Provisional Translation (as of April 2025)*

PMSB/ELD Notification No. 1023-3
October 23, 2024

To Directors of Prefectural Health Supervising Department (Bureau)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(official seal omitted)

# Basic Principles on Japanese Clinical Trial Data for Drugs for Rare Diseases, etc., for Which Confirmatory Clinical Trials Have Been Conducted Only Overseas

With the globalization of drug development, it has become the standard to simultaneously develop new drugs worldwide through multi-regional clinical trials in recent years. The number of Japanese participants in multi-regional clinical trials has been shown in "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare, dated September 28, 2007) etc. and consistency and similarity between the overall population and Japanese population have been evaluated.

When Japanese participants were not included in multi-regional clinical trials, domestic clinical trials have traditionally been conducted to confirm the efficacy and safety of the drug in Japanese population for new drug application.

However, for diseases with an extremely small number of patients, for example, the number of Japanese patients is very limited, and from the perspective of trial feasibility, it could be difficult to evaluate the consistency between the overall population and Japanese population in multi-regional clinical trials or the similarity between the results of overseas clinical trials and those of a domestic clinical trial. Conventionally, when there was insufficient data on Japanese participants to make population-based evaluations difficult, whether it is possible to apply data from foreign populations to the Japanese population have been comprehensively examined based on detailed medical information on individual participants.

Based on the review at “Review Committee on Regulatory Affairs to Strengthen Drug Discovery and Development/Ensure Stable Supply”, the basic principles on Japanese clinical trial data for drugs for rare diseases, etc., for which confirmatory clinical trials have been conducted only overseas, have been compiled as described below. We ask you to understand this compilation and inform related parties under your jurisdiction of this matter.

Description

1. Introduction

The basic principle to the approval review of drugs in Japan is to evaluate the efficacy and safety of the drug in Japanese patients in the Japanese medical environment based on the results of multi-regional clinical trials in which Japan participated or domestic clinical trials.

For drugs in which clinical development is preceding outside Japan, access to the drug for Japanese patients may be delayed if additional clinical trials have to be conducted in Japan. Furthermore, there were cases where development in Japan was abandoned owing to additional clinical trials in Japanese patients being required by the regulatory authorities.

This document is intended to elucidate cases where it is considered possible to file an application for approval without clinical trial results in Japanese patients so as to minimize the disadvantage of delayed or lost access to drugs for Japanese patients owing to the need for additional clinical trials while ensuring the efficacy and safety of the drug in Japanese patients.

As for the multi-regional clinical trials, it is necessary for Japan to participate as much as possible, even if the number of Japanese participants is very small. This is because comparisons between the results of the overall population and those of Japanese population could be made to some extent through comprehensive and multifaceted evaluations that also consider clinical perspectives, and also Japan’s involvement is of great importance from the perspective of providing information to the medical community.

2. Cases where the application for approval can be filed without clinical trial results in Japanese patients

(1) If criteria [1]-[3] are all met, the application for approval may be filed without clinical trial results in Japanese patients; however, it should be noted that this doesn’t mean that clinical trial results in Japanese patients must be needed for filing an application for approval, when the criteria cannot be fulfilled.

[1] The pivotal clinical trial has already been appropriately conducted overseas (including cases where an interim analysis has been completed and the primary evaluation can be made in the interim analysis).

However, if drugs have already been approved overseas based on case reports, real-world evidence, etc., instead of clinical trials, completion of overseas clinical trials would not be necessary.

[2] Conducting additional clinical trials are impracticable due to a very small number of patients or other factors.

The difficulty of conducting a clinical trial is not necessarily determined only by the number of patients but is comprehensively determined based on the seriousness or other characteristics of the indication, high unmet medical needs, and other factors. For example, in the case of fatal diseases or diseases that rapidly and irreversibly progress, it may be determined difficult to conduct clinical trials regardless of the number of patients. This is because, despite the uncertainty associated with the lack of additional clinical trials in Japanese patients, there is a greater disadvantage to patients if conducting additional clinical trials would require a considerable amount of time for approval.

[3] The benefits for Japanese patients are expected to outweigh the risks based on comprehensive considerations with the obtained information on efficacy and safety.

(2) However, if there is specific evidence indicating that there are clinically meaningful ethnic differences between non-Japanese and Japanese patients based on the characteristics of the drug or the data of similar drugs, and it is determined that additional information regarding the safety and appropriate dosage is needed, clinical trials (including clinical pharmacology studies) in the Japanese population may be deemed necessary.

3. Other

If the submission of clinical trial results in Japanese patients or other data is required after approval, the use of the conditional approval system should be considered.

Even when applying for approval without clinical trial results in Japanese patients, the applicant should consider conducting clinical trials (including the Japan compassionate use program) in parallel with the application for approval to collect as much information of administration to Japanese patients as possible on the drug in order to ensure access to the drug for patients as much as possible and prepare for its proper use in actual clinical settings in Japan. If there are some data collected in such clinical trials which can be

submitted during the review process, the applicant shall submit them. The submitted data shall be verified by the approval review, and if necessary, the information shall be provided to the medical community via the package insert or other means. It should be noted that clinical trials are not necessarily required, and as long as the scientific validity and feasibility of the clinical trial are considered, and if it is appropriate for the purpose of collecting information, it may be considered sufficient to collect information when the drug is administered to Japanese patients through post-marketing surveillance or studies using medical information databases, such as MID-NET, or patient registries.