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New Horizon in Clinical Development Strategy in Japan Based on New Guideline on Japanese Phase 1 Studies Prior to Multi-Regional Clinical Trials

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Although the new guideline on Japanese Phase 1 studies prior to Japan's participation in multi-regional clinical trials (MRCTs) notified in December 2023 states that, in principle, an additional Japanese Phase 1 study prior to MRCTs is not needed, its interpretation was still controversial. Here, we summarized and discussed the regulatory, academia, and industry perspectives on the new guideline by referring to a session we organized at the Drug Information Association Japan 2024 annual meeting.

1 | Background

To facilitate more rapid availability of drugs to patients worldwide, it is essential to utilize multi-regional clinical trials (MRCTs) throughout the clinical development, preferably not only in the confirmatory stage but also in the exploratory stage. In Japan, the Ministry of Health, Labour and Welfare (MHLW) has notified several Japan-specific guidelines for MRCTs [1–3], which contributed to a significant reduction of the time lag to approval of new drugs between Japan and the United States (US)/the European Union [4]. However, the guidelines required, in principle, to conduct a Japanese Phase 1 study (J-Ph1) to evaluate the safety and pharmacokinetics (PK) of investigational drugs in Japanese before joining MRCTs [1]. This requirement would be important in terms of safety risk mitigation in Japanese participants to be enrolled in MRCTs. On the other hand, the conduct of an additional J-Ph1 prior to MRCTs could have a negative impact on the strategy for overseas pharmaceutical companies, especially emerging biopharma companies (EBPs), in developing their innovative drugs in Japan, contributing to "drug loss," which has recently been a major problem in Japan [5].

To address the drug loss in Japan, the MHLW released a new guideline in December 2023 [6], which states that, in principle, an additional J-Ph1 before MRCTs is not needed unless it is deemed necessary after assessing whether the safety and tolerability of Japanese participants in the MRCTs can be explained, and the safety is clinically acceptable and manageable based on all the available data. Figure 1 shows a summary of the key consideration points introduced by the guideline. However, its interpretation, especially how to evaluate and judge the differing risks of conducting versus not conducting J-Ph1 before joining MRCTs (Figure 1), was controversial in Japan since the implementation of the guideline has just begun.

In Drug Information Association (DIA) Japan, we launched a community of clinical pharmacology (CP) in 2022, and have organized several sessions at the DIA Japan annual meetings since 2022. In 2024, we organized a session aimed at

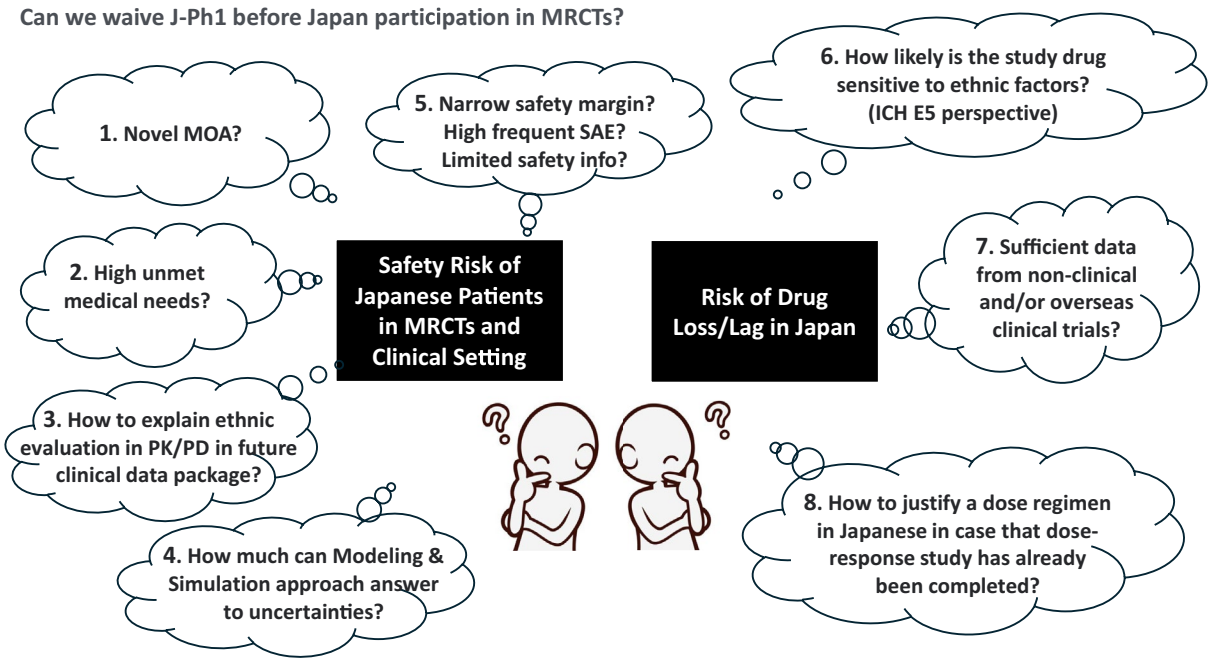

FIGURE 1 | Consideration points in evaluating the necessity of Japan Phase 1 study before initiating MRCTs. ICH, International Council for Harmonisation; J-Ph1, Japanese Phase 1 study; MOA, mode of action; MRCT, multi-regional clinical trial; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event.

ensuring alignment about the guideline among regulators (i.e., Pharmaceuticals and Medical Devices Agency, PMDA), academia, and industry. Here, we summarized and discussed the regulatory, academia, and industry perspectives on the interpretation and expectations for the guideline by referring to presentations and discussions provided throughout the session.

2 | Regulatory Perspective

Firstly, Mr. Kobayashi explained that conducting additional J-Ph1 is not the sole cause of the drug loss because other factors, such as not streamlining clinical trials and insufficient dissemination of information overseas on the Japanese pharmaceutical affairs system, are complicatedly interacting. Then, he provided an overview of the guideline, particularly focusing on what has changed and what has remained the same. Although the principle regarding the conduct of J-Ph1 before MRCTs has been changed from "necessary" to "unnecessary," it should not be considered that J-Ph1 before MRCTs is no longer needed, and it is important to make a comprehensive judgment based on product characteristics [1–3, 6]. In addition, it was also reminded that Japan's participation from the early phase of clinical development, including Phase 1 studies, is recommended in the guideline as well [6]. Regarding how to evaluate potential differences in PK or pharmacodynamics (PD) of an investigational drug between Japanese and non-Japanese in case of J-Ph1 waiver, he introduced some options such as a population analysis approach based on sparse data from Phases 2 and/or 3 MRCTs if the drug characteristics allow and the conduct of CP studies in Japanese in parallel with the MRCTs.

3 | Academia Perspective

Prof. Nagai provided a few examples to review compounds with widely known ethnic differences in PK, dose–response relationships, and safety between Japanese and non-Japanese, such as statins, anti-viral drugs for hepatitis C, and direct oral anticoagulant agents. In this review, it was recapped that genetic polymorphisms in metabolic enzymes (e.g., cytochrome p450 2C19 or 2D6) and transporters (e.g., organic anion transporting polypeptide 1B1, breast cancer resistance protein) could be a significant ethnic factor that can affect the PK, which in turn may have some impact on the PD and safety outcomes in Japanese [7, 8]. As the guideline recommends utilization of modeling and simulation (M&S) approaches in judging the necessity of J-Ph1 before MRCTs, Prof. Nagai introduced best practices that model-based approaches and more flexible designs of the early-phase clinical trial were helpful for understanding potential ethnic differences [8, 9].

4 | Industry Perspective

Dr. Tsuda shared two cases for the company to challenge a waiver of J-Ph1. Interestingly, although the investigational drugs in both cases were monoclonal antibodies with linear PK, a favorable safety profile from available data from the investigational drugs, and safety information from other compounds with the same mode of action, the PMDA provided different opinions (accepted/rejected) regarding a waiver of J-Ph1 in each case. In the rejected case, the PMDA requested (1) safety data after multiple doses, and (2) a concrete Phase 2 MRCT design at the timing of the PMDA consultation meeting. However, given that this information is often unavailable in planning J-Ph1 before MRCTs, it would be a concern that the company must take a potential risk of failure/

delay in Japan's participation in MRCTs to challenge a waiver of J-Ph1.

5 | Discussion

During a panel discussion part of the session, it was discussed whether the guideline had any impact on each field. In the PMDA, there has been no significant impact so far, whereas the number of consultation requests including a waiver of J-Ph1 has recently increased a little bit. In the industry, especially in a global company, global headquarters started to put more pressure on the Japan branch about a waiver of J-Ph1 because global colleagues often misunderstand that J-Ph1 is no longer needed under the guideline. Therefore, it is important to have an opportunity to confirm if we are on the same page regarding interpretation on the guideline not only within the Japan team but also with the global team from regulators/academia/industry, especially with EBPs. Fortunately, the PMDA Washington, D.C. office was launched in November 2024 to promote regulatory cooperation and information exchange with the US government on site and to provide the information regarding Japanese regulations to EBPs located in the United States [10].

Regarding conditions to waive J-Ph1 before MRCTs, while all the panelists acknowledged that it would be difficult to specify some conditions as a general case because no investigational drugs have the same characteristics and conditions, it was agreed that the consideration points #1, 5, 6, and 7 in Figure 1 should be important in ensuring the safety of Japanese patients participating in MRCTs. Prof. Nagai agreed with this opinion and additionally pointed out that it would be possible to speculate potential ethnic differences or similarities in exposure between Japanese and non-Japanese with high confidence based on human PK data from overseas clinical trials as well as information on the clearance pathway suggested by in vitro studies and literature without having J-Ph1 before Japan's participation in MRCTs. Since the MHLW released the ICH E5 guideline in 1998, important data for understanding the mechanism and prevalence of genetic polymorphisms in metabolic enzymes and transporters have been accumulated and investigated by conducting a lot of J-Ph1. This precious information is now a kind of legacy not only for Japan but also for the global development program. Therefore, it is time to utilize the legacy scientifically for more efficient drug development, rather than merely keeping or continuing to accumulate it, Dr. Tsuda added with all the panelists in agreement. As one option to utilize the legacy, Prof. Nagai commented that it is highly expected for the PMDA to conduct and report comprehensive analyses for ethnic differences using a huge amount of data submitted electronically by pharmaceutical companies as the PMDA had stated. We believe that such analyses will help us justify the necessity of additional J-Ph1 before Japan's joining MRCTs.

From the audience, one investigator reminded that there were some cases where the genetic polymorphisms in metabolic enzymes or transporters could not entirely explain significant ethnic differences or similarities in drug disposition and response. We definitely agree that potential ethnic differences in drug disposition and response should be carefully evaluated to secure the safety of Japanese participants in Phases 2 and/or 3 MRCTs. However, it was also suggested that a well-designed Phase 1 study, such as enabling evaluation of body weight impact on the exposure by enrolling subjects with a wide range of body weight, or stratifying subjects based on their genetic polymorphism information for metabolic enzymes or transporters, would be more important than conducting an additional J-Ph1 in terms of devising a strategy for the overall clinical data package globally.

At the end of the session, it was emphasized that the guideline gave us a good opportunity to reconsider the overall drug development strategy more flexibly not only for Japan but also for the global. Actually, some global companies initiated making more effort to conduct first-in-human studies and/or CP studies in Japan rather than in the United States or other regions. However, there are some hurdles to streamline this approach, such as the need for Japanese translation for study materials and the complicated process of the Institutional Review Board of clinical research facilities in Japan. Therefore, we believe that more collaboration among regulators, academia, and industry must be required to overcome these hurdles.

There were a couple of limitations to the session. Firstly, all the presenters at the session were neither investigators who were responsible for Phases 2 and 3 MRCTs nor patients. Secondly, even though the guideline was intended for EBPs, no discussion was made by them during the session.

6 | Future Expectations

As the scientific and fruitful discussion among regulators, academia, and industry was successfully made in this session, the more we collaborate, the more streamlined drug development for both Japan and the global market will be achieved under the new guideline.

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Disclosure

Y Kobayashi works for the Pharmaceuticals and Medical Devices Agency, but the views expressed in this article are those of the author and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency.

Conflicts of Interest

The authors declare no conflicts of interest.

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