Provisional Translation (as of September 2025) *

Early Consideration on Handling of Japanese Data for Confirmation of Comparability of Biosimilars to the Original Biopharmaceuticals

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Office of Cellular and Tissue-based Products

1. Introduction

In Japan, in the development of biosimilars, at least either of a clinical trial to confirm the pharmacokinetics (PK) equivalence or a clinical trial to confirm the efficacy equivalence has been required to include Japanese subjects in order to evaluate the comparability of the biosimilars to the original biopharmaceuticals. However, the purpose of clinical trials of biosimilars is to confirm the comparability of the biosimilars to the original biopharmaceuticals. For generic drugs, Japanese data are not mandatory to evaluate the bioequivalence. Based on the above, the "Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars" (Administrative Notice dated January 25, 2024) was revised. As a result of the revision, it became possible to extrapolate the data of clinical trials conducted in non-Japanese subjects to Japanese subjects if ethnic factors were considered to have no impacts on the results of the clinical trial [1)].

The purpose of this document is to complement the contents shown in the relevant administrative notice and to present current regulatory perspective more clearly based on the experiences in PMDA regarding the principles on handling of Japanese data to confirm the comparability of biosimilars to the original biopharmaceuticals. However, these principles represent general principles and the evaluation should be carefully performed by individual biosimilar based on its properties and clinical trial design. Therefore, we recommend utilization of consultations with the PMDA as early as possible.

2. The Principles on Handling of Japanese Data

If data of clinical trials conducted in non-Japanese subjects alone are submitted as the evaluation data for approval application for a biosimilar instead of conducting clinical trials that include Japanese subjects, the applicant needs to explain that ethnic factors do not affect the clinical trial results from the following viewpoints:

2.1. Impact of ethnic factors on biosimilars

At the time of consultation and approval application, the sensitivity of a product under development to (1) intrinsic ethnic factors and (2) extrinsic ethnic factors should be explained based on the published literature, etc. on the original biopharmaceutical using the below table as a reference. Then, the applicant should explain the justification for extrapolating the data of clinical trials conducted in non-

* 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.

Japanese subjects to Japanese subjects. Regarding the principles on the impacts of ethnic factors on drugs, the "Ethnic Factors in the Acceptability of Foreign Clinical Data" (February 5, 1998, ICH E5(R1)), "Guideline on general principles for planning and design of multi-regional clinical trials" (November 16, 2017, ICH E17), and "Questions and Answers (Q&A) on basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan" (Administrative Notice dated December 25, 2023) can be used as references [2,3,4]. If a product under development has been used in multiple races/regions and patients with a wide range of body weights in clinical trials conducted overseas, it is useful to discuss ethnic factors based on the data of the relevant clinical trials.

(1) Intrinsic ethnic factors

Presence or absence of differences regarding intrinsic ethnic factors including genetic factors, physiological and pathological factors, and drug properties of the biosimilars.

(2) Extrinsic ethnic factors

Presence or absence of differences regarding extrinsic ethnic factors including social factors such as medical practice environment (treatment environment including diagnostic approach and standard treatment) for a target disease of the biosimilar.

2.2. Subgroup analysis of the original biopharmaceuticals

Whether or not differences regarding ethnic factors may affect the results of PK, efficacy, and safety between Japanese and non-Japanese subjects should be explained based on subgroup analyses of clinical trial data or post-marketing data of the relevant original biopharmaceutical.

2.3. Quality attributes of biosimilar and the original biopharmaceutical

In assessment of quality comparability between a biosimilar and the original biopharmaceutical, differences in the quality attributes should be explained. If there is any difference in quality attributes, whether or not the difference will affect ethnic differences between Japanese and non-Japanese subjects in terms of PK, efficacy, and safety (including immunogenicity) should be explained based on published literature, etc.

3. References

1) Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Administrative Notice dated January 25, 2024)
https://www.pmda.go.jp/files/000267480.pdf
2) ICH Harmonised Guideline. E5(R1): Ethnic Factors in the Acceptability of Foreign Clinical Data

(February 5, 1998)
https://www.pmda.go.jp/files/000156836.pdf

3) ICH Harmonised Guideline. E17: General Principles for Planning and Design of Multi-Regional Clinical Trials (November 16, 2017)
https://www.pmda.go.jp/files/000224562.pdf

4) Questions and Answers (Q&A) for Basic Principles for Conducting Phase 1 Studies in Japanese Prior to Initiating Multi-Regional Clinical Trials Including Japan for Drugs in Which Early Clinical Development Is Preceding Outside Japan (Administrative Notice dated December 25, 2023)
https://www.pmda.go.jp/files/000266728.pdf

Table Impacts of ethnic factors on biosimilars

Item		Not sensitive to ethnic factors	Sensitive to ethnic factors	Properties of a product under development *
Intrinsic ethnic factors	Pharmacokinetics	Linear	Non-linear	
	Pharmacodynamic curve	Flat	Steep	
	Therapeutic dose range	Wide	Narrow	
	Metabolism	Minimally metabolized or metabolized through multiple pathways	Highly metabolized, especially through a single pathway	
	Genetic factors	Small ethnic differences in genes that substantially affect PK, efficacy and safety	Large ethnic differences in genes that substantially affect PK, efficacy and safety	
	Bioavailability	High	Low	
	Potential for protein binding	Low	High	
	Potential for drug-drug, drug-food, and drug-disease interactions	Low	High	
	Impacts of BMI and body weight	Small	Large	
	Impacts estimated based on population pharmacokinetic analysis, etc.	Small	Large	
	Drugs that are rarely transferred to the systemic circulation and have a localized action	Applicable	Not applicable	
Extrinsic ethnic factors	Potential for inappropriate use	Low	High	
	Likelihood to be used with many concomitant medications	Low	High	
	Medical practice environment such as diagnostic approach and standard therapy	There are no differences between Japan and overseas	There are differences between Japan and overseas	

*: Relevant items should be explained according to the properties of each product under development.