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Commentary

PMDA initiatives to enhance drug development via multi-regional clinical trials

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INTRODUCTION

With recent changes in drug discovery and development (e.g., an increase in emerging or smaller foreign companies with no or only small Japanese subsidiaries), and the shift from small molecule compounds to novel modalities, the relative decline of international competitiveness of Japanese pharmaceutical companies and so-called drug lag (delayed approval in Japan)/drug loss (not developed in Japan) issues have been reported [1-3]. As of March 2023, 86 drugs that were approved in Europe and the U.S. between 2016 and 2020 had not been approved in Japan [4]. The Japanese government initiated the "Council of the Concept for Early Prevalence of the Novel Drugs to Patients by Improving Drug Discovery Capabilities" and established multiple strategic objectives to strengthen drug discovery and development in Japan [1]. The Pharmaceuticals and Medical Devices Agency (PMDA) plays a significant role in shaping these policies and is currently reviewing and working to improve pharmaceutical regulations in Japan. These activities include PMDA's support in promoting multiregional clinical trials (MRCTs) and support in the development of drugs for pediatric patients, intractable diseases, and rare diseases. In this commentary, recent PMDA actions regarding these issues are outlined.

REASSESS THE CONCEPT OF CONDUCTING PHASE I STUDIES IN JAPANESE SUBJECTS

The PMDA and Ministry of Health, Labor, and Welfare have developed guidelines to promote MRCTs [5-7]. Although the need to conduct a Japanese phase I study should be determined in consideration of the pharmacokinetics (PK)/pharmacodynamics (PD) properties and safety of the drug, the former guidelines stated that a Japanese phase I study prior to an MRCT was required "in principle" to evaluate tolerability and PK in Japanese subjects. In practice, for Japanese patients to participate in MRCTs without delay, the PMDA has not always requested a Japanese phase I study prior to participation in MRCTs, rather, it has decided on a case-by-case basis based on scientific data. However, in some cases, companies voluntarily conducted a Japanese Phase I study without consulting the PMDA. Additionally, startups based in other countries who were not familiar with the regulations concerning pharmaceuticals in Japan faced challenges in comprehending the situation. In light of these circumstances, the PMDA has established new guidelines aimed at specifying instances in which a phase I

study in a Japanese population is not needed prior to participation in a phase II or III MRCT [8]. The new guidelines clearly state that an additional phase I study in Japanese subjects is not needed unless it is deemed necessary after assessing whether the safety or tolerability of the dosage to be evaluated in MRCTs in Japanese patients can be explained and the safety is considered to be clinically acceptable/manageable based on the available data. The guidelines advise that Japan's participation in clinical trials from an early stage of drug development is still desirable. This is because it's crucial to identify key ethnic factors and improve Japan's drug discovery and development capabilities. The guidelines not only include fundamental principles but also illustrate instances where a phase I study in Japanese subjects is unnecessary, as demonstrated below:

1) To minimize the disadvantages caused by the delay in the introduction of the drug to Japan, in the case of drugs with highly unmet medical needs (e.g., drugs for rare diseases, drugs for diseases that are refractory and serious, or drugs for pediatric patients), it is possible to initiate MRCTs without a phase I study in a Japanese population.

2) The case where the safety of Japanese participants is considered clinically acceptable/manageable based on whether PK and/or safety are less likely to be sensitive to ethnic factors based on clinical and nonclinical data and existing knowledge.

Even for drugs that meet 1) or 2) above, the necessity of a phase I study in Japanese subjects should be considered more carefully if the drug is expected to frequently cause serious adverse events and has a narrow safety margin, as observed in some anticancer drugs, with limited safety data such as no experience of administration to Japanese subjects, regardless of age and/or indication.

Questions and answers to the guidelines were also issued to help drug developers decide whether to conduct a phase I study in a Japanese population [9]. This document shows points to consider when determining whether the safety of Japanese participants is clinically acceptable and manageable in the MRCT, in which Japanese patients will participate. A comprehensive evaluation of the risks of the study drug is paramount, and developers should mainly take into account the safety profile of the study drug and the effect of ethnic factors on the PK of the study drug to evaluate whether there is a possibility that the risk of Japanese participants is greater than that of non-Japanese participants. Whether PK is susceptible to ethnic factors should be investigated based on linearity, metabolic pathways, susceptibility to genetic polymorphisms, bioavailability, and the analysis of covariates in population PK. Evaluation of PK and safety in multiple regions and ethnic groups from the early development phase based on the characteristics of the study drug will provide useful information for the planning and implementation of subsequent MRCTs. Regardless of whether a phase I study is conducted in Japan, it is important to assess the differences in PK and/or PD between Japanese and non-Japanese populations through measures such as collecting PK and/or PD data in MRCTs prior to applying for marketing authorization in Japan.

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SUPPORT PROMOTION OF THE DEVELOPMENT OF DRUGS FOR CHILDREN, INTRACTABLE DISEASES, AND RARE DISEASES

The development of many pediatric and orphan drugs in Japan is delayed or absent, partly because of the small market size of these drugs. Therefore, it is important to promote the development of these drugs. The PMDA has established the Consultation Center for Pediatric and Orphan Drugs Development to provide consultation on plans for pediatric drug development and to implement the early designation of orphan drugs. The consultation center offers incentives to companies through reduced consultation fees for eligible products. The following measures are expected to help the development of pediatric and orphan drugs, which are often difficult to develop due to the small number of patients.

- Conducting MRCTs
- Application of modeling and simulation methods based on appropriate PK/PD data
- Clarification of cases in which data on Japanese patients are not necessary in confirmatory studies

Obtaining PK/PD data from phase I studies in multiple regions, including Japan, may lead to a more efficient use of these measures.

INTERNATIONAL DISSEMINATION OF PHARMACEUTICAL REGULATIONS IN JAPAN

To promote the introduction of innovative drugs to Japan from overseas, it is necessary to have a system that actively provides consultation support for overseas startups. The PMDA is working to establish an overseas base in Washington, DC (US), which will promote further international regulatory collaboration and disseminate medical-product-related information on and from Japan. The PMDA office aims to clear up misconceptions surrounding Japanese regulations and promote pharmaceutical regulatory systems, including the innovative drug designation program that provides priority reviews, preferential premiums on drug prices, and a conditional approval system that allows for early access in instances where conducting confirmatory clinical studies is challenging. In addition, the use of abridged review systems is expected to be promoted in Asian countries for drugs approved in Japan to provide early access to innovative drugs to patients in Asian countries. This will position Japan as a gateway to Asia. The PMDA Asia Office, the first overseas base of PMDA, was established in Bangkok, Thailand on July 1, 2024. The Asian Office collaborates with regulatory authorities in Asian countries to expedite the availability of medical products approved in Japan to patients in ASEAN and other Asian nations.

CONCLUSION

In response to the current phenomenon known as drug lag/drug loss, the PMDA has taken new measures, which include the development of new guidelines. The measures introduced in this commentary do not aim to reduce the significance of data obtained from early clinical trials (phase I studies) and subsequent phase trials in Japanese patients. Instead, they are

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a component of the efforts to promote more efficient development of novel drugs in Japan and are anticipated to reduce drug lag and drug loss in the country. To achieve this goal, further improvements in pharmaceutical regulations and clinical trial environments are currently under consideration. The PMDA publicizes these significant changes in the drug development environment in Japan to guide pharmaceutical companies, investors, and foreign regulatory agencies to accurately understand these changes.

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