Basic Principles Concerning Japanese Data in Cases Where Confirmatory Clinical Trials for Pharmaceuticals Used in Rare Diseases Have Been Conducted Exclusively Outside Japan[1]

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1.Introduction

The development of new pharmaceuticals has increasingly become a globalized endeavor, with simultaneous worldwide development being facilitated through international joint clinical trials. In assessing the number of Japanese subjects included in such trials, consistency and similarity between the overall population and the Japanese subpopulation have been evaluated based on principles outlined in documents such as *Basic Principles on International Joint Clinical Trials* (Notification No. 0928010, issued by the Director of the Pharmaceutical and Food Safety Bureau on September 28, 2007).

In cases where Japan has not participated in international joint clinical trials, it has traditionally required domestic trials to confirm the efficacy and safety of treatments in Japanese patients before granting regulatory approval. However, for certain diseases—especially those with very limited patient populations—recruiting a sufficient number of Japanese participants in either international or domestic trials may not be feasible. As a result, assessing the consistency between the overall study population and the Japanese subpopulation, or making meaningful comparisons between international trial results and Japanese data, becomes particularly challenging.

Historically, when the available Japanese data were too limited to allow for robust population-level evaluations, a comprehensive analysis has been undertaken to determine the extent to which foreign clinical data could be extrapolated to the Japanese population. This has been achieved through a detailed examination of individual patient medical information.

This document presents the fundamental guide principles regarding the utilization of Japanese data in instances where confirmatory clinical trials for pharmaceuticals intended for rare diseases have been conducted exclusively outside Japan. These principles have been formulated based on discussions within the *Review Panel on Pharmaceutical Regulations for Strengthening Drug Discovery Capabilities and Ensuring Stable Supply*. Stakeholders are

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requested to review the following provisions and ensure dissemination of relevant entities within their jurisdiction.

2. Conditions Under Which an Application for Approval May Be Submitted Without Clinical Trial Data in Japanese Patients

(1) Approval applications may be considered even in the absence of clinical trial data specific to Japanese patients, if all of the following conditions (1-3) are met. However, these conditions are not necessarily exhausting.

1- A primary clinical trial has been appropriately conducted overseas (including cases where an interim analysis, if capable of serving as the primary evaluation, has been completed). If a pharmaceutical has been approved overseas based on case reports or real-world evidence rather than clinical trials, completion of overseas clinical trials is not a prerequisite.

2- Conducting additional clinical trials in Japanese patients is often impractical due to factors such as an extremely limited patient population. However, the impracticality of conducting these trials should not be assessed solely based on patient numbers. It should instead be evaluated comprehensively, considering factors such as disease severity, unmet medical need, and other relevant aspects. For example, in the case of life-threatening or rapidly progressing, irreversible diseases, delaying approval due to the need for additional clinical trials could impose a significant burden on patients. In such situations, the necessity of further trials should be critically evaluated, with a focus on factors beyond just the patient population size.

3- The available efficacy and safety data indicate, in a comprehensive manner, that the benefit-risk profile for Japanese patients is favorable.

However, if substantial evidence suggests the presence of clinically significant ethnic differences between Japanese and non-Japanese populations—based on the pharmacological characteristics of the drug or the behavior of related pharmaceuticals—additional safety and dosage information may be deemed necessary. In such cases, conducting clinical trials (including clinical pharmacology studies) in Japanese patients may be required.

3. Additional Considerations

The submission of clinical trial data involving Japanese patients shall be required post-approval, the conditional approval framework shall be considered as an alternative regulatory pathway.

Even in cases where an approval application is submitted without clinical trial data specific to Japanese patients, efforts should be made to ensure that Japanese patients have access to the pharmaceutical and that appropriate measures are taken for its safe and effective use in Japan's clinical settings.

Parallel to the approval application, efforts should be made to conduct additional studies (including expanded access trials) to collect data on Japanese patients who receive the drug. Any data obtained from these studies that can be submitted during the regulatory review process should be provided accordingly.

The data submitted during the review process will be scrutinized by the regulatory authorities, and where necessary, relevant information should be communicated to medical institutions through appropriate labeling and documentation.

The requirement for clinical trials should not be absolute; alternative means of data collection—such as post-marketing surveillance, the utilization of MID-NET (a medical information database network), or patient registries—should also be considered. If these alternative methods provide sufficient data, they may be deemed adequate substitutes for clinical trials.