厚生労働省 ひと、くらし、みらいのために Ministry of Health, Labour and Welfare

The Background and Content of the Notification

Multi-Regional Clinical Trials Symposium 2025 – August 4, 2025

Pharmaceutical Evaluation Division,

Pharmaceutical Safety Bureau,

Ministry of Health, Labour and Welfare

Daisuke Sato

Ministry of Health, Labour and Welfare of Japan

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● Background of the Notification

Actual Conditions of Drug Lag/Drug Loss

- As of March 2023, there are **86 drugs (60.1% of unapproved drugs)** which are approved in the US and EU but **not yet started development in Japan**. It is pointed out that there are **drug lag/loss cases where application for approval are not performed (i.e. companies do not develop the drug)** in the first place.
- The analysis of trends for 86 drugs of which development are not yet started found that **the percentages of startup company-originated, orphan or pediatric drugs are relatively large.**

Status of drug lag/loss in Japan, EU and the US

(Number of drugs)

	Approved	Total of unapproved	Included number of unapproved	
			Under development	**Not yet developed**
US	136	7	3	4
EU	86	57	26	31
Japan	0	**143**	57	**86** (drugs)

Break down →

Breakdown of drugs not yet started development in Japan

Startup-originated	Orphan	Pediatric
56% (48 drugs)	**47**% (40 drugs)	**37**% (32 drugs)

※Of 86 drug loss items, items that are not startup-originated, orphan or pediatric drugs are 14 (16%).

※Source: Based on public information from PMDA, FDA and EMA and "Asu-no-Shinyaku" (TECHNOMICS, INC.), prepared by Office of Pharmaceutical Industry Research(OPIR) and summarized by MHLW

※１：Of NMEs approved in EU and US between 2016 and 2020, items that were not approved in Japan as of the end of 2022 are counted as unapproved.

※２：Items that had not development information as of March 2023 are counted as not yet started development in Japan.

※３：Development companies that had approval in EU and US within 30 years of the establishment and their sales in previous year of approval are less than USD 500 million are counted as start-up.

※４：Drugs that were designated as orphan drug by the time of approval in EU and US are counted as orphan.

※５：Drugs that obtained pediatric indication in EU and US as of the end of 2022 are counted as pediatric.

Excerpt from the Expert Panel Report on Comprehensive Measures for the Rapid and Stable Supply of Pharmaceuticals

Chapter 2: Direction of Measures for Achieving Rapid and Stable Supply of Pharmaceuticals
2.1 Ensuring Stable Supply of Pharmaceuticals
2.1.1 Restructuring of the Generic Drug Industry (Government-led Infrastructure Development for Stable Supply)
(omitted)

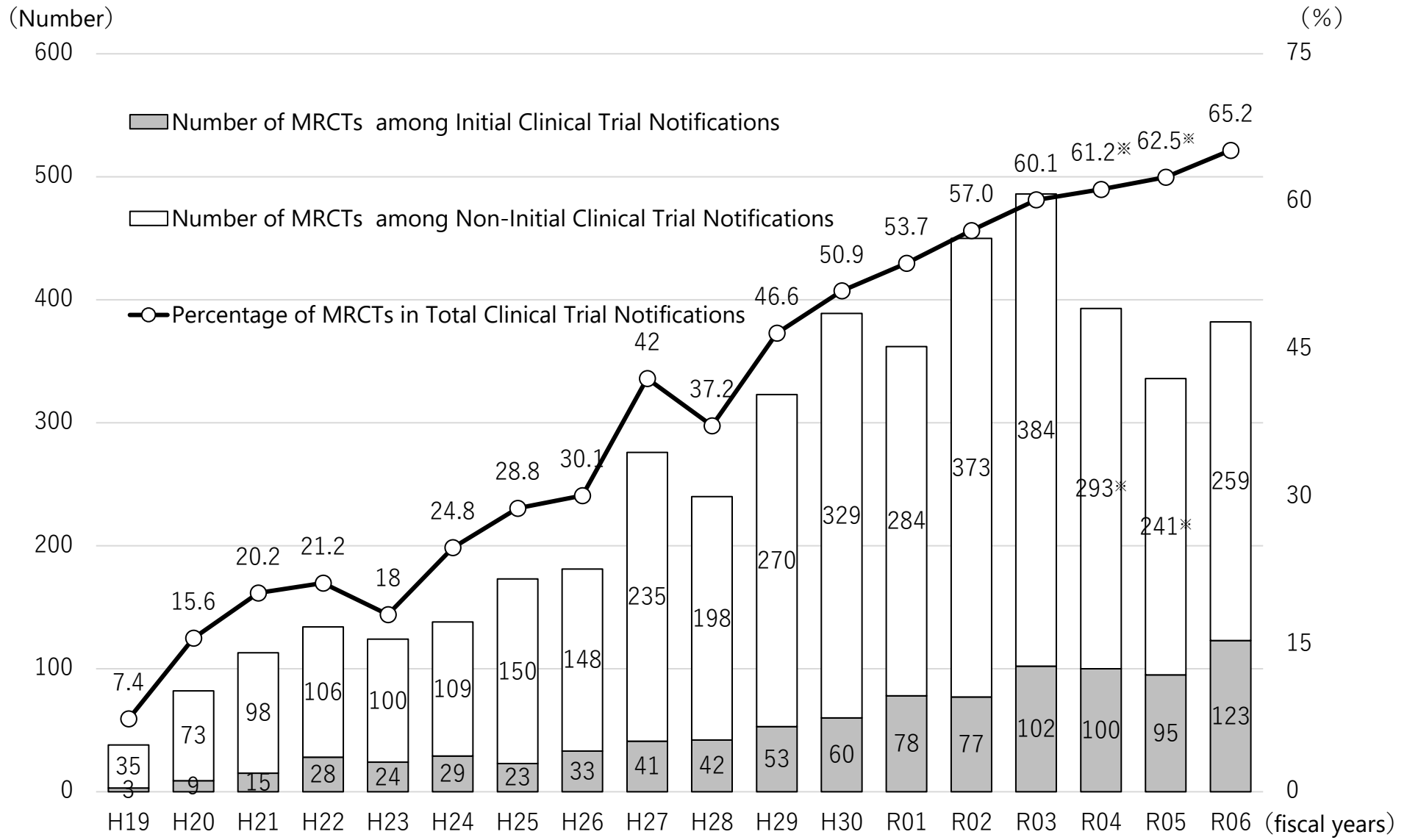
2.2 Strengthening Drug Discovery Capabilities and Eliminating Drug Lag / Drug Loss
2.2.2 Eliminating Drug Lag / Drug Loss
(Promotion of Multi-Regional Clinical Trials and Improvement of Clinical Trial Environment)

•Currently, clinical trial performance of Japan is lower than that of other countries. Regarding Multi-Regional Clinical Trials, there are opinions that Japan is avoided by pharmaceutical companies due to difficulty in enrolling Japanese patients.
•To gain more attention from other countries, the government must take the lead in promoting Japan's presence worldwide. This includes encouraging domestic clinical trial sites to participate in Multi-Regional Clinical Trials and **clarifying the necessity of data from Japanese people for pharmaceutical approval**.

(Regulatory Aspects)
(omitted)

(Proactive Information Dissemination Overseas)
(omitted)

Trends in the Number of Clinical Trial Notifications for Multi-Regional Clinical Trials



※Note: The data excludes clinical trial plan notifications submitted due to the change in the format of the clinical trial notification (revised in August 2020).

Study Group on Pharmaceutical Regulations to Strengthen Drug Development and Ensure Stable Supply

- "Study Group on Pharmaceutical Regulations to Strengthen Drug Development and Ensure Stable Supply" was established to discuss issues related to regulations and published the report on April 24, 2024. Discussed issues include;
  - drug loss
  - ensuring stable supply of drugs
  - promoting the development of pediatric drugs, etc.

Matters considered

Promotion of development	How orphan drugs should be designated How the regulatory review process should be conducted to promote the development of pediatric drugs
Clinical trials	The need for Japanese data in the approval review process in Japan Further streamlining of clinical trials (ecosystem)
Post-marketing safety measures	How post-marketing drug-use surveys, etc. should be conducted How real-world data should be used
Quality	How the regulatory review process related to the manufacturing process of pharmaceuticals should be conducted
Transmission of information	Transmission of information to foreign countries about the pharmaceutical regulatory system in Japan

Schedule

July 10, 2023	**Orphan drugs, pediatric drugs**
August 7	**Phase I study in Japanese**
September 13	**Phase I study in Japanese**
October 13	**Manufacturing process, etc.**
November 15	**Transmission of information to overseas, GMP**
December 13	**Accelerated approval, Japanese data**
January 12, 2024	**Post-marketing drug use-survey, RWD**
February 8	**Accelerated approval, Japanese data**
March 21	**Post-marketing drug use-survey, RWD, clinical trial ecosystem, PMDA, etc.**
April 24	**Finalizing the report**

Summary of Discussion Topics

Promotion of development

How orphan drugs should be designated

How the regulatory review process should be conducted to promote the development of pediatric drugs

Clinical trials

The need for Japanese data in the approval review process in Japan

- For drugs that have undergone early clinical trials overseas, the approach to confirming safety for Japanese participants should be clarified when Japan joins the Phase III of Multi-Regional Clinical Trials (including the necessity of Phase I trials).
- For drugs used in rare diseases that have only undergone confirmatory trials overseas, the approach to regulatory approval in Japan should be clarified.

Further streamlining of clinical trials (ecosystem)

Post-marketing safety measures

How post-marketing drug-use surveys, etc. should be conducted

How real-world data should be used

Quality

How the regulatory review process related to the manufacturing process of pharmaceuticals should be conducted

Transmission of information

Transmission of information to foreign countries about the pharmaceutical regulatory system in Japan

Overview of Considerations: Necessity of Japanese Phase I Trials

The 2nd Expert Panel Meeting on Study Group on Pharmaceutical Regulations to Strengthen Drug Development and Ensure Stable Supply
August 7, 2023
Document 1 (Excerpt)

Changes in the Drug Development Environment and Process

•Due to changes in the drug discovery environment, even major pharmaceutical companies are increasingly relying on **drug discovery seeds from emerging biopharma companies**.

•These overseas biopharma companies, due to business constraints, **rarely conduct development in Japan simultaneously with the US/EU during early stages**. As a result, Japanese development often begins **after Phase II trials**, typically when the drug is licensed to a major pharmaceutical company.

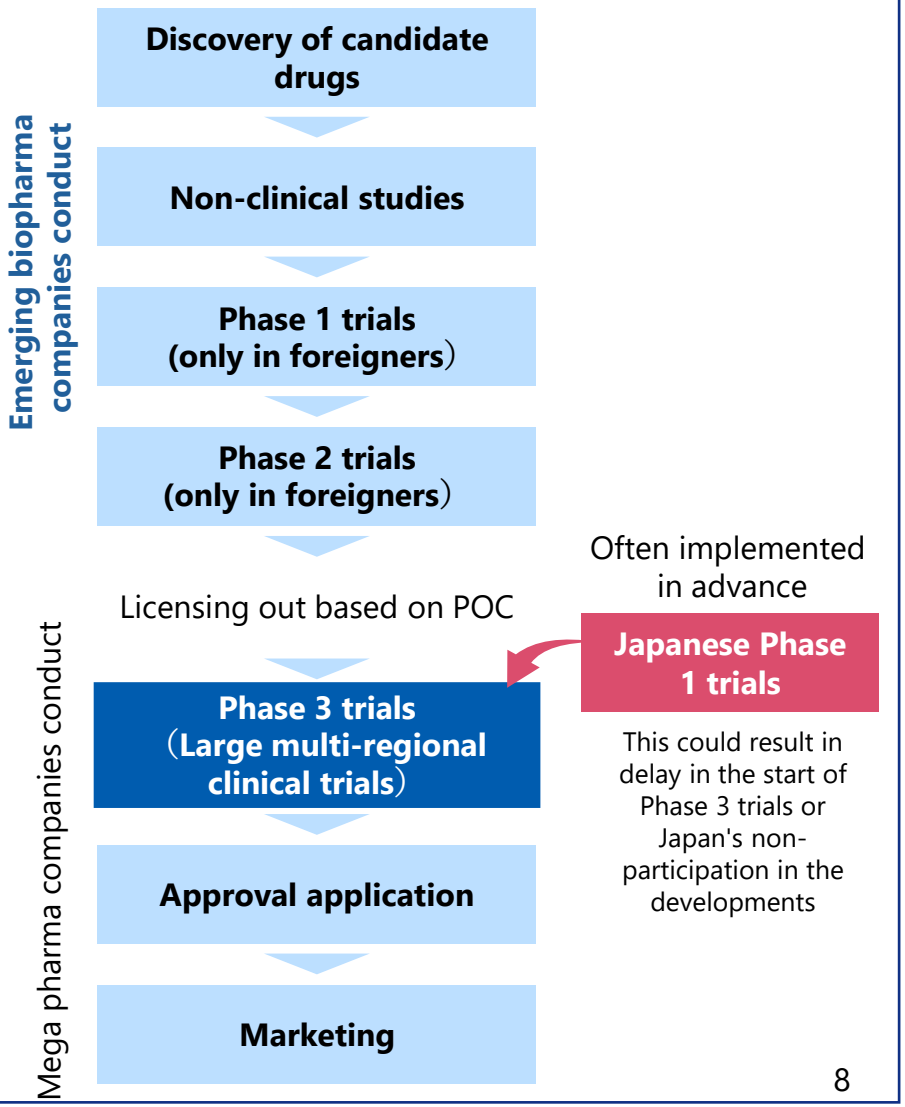
Necessity of Japanese Phase I Trials（before discussion）

•When Japan participates in Multi-Regional Clinical Trials, it is considered necessary to conduct Phase I trials in Japanese participants **if sufficient explanation regarding safety in Japanese participants is not provided.**

•However, conducting a Japanese Phase I trial requires **significant time and cost**, which may **delay the start of Phase III trials** or lead companies to **abandon development in Japan** altogether.

•To balance **ensuring safety in clinical trials** and **accelerating the practical use of new drugs**, it is necessary to **clarify the concept regarding the necessity of Japanese Phase I trials prior to international joint trials**.

Flow of development of drugs discovered by emerging biopharma companies (An example)



Opinions from the Pharmaceutical Industry

In light of the situation where conducting Japanese Phase I trials prior to participating in Multi-Regional Clinical Trials may lead to delays in Japan's participation, non-participation, or even abandonment of development in Japan, the pharmaceutical industry has expressed the following opinions regarding the necessity of Japanese Phase I trials:

- The current principle indicates that **Phase I trials** on **Japanese people are required before participating in Multi-Regional Clinical Trials, but it should be reconsidered. Participation in Multi-Regional Clinical Trials should be allowed regardless of Phase I trials conduction for Japanese** if safety and risks in tolerability can be explained and deemed acceptable/manageable based on available data.
- There is a **gap between PMDA and companies** regarding the criteria for determining the necessity of Japanese Phase I trials. To bridge this gap, the **perspectives and rationale for safety and tolerability risk assessment should be documented as concretely as possible**, thereby enhancing mutual understanding among stakeholders including PMDA, clinical trial sites, and companies (including ventures).

Note: These opinions were gathered from the Multi-Regional Clinical Trials Working Group, including input from JPMA, PhRMA, and EFPIA.

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●Contents of the Notification

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

- For drugs whose early clinical development preceded outside Japan and consideration of Japan's participation in the subsequent multi-regional clinical trials began at the time of the implementation of the trials, participation of the Japanese subjects in multi-regional clinical trials may significantly affect the success or failure of the introduction of the drug to Japan afterward.
- Basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials were summarized and the notification* was issued, from the perspective of ensuring the safety of Japanese participants in multi-regional clinical trials and minimizing the disadvantages to patients caused by the delay in the introduction of the drug in Japan.

  *"Basic principles for conducting phase I studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is proceeding outside Japan" (PSB/PED Notification No. 1225-2 issued on December 25, 2023 by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
- The details of this notification have been translated into English and published, and information will be provided to overseas venture companies.

Basic principles

- **Phase I studies prior to initiating multi-regional clinical trials are not required on a racial/ethnic or national/regional basis. In principle, they are not required unless it considered as necessary based on consideration for safety, etc. of Japanese participants in clinical trials from the available data**.
- On the other hand, from the perspective of providing information to medical institutions, **it is desirable to collect information on pharmacokinetics, etc. in Japanese as much as possible**, such as through participation of Japanese in phase I study when they are conducted as a multi-regional clinical trial.

Principles for individual drugs

- It is possible to participate in multi-regional clinical trials without conducting a phase I study in Japanese after appropriate informed consent is obtained, in case of drugs with high unmet medical needs, such as drugs for rare diseases, intractable and serious diseases, or pediatrics (regardless of whether it is developed for adults).
- For other drugs as well, a Japanese phase I study is not required if the safety of Japanese participants can be judged to be acceptable based on non-clinical data, results of foreign clinical trials in multiple races, etc. On the other hand, conducting a phase I study should be considered when the number of patients is large and there is sufficient time to conduct a phase I study. However, this does not apply when the risk in Japanese is considered to be not significantly greater than in non-Japanese.
- **The necessity of a phase I study in Japanese should be judged more carefully if the drug is expected to have high rates of serious adverse events, as observed in such as anti-cancer drugs, and if the drug has limited safety information** such as little experience of administration in Japanese.

Others

- Regardless of conducting phase I studies in Japanese, it is important to examine domestic and international differences in pharmacokinetics and pharmacodynamics prior to application for approval.
- When deemed necessary by the sponsor, additional safety measures for Japanese participants in multi-regional clinical trials will be set.
- Eventually, PMDA may provide necessary instructions or advice in clinical trial consultations, etc.

Basic principles

- In general, it is not mandatory to conduct a phase 1 study in each race/ethnicity or country/region before initiating an MRCT. In principle, an additional phase 1 study in Japanese is not needed unless it is deemed necessary after assessing whether the safety/tolerability of the dosage to be evaluated in the MRCTs in Japanese participants can be explained and the safety is clinically acceptable/manageable based on the data available prior to Japan's participation.
- On the other hand, it is desirable to consider measures such as including Japan when the phase 1 study is conducted as an MRCT to collect information on Japanese, such as pharmacokinetics (PK), as much as possible to provide detailed information to study sites that will participate in the MRCTs and to appropriately design subsequent MRCTs taking into account potential regional differences in intrinsic ethnic factors such as PK that may affect the efficacy and safety of the drug.
- For this reason, it is necessary to make a judgment for each individual drug based on the balance between items such as the magnitude of the risk of the drug, sensitivity to ethnic factors, medical needs, and disadvantages of not participating in MRCTs from Japan.

Examples of decisions for individual drugs

（1）Japan can participate in MRCTs without conducting a phase 1 study in Japanese provided appropriate informed consent is obtained for drugs with high unmet medical needs, such as drugs for rare diseases, diseases that are refractory and serious, or pediatrics regardless of whether it is developed in adults, where participation in planned or ongoing MRCTs is considered desirable to develop the drug in Japan.

（2）Except for drugs described in (1), Japan can participate in MRCTs without conducting a phase 1 study in Japanese if the safety of Japanese participants, at a minimum, can be judged to be clinically acceptable/manageable considering facts such as PK and/or response safety are less likely to be sensitive to ethnic factors such as race based on non-clinical data, preceding foreign clinical trial results in multiple races, available knowledge including information on similar drugs, and/or modeling & simulation. On the other hand, conduct of a phase 1 study in Japanese should be considered when the study sponsor determines it is feasible in situations where the number of patients in Japan is large and there is sufficient time to conduct a phase 1 study in Japanese prior to the MRCTs. However, this does not apply when the risk in Japanese is considered to be not significantly greater than in non-Japanese or when the safety margin in humans is broad based on available information.

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

Others

- Regardless of conducting a phase 1 study in Japanese, it is important to assess the differences in PK and/or PD between Japanese and non-Japanese through measures such as collecting PK and/or PD data in Japanese in MRCTs prior to marketing authorization applications.

- If a phase 1 study in Japanese is not conducted, the study sponsor should set additional safety measures for Japanese participants in MRCTs if the sponsor deems it necessary.

- The necessity of a phase 1 study in Japanese and the appropriateness of the safety measures in MRCTs will be ultimately concluded for each individual drug, and if PMDA judges it is necessary in order to secure the safety of the Japanese participants, PMDA may give instructions or advice on the necessity of a phase 1 study in Japanese or on implementation or changes to the additional safety measures for Japanese participants in MRCTs in a consultation for clinical trials.

Q & A

Q1 What points should be considered to determine whether the safety of Japanese participants is clinically acceptable and manageable in the multi-regional clinical trial (MRCT) in which Japan will participate?

(Answer)
The risks of the study drug should be comprehensively examined, mainly taking into account the points described in the following 1) and 2), to confirm that there is a possibility that the risk for Japanese participants is greater than that for non-Japanese participants, and then determine whether the safety of Japanese participants in the MRCT is clinically acceptable and manageable in the proposed dosing regimen.
However, the points to consider should be selected according to the characteristics of each study drug, and other aspects may need to be considered depending on the study drug.

1) Safety of study drug

- The results of non-clinical studies suggest no significant risk (findings leading to death or not-recovered) with an unclear mechanism of onset at the dose used in the MRCT.
- The maximum dose used in the MRCT has a sufficient safety margin, and no clinically significant risks have been identified in the preceding foreign clinical trial(s) in which the safety has been assessed which sufficiently covers the clinical exposure expected in Japanese participants in the MRCT.
- There are clear approaches and monitoring methods for mitigating potential risks and the potential risks are manageable by defining appropriate measures/monitoring in the MRCT.
- No clinically significant risks that increased in incidence or severity dose-dependently have been identified in the preceding foreign clinical trial(s)
- When there are similar drugs (e.g., the same active substance, the same mechanism of action, biosimilar drugs, etc.) which can be used as a reference in the safety evaluation, no clinically significant risk of the study drug is anticipated from the safety data of those drugs.

Q & A

Q1 What points should be considered to determine whether the safety of Japanese participants is clinically acceptable and manageable in the multi-regional clinical trial (MRCT) in which Japan will participate?

(Answer)
2) Effect of ethnic factors on study drug

- Ethnic differences in pharmacokinetics are unlikely based on comprehensive considerations of the following points:
  - The pharmacokinetics of the study drug is linear.
  - The drug is poorly metabolized or multiple metabolic pathways are involved.
  - It has not been reported that there are ethnic differences in the genetic polymorphisms of metabolic enzymes or transporters involved, or that the prevalence of polymorphisms with increased blood concentration of the study drug is higher in Japanese than in non-Japanese.
  - The pharmacokinetics of the drug is not significantly affected by BMI and body weight.
  - No significant impact of ethnic factors on the pharmacokinetics of the study drug is estimated based on an appropriate population pharmacokinetic analysis, etc.
- The drug has characteristics that make the safety and PK unlikely to be affected by ethnic factors (e.g., antibodies, peptides, endogenous substances, drugs that are poorly absorbed into systemic circulation and that act locally, etc.)
- There is no significant impact of ethnic factors such as race, region, body weight on the safety or pharmacokinetics based on previous clinical trial(s) in which the drug has been administered in multiple races/regions, or participants covering a wide range of body weight.
- When there are similar drugs (e.g., the same active substance, the same mechanism of action, biosimilar drugs, etc.) which can be used as a reference in a safety evaluation, no clinically significant ethnic differences in the safety are observed with those drugs, and the same is anticipated for the study drug.

Q & A

Q2: What additional measures can be taken to ensure the safety of Japanese participants in the MRCT?

(Answer) Safety measures differ depending on the characteristics of each study drug. The appropriate measures should be selected based on prior information about the drug, the design of the study, and how additional safety measures could affect the safety evaluation. For example, the following measures can be taken, and other safety measures may be more appropriate in certain cases.

- Set up a cohort to evaluate the safety (including pharmacokinetics, if necessary) of a small number of Japanese participants prior to the main part of the study.
- Until the safety evaluation is completed for a certain number of Japanese participants, administer the drug to a small number of Japanese participants (e.g., one participant at a time) with appropriate intervals between each administration.
- Increase the frequency of visits and monitoring during the early stage of administration.
- During the initial stage of administration, Japanese participants will either be hospitalized or observed at the study site for a certain period of time.
- Until the safety evaluation is completed for a certain number of Japanese participants, execute safety monitoring with special attention to Japanese participants in an organization composed of third parties, such as an independent data monitoring committee

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● Related Projects

Pharmaceutical Development Support Project

Project Objective

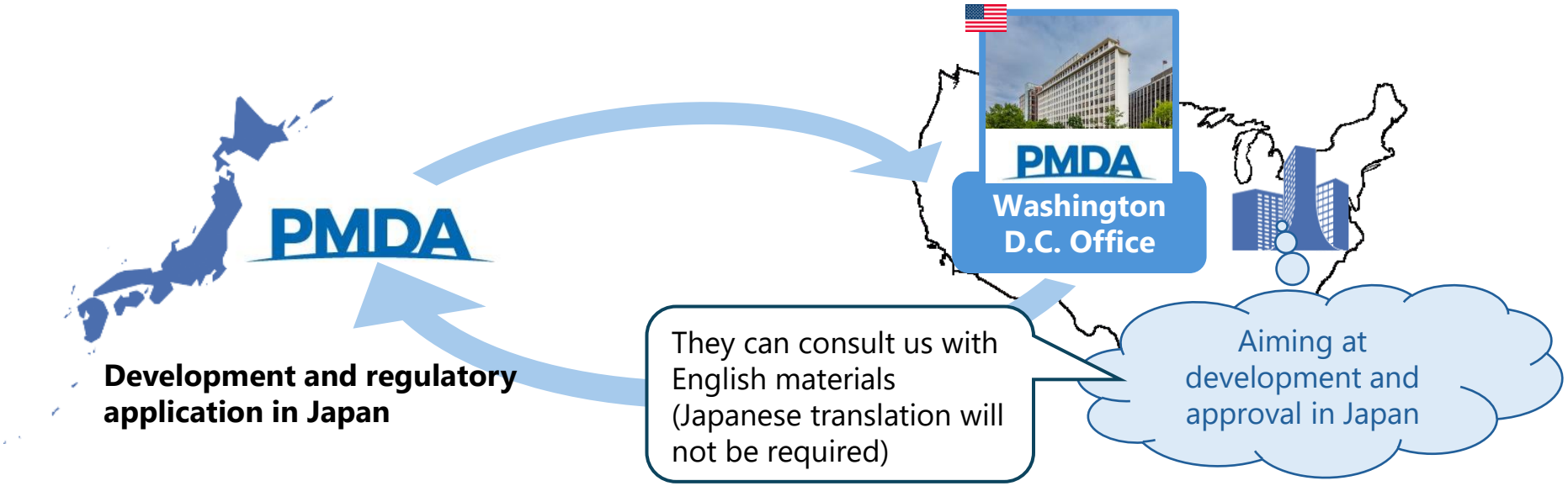
- In recent years, there has been growing concern over the **expansion of "drug loss"**, where drugs approved in the US and Europe are **not developed in Japan**.
- This issue stems from factors such as:
  - Decline in Japan's drug discovery capabilities and market attractiveness
  - Structural changes in the drug discovery environment, including a shift to **business models that rely on overseas biopharma companies for innovative drug seeds**

- To address this, the project aims not only to support domestic SMEs but also to **encourage overseas biopharma companies to develop and apply for approval in Japan**.
- A **PMDA U.S. Office** was established as a consultation and support hub. In collaboration with the Ministry of Health, Labour and Welfare, **free consultations and dissemination of information about Japan's regulatory system in English** will be provided in the U.S. and other regions.
  (Coordination with the U.S. FDA for MRCTs etc. is also expected.)
- Priority will be given to **items solicited for development through the "Study Group on Unapproved and Off-label Drugs of High Medical Need."** Consultation for conducting clinical trials in Japan is also available.

Breakdown of drugs not yet started development in Japan

Startup-originated	Orphan	Pediatric
56 % (48 drugs)	47 % (40 drugs)	37 % (32 drugs)

※Of 86 drug loss items, items that are not startup-originated, orphan or pediatric drugs are 14 (16%).



Clinical Trial Ecosystem Implementation Promotion Project

Project Objective

- One of the causes of **drug loss** is the tendency to **avoid Japan in multi-regional clinical trials**, due to delays in enrolling Japanese patients.
- This project aims to **create an environment conducive to conducting clinical trials in Japan**, by:
  - **Reducing costs**
  - **Alleviating procedural burdens**

① Survey on Burdens at Medical Institutions

- ◆ In collaboration with medical institutions, the project will investigate the actual burdens caused by excessive or redundant demands from sponsors (companies) under GCP (Good Clinical Practice).
- ◆ The survey will also include **comparisons with overseas practices**.

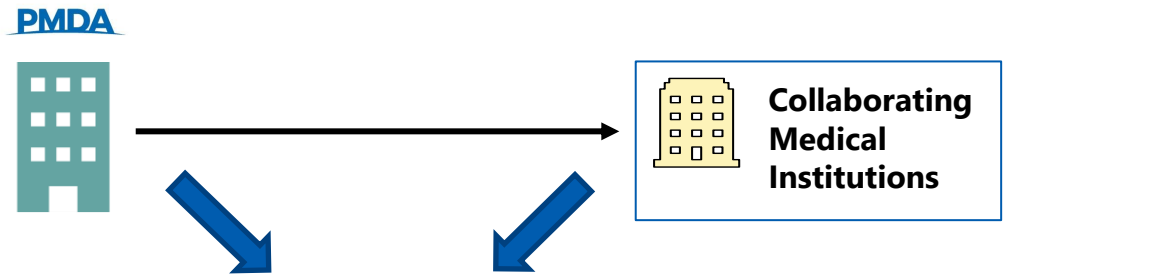
② Implementation of the Clinical Trial Ecosystem

Based on the findings from ①, the project will promote:

- **Simplification and rationalization of trial procedures**
- **Wider adoption of centralized IRB reviews**
- **Clarification of required data quality standards through guidelines**

PMDA will conduct **ongoing monitoring of rationalization efforts** and implement necessary improvements.

- In FY2025, the revision of the international clinical trial guideline (ICH-GCP) is scheduled. The project will accelerate the implementation of the ecosystem and support internationally harmonized operations in line with ICH-GCP.



Thank you for your attention.