独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulatory and Scientific Considerations for Biosimilars in Japan

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Definition of Biosimilar in Japan

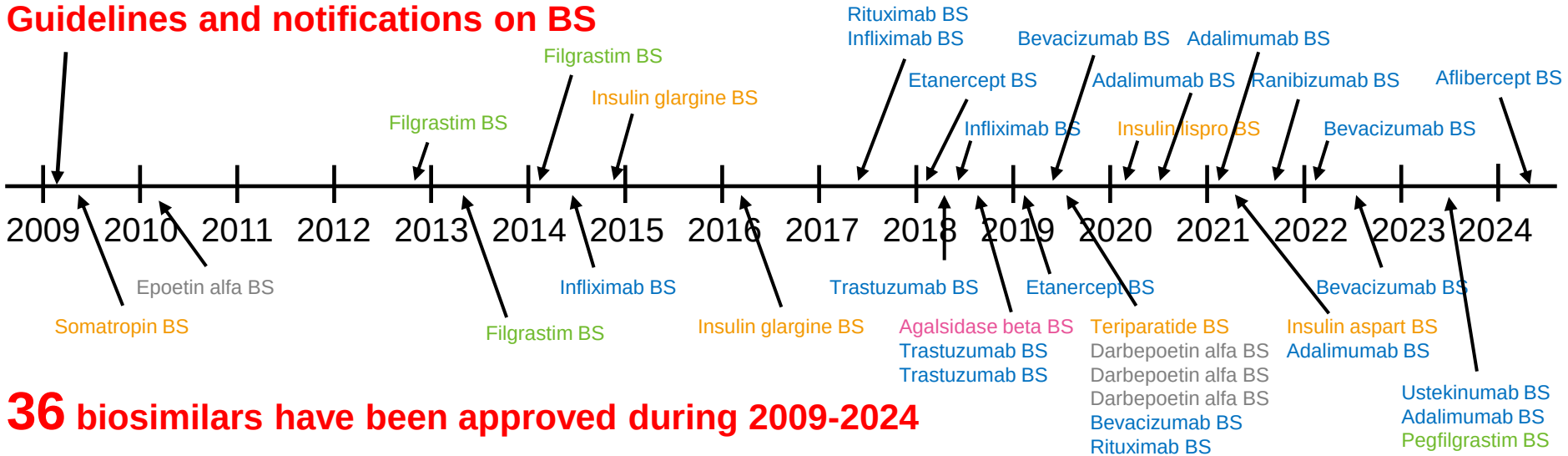
A biosimilar is a product comparable with regard to quality, safety, and efficacy to a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients (original biopharmaceutical), which is developed by a different marketing authorization holder.

＜Scope of application＞

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

Approved Biosimilar Products in Japan

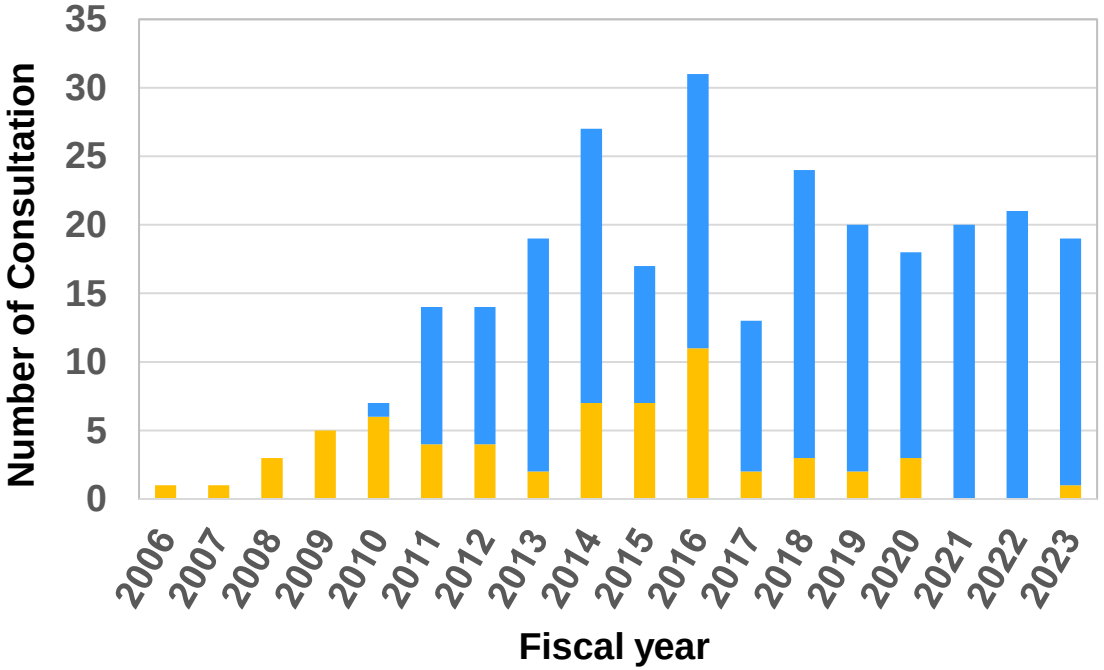
Guidelines and notifications on BS



36 biosimilars have been approved during 2009-2024

- 21 Monoclonal Antibodies (mAbs) / Fusion proteins
- 6 Hormones
- 4 Erythropoietins
- 4 Cytokines
- 1 Enzyme

PMDA Consultations for Biosimilars



: mAbs/Fusion proteins
: Others

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

Guideline and Notifications for Biosimilars in Japan

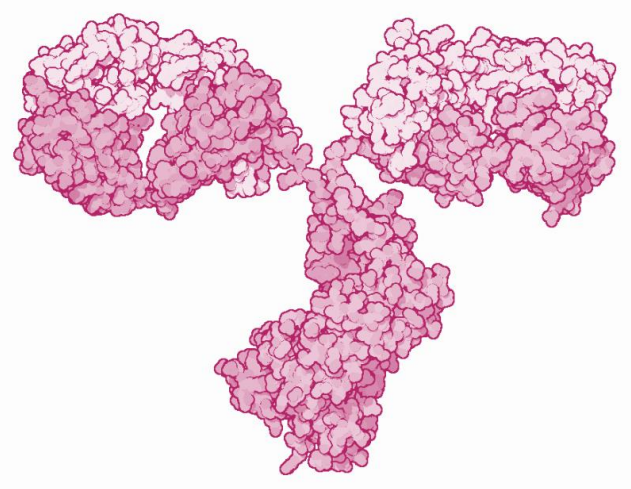
- Marketing Approval for Biosimilars
  (*PFSB Notification 0304004 / March 4, 2009*)
- Nonproprietary Name and Drug Name of Biosimilars
  (*PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013*)

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

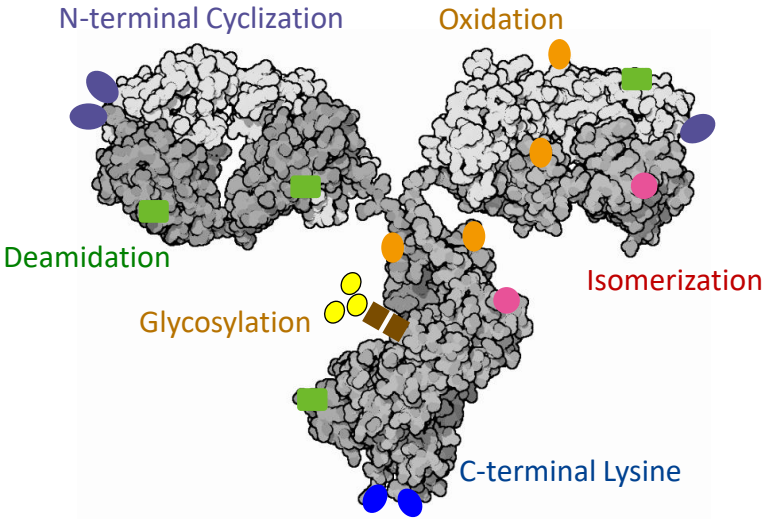
◆ Questions & Answers on Guideline
(*PSB/PED Administrative Notice / January 25, 2024*)

Evaluation of Comparability

The original biopharmaceutical and the biosimilar are not identical due to the complex structures and heterogeneity associated with post-translational modification.



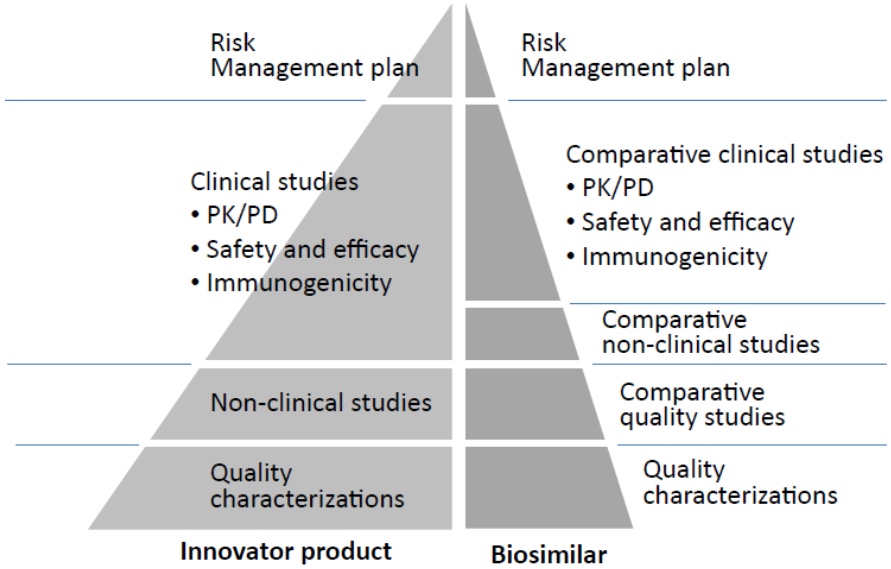
Original biopharmaceutical



Biosimilar

Molecule of the Month © David S. Goodsell and RCSB PDB

Evaluation of Comparability

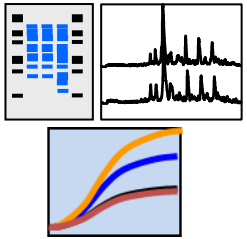


Comparability of a biosimilar with an originator biological product is demonstrated when their quality attributes are highly similar, and any differences in the quality attributes have no adverse impact on clinical safety or efficacy.

The extent and necessity of non-clinical and clinical study data required will defer depending on the extent to which similarity of the quality attributes with the original biopharmaceuticals.

http://www.nihs.go.jp/dbcb/TEXT/yakuseiyakushinnhatsu_0204_1.pdf
Drug Metab Pharmacokinet. 2019; 34(1): 64–70.

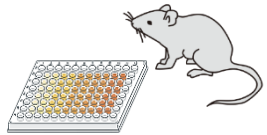
Evaluation of Comparability



Comparative Analytical Assessments

- It is recommended to compare the quality attributes using multidimensional evaluations by multiple orthogonal analytical methods.
- Comparative studies on the structural/physicochemical properties, biological activity, and impurities should be conducted.

Comparative Non-clinical Studies



- *in vitro* bioactivity tests conducted as quality studies are applicable as nonclinical pharmacology tests.
- If there are no safety concerns, non-clinical safety studies may be omitted.

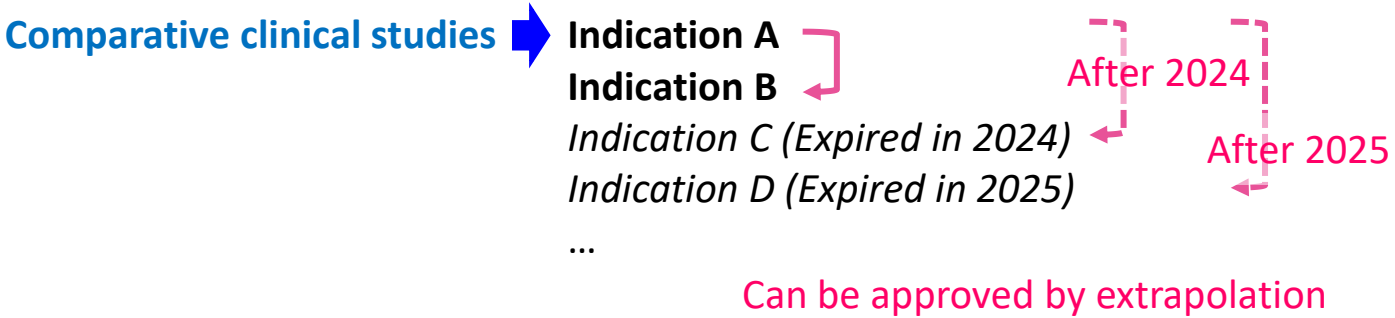
Comparative Clinical Studies

- Comparative clinical studies are required since the comparability cannot be demonstrated based on the data on quality attributes and the results of non-clinical studies only.
- If PK and PD studies can assure comparability in the clinical endpoint of interest, comparative efficacy study can be omitted.

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars (*PSEHD/PED Notification No. 0204-1 / February 4, 2020*)
https://www.pmda.go.jp/files/000267479.pdf

Extrapolation of the indication

- If the indications are pharmacologically expected to be similar and if there is no safety concern more than the originator product, the indications can be added to the biosimilar (extrapolation).
- All indications of originator biologics should be obtained after the reexamination period (new drug data protection period) has expired.



Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars (*PSEHD/PED Notification No. 0204-1 / February 4, 2020*)
https://www.pmda.go.jp/files/000267479.pdf

Post-Marketing Surveillance

- It is necessary to formulate an appropriate risk management plan (RMP), considering the risks that could not be sufficiently evaluated by the comparability studies.
- Additional pharmacovigilance practices (drug use results surveys, post-marketing database investigations, etc.) may be required if clinical studies have not been conducted in the proposed indications, and there are safety concerns with the biosimilar.

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars (*PSEHD/PED Notification No. 0204-1 / February 4, 2020*)
https://www.pmda.go.jp/files/000267479.pdf

Preliminary Questions : Need for Bridging Study in Japan

＜Preliminary Questions＞

In the Q10 and Q11 of the “Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars”（January 25, 2024, PSB/PED Administrative Notice）, it stated that if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects.

From your perspective, how should the companies present the evaluation of ethnic factors to better clarify whether a bridging study is needed?

＜Outline of the Answer＞

It is acceptable not to conduct a bridging Study (a PK or equivalence study conducted in a development area), if there is no particular concern for (1) to (3).

(1) the biosimilars and the original products do not have differences in quality characteristics that affect ethnic factors

(2) the biosimilars do not have characteristics that are easily influenced by ethnic factors

(3) there are no differences in PK, efficacy and safety between Japanese and non-Japanese patients by presenting the data of original products

Revision of Questions & Answers on Guideline

＜Q&A10（Old version）＞

Q. If you have a basic idea about the acquisition of clinical data on Japanese, please indicate it.

A. At least either the clinical trial to verify PK equivalence with original biopharmaceuticals or the clinical trial to verify efficacy (including PD) equivalence with the original biopharmaceuticals must be realized with the clinical trial with Japanese subjects. Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials“ (Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) cannot be directly applied to the number of Japanese cases when the study is conducted as an international joint clinical trial that includes Japanese subjects. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese population and those of the overall population.

Revision of Questions & Answers on Guideline

Examples of Clinical Data Packages Based on old version Guideline Q&A

Biosimilar A

Objective	Subject
PK study	Japanese Healthy Subject
Efficacy study	Non-Japanese Patient
PK study (Reference data)	Non-Japanese Healthy Subject

Biosimilar B

Objective	Subject
PK study	Non-Japanese Healthy Subject
Efficacy study	Japanese and Non-Japanese Patient

Revision of Questions & Answers on Guideline

＜Q&A10（Revised）＞

Q. Is it acceptable to use data from clinical trials conducted in non-Japanese subjects that confirm the equivalence of PK and efficacy (including PD) with original biopharmaceuticals for approval application?

A. Clinical trials of biosimilars are intended to confirm the equivalence of PK and efficacy (including PD) to original biopharmaceuticals. Therefore, if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects. If the sponsors conduct global clinical trials with Japanese subjects and the ethnic factors of subjects are considered to affect the study results, Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials"(Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) cannot be directly applied to the number of Japanese. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese population and those of the overall population with reference to the above notification.

Questions & Answers on Guideline *(PSB/PED Administrative Notice / January 25, 2024)*
https://www.pmda.go.jp/files/000267480.pdf

Revision of Questions & Answers on Guideline

If applicant can explain the ethnic factors of subjects do not affect the study results, it is acceptable not to conduct a clinical trial that includes Japanese subjects.

Biosimilar C

Objective	Subject
PK study	Non-Japanese Healthy Subject
Efficacy study	Non-Japanese Patient

Revision of Questions & Answers on Guideline

＜Q&A11（Newly established）＞

Q. In Q&A10, it stated that if the ethnic factors of subjects are not expected to affect the clinical trial results, how do you evaluate this?

A. For example, it is possible to identify ethnic factors and their impact based on the original biopharmaceuticals and to confirm the results of Japanese subgroup analysis of clinical trials from currently available evidence of original biopharmaceuticals. Additionally, if some differences of quality attribute between a biosimilar and the original biopharmaceutical was observed, it is important to evaluate ethnic factors and their impact focusing on the differences.

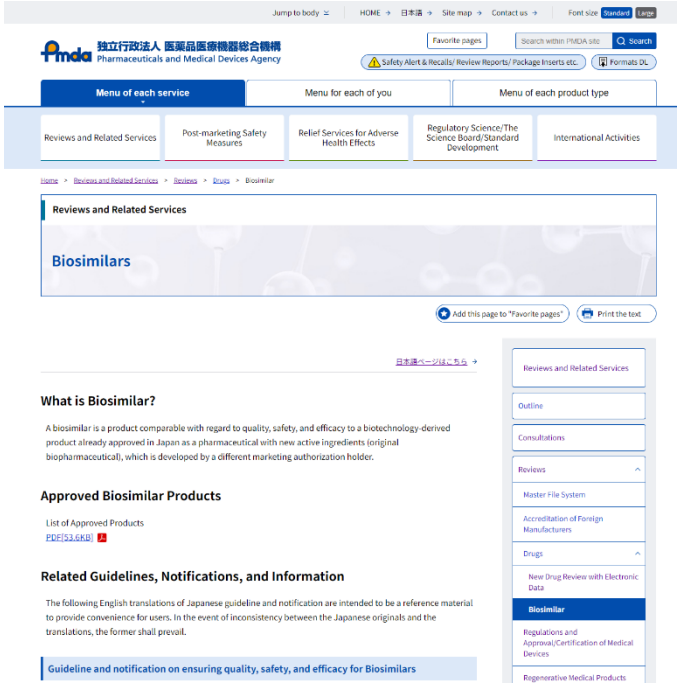
Questions & Answers on Guideline *(PSB/PED Administrative Notice / January 25, 2024)*
https://www.pmda.go.jp/files/000267480.pdf

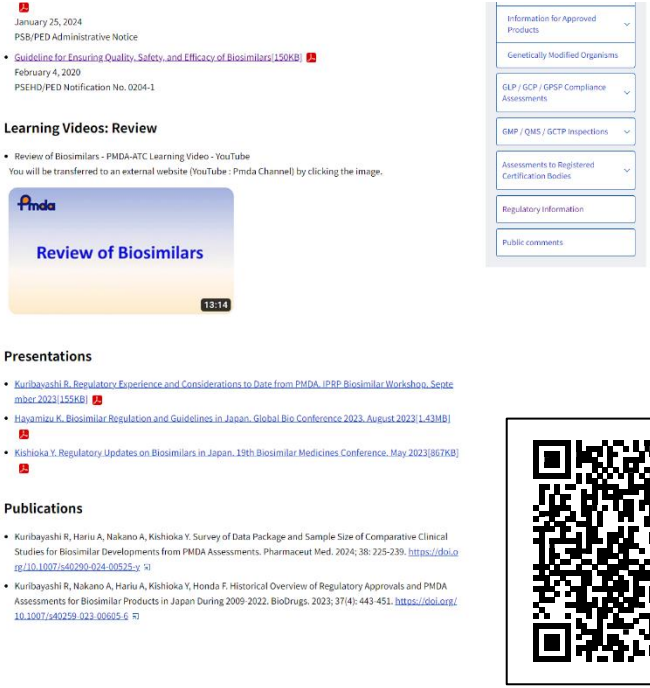
Reevaluation the Need for Comparative Efficacy Studies

https://admin.iprp.global/sites/default/files/2024-07/IPRP_BWG_Final%20IPRP%20Scientific%20Workshop%20Summary%20Report_2024_0506.pdf

PMDA Website on Biosimilars

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





Recent Publication

- Kuribayashi R, Goto K, Hariu A, Kishioka Y. Revisions to the Requirement of the Japanese Clinical Study Data for Biosimilar Developments in Japan. Expert Opinion on Biological Therapy. 2024; 24(7): 637-645.
  https://doi.org/10.1080/14712598.2024.2377300
- Kuribayashi R, Hariu A, Nakano A, Kishioka Y. Survey of Data Package and Sample Size of Comparative Clinical Studies for Biosimilar Developments from PMDA Assessments. Pharmaceut Med. 2024; 38: 225-239.
  https://doi.org/10.1007/s40290-024-00525-y
- Kuribayashi R, Nakano A, Hariu A, Kishioka Y, Honda F. Historical Overview of Regulatory Approvals and PMDA Assessments for Biosimilar Products in Japan During 2009-2022. BioDrugs. 2023; 37(4): 443-451.
  https://doi.org/10.1007/s40259-023-00605-6

Thank you for kind attention !