services > Reviews > Drugs > Biosimilar

https://www.pmda.go.jp/english/review-services/reviews/0005.html

Biosimilars

日本語ページはこちら →

What is Biosimilar?

A biosimilar is a product comparable with regard to quality, safety, and efficacy to a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients (original biopharmaceutical), which is developed by a different marketing authorization holder.

Approved Biosimilar Products

List of Approved Products[40.8KB]

Related Guidelines, Notifications, and Information

The following English translations of Japanese guideline and notification are intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese originals and the translations, the former shall prevail.

Presentations

- Fukushima S. Regulatory Trends of Antibody Therapeutics in Japan. Global Bio Conference 2025. September 2025[796KB]
- Tanaka K. Current Regulation on Biosimilar in Japan. International Regulatory Science Forum 2025. March 2025[1.15MB]
- Otaki N. Regulatory and Scientific Considerations for Biosimilars in Japan. The 12th Joint Conference of Taiwan and Japan on Medical Products Regulation. October 2024[1.0MB]
- Shirahata Y. Current regulation on CMC of Biopharmaceuticals in Japan. Global Bio Conference 2024. September 2024[1.53MB]
- Kuribayashi R. Regulatory Experience and Considerations to Date from PMDA. IPRP Biosimilar Workshop. September 2023[155KB]

Publications

- Goto K, Hariu A, Kuribayashi R. Survey on the Role of Comparative Efficacy Studies Required for Biosimilar Monoclonal Antibody Approval in Japan to Justify the Quality Attribute Diferences Between Biosimilars and Their Reference Products Based on the Pharmaceuticals and Medical Devices Agency (PMDA) Assessments. Pharmaceut Med. 2025; 39: 477-91. https://doi.org/10.1007/s40290-025-00583-w
- Hariu A, Saino Y, Kuribayashi R. Consideration of the biosimilar drug lag and loss among Japan, the USA, and the EU. Naunyn Schmiedebergs Arch. Pharmacol. 2025. http://doi.org/10.1007/s00210-025-04494-0
- Kuribayashi R, Hariu A, Saino Y, Shinohara K. Efforts of the Pharmaceuticals and Medical Devices Agency of Japanese regulatory agency in supporting biosimilar development and disseminate information. Naunyn Schmiedebergs Arch Pharmacol. 2025; 398(7): 9357-65. https://doi.org/10.1007/s00210-025-03874-w
- Kuribayashi R, Goto K, Ogawa T. Trend Analysis of Regulatory Approvals for Generics and Biosimilars in Japan: 15 Years History of PMDA During Fiscal Years 2009–2023. AAPS J. 2024; 26(6): 113. https://doi.org/10.1208/s12248-024-00989-5
- Kuribayashi R, Goto K, Hariu A, Kishioka Y. Revisions to the requirement of the Japanese clinical study data for biosimilar developments in Japan. Expert Opin Biol Ther. 2024; 24(7):637-645. https://doi.org/10.1080/14712598.2024.2377300

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Recent publication from PMDA colleagues

- Goto K, Hariu A, Kuribayashi R. Survey on the Role of Comparative Efficacy Studies Required for Biosimilar Monoclonal Antibody Approval in Japan to Justify the Quality Attribute Diferences Between Biosimilars and Their Reference Products Based on the Pharmaceuticals and Medical Devices Agency (PMDA) Assessments. Pharmaceut Med. 2025; 39: 477-91. https://doi.org/10.1007/s40290-025-00583-w
- Kuribayashi R, Hariu A, Saino Y, Shinohara K. Efforts of Pharmaceuticals and Medical Devices Agency of Japanese Regulatory Agency in Supporting Biosimilar Development and Disseminate Information. Naunyn-Schmiedeberg's Archives of Pharmacology. 2025. https://doi.org/ 10.1007/s00210-025-03874-w
- Hariu A, Saino Y, Kuribayashi R. Consideration of the biosimilar drug lag and loss among Japan, the USA, and the EU. Naunyn Schmiedebergs Arch. Pharmacol. 2025. http://doi.org/10.1007/s00210-025-04494-0
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Thank you for your kind attention

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