Survey Results on the Notification of Conducting Phase I Study in Japanese Prior to MRCT

Industry Members of MRCT WG
(JPMA / PhRMA / EFPIA)

August 4th, 2025

Basic Information of the Survey

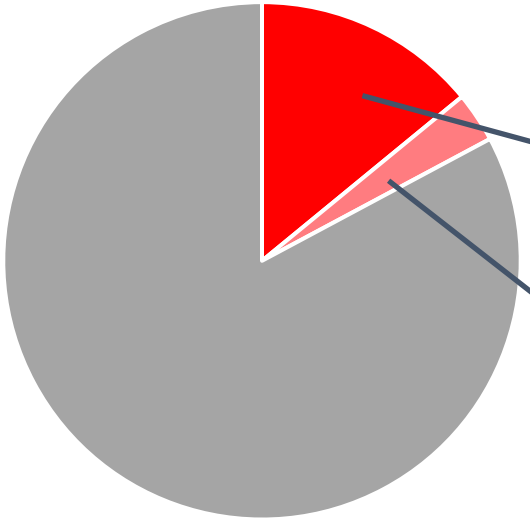
- Survey Period: September 30, 2024 – October 22, 2024
- Objective: To evaluate the immediate impact and challenges following the issuance of the notification of conducting phase I study in Japanese prior to MRCT
- Survey Target: JPMA (Regulatory Development sub-Committee of the Regulatory Affairs Committee, Clinical Evaluation Expert Committee and Data Science Expert Committee of the Drug Evaluation Committee), PhRMA S&R, EFPIA Technical Committee (Regulatory Affairs Committee, Clinical Committee, Anticancer Drug Development Committee)
- Method: Sending files to target companies, collecting responses through the survey company, and aggregating data after anonymization
- Response rate: 80% (64 / 80 companies)
    - Of these, 39 are Japanese company (response rate: about 75%) and 25 are foreign-affiliated company (response rate: about 89%).

Survey Content

1. Projects in which a PMDA consultation regarding Phase I study in Japanese prior to MRCT was conducted after January 2024.
2. Projects in which a Phase I study in Japanese was not conducted, and a CTN for a MRCT was submitted without a PMDA consultation regarding the Phase I study in Japanese after January 2024.
3. Changes in development strategies following the issuance of the notification.
4. Impacts resulting from the issuance of the notification, related issues, and other relevant matters.

Have you conducted a PMDA consultation (including a preliminary meeting only) regarding participation in an MRCT without conducting a Phase I study in Japanese after January 1, 2024? If so, please specify the number of cases and the corresponding therapeutic areas.

Yes: 11 companies
(17.2%)



No: 53 companies
(82.8%)

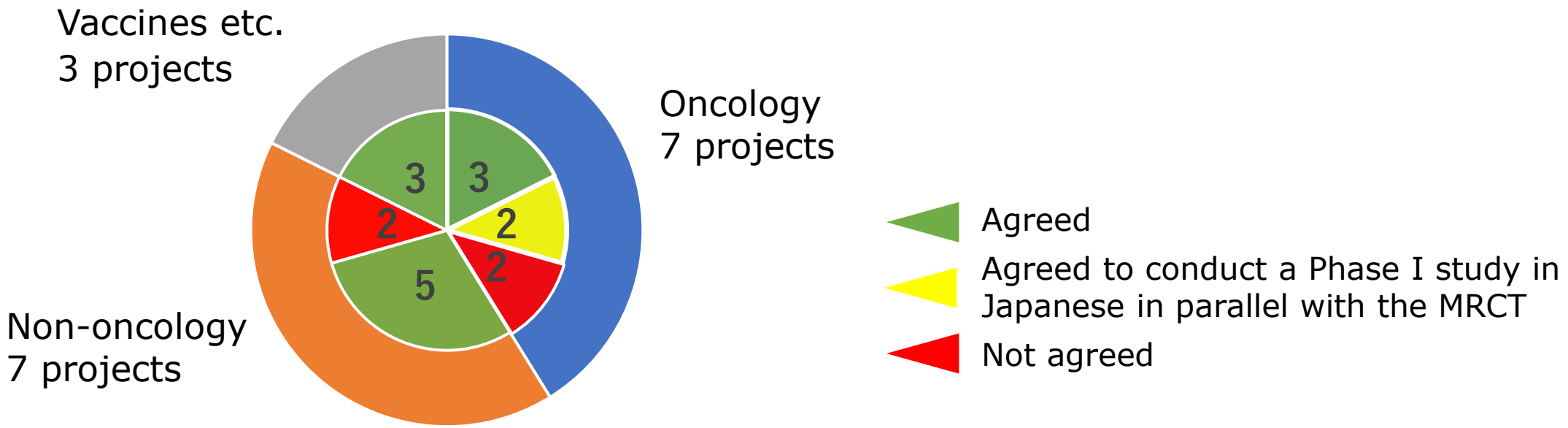
Foreign-affiliated company: 9 companies, 15 projects
(6 companies for 1 project, 2 companies for 2 projects, 1 company for 5 projects)

6 oncology projects, 6 non-oncology projects, 3 vaccine projects etc. (Products involving vaccines and other interventions for healthy populations)

Japanese company: 2 companies, 2 projects
(2 companies for 1 project)
1 oncology project, 1 non-oncology project

PMDA consultation conducted
Total: 11 companies, 17 projects

Have you reached an agreement with PMDA to participate in the MRCT without conducting a Phase I study in Japanese?



Of 17 products for which PMDA consultation was conducted,

13 projects were agreed to be directly participated in MRCT.
(5 Oncology projects, 5 Non-oncology projects, 3 Vaccine projects)

4 projects were not agreed upon
(2 Oncology projects, 2 Non-oncology projects)

Please describe the MRCT you planned to participate.

Have you reached an agreement with the PMDA to participate in the MRCT without conducting a Phase I study in Japanese?

Have you implemented any safety measures specific to Japanese during the MRCT?

Oncology: 7 projects

Therapeutic area	Agreement to participate in MRCT	Planned MRCT	Safety measures specific to the Japanese participants at MRCT
Oncology (7)	Agreed-upon (3)*	Pivotal study (3)	The company proposed safety measures specific to Japanese participants, and the PMDA agreed. (3)
	Agreed to conduct a Phase I study in Japanese in parallel with the MRCT (2)	Pivotal study (2)	Although the company stated that safety measures specific to Japanese participants were unnecessary, the PMDA requested their implementation. (2)
	Not agreed-upon (2)	Pivotal study (1) Dose-finding study regarded as pivotal study (1)	NA

(number of projects)

＊including one case where participation in the MRCT was agreed upon prior to the completion of the tolerability assessment in the ongoing Phase 1 study in Japanese.

Please specify the main rationale provided by the company during the consultation for claiming that "the safety of Japanese participants in MRCT is clinically acceptable/ manageable."

Oncology: 7 projects

Agreement to participate in MRCT	Rationale
Agreed-upon (3 projects) Agreed to conduct a Phase I study in Japanese in parallel with the MRCT (2 projects)	• New route of administration (topical formulations) ✓ No differences are expected between Japanese and non-Japanese patients (clinical study data on oral formulations are available) • Data from foreign clinical studies ✓ Manageable safety profile / no DLT was observed • Information on similar drugs ✓ No risk specific to Japanese patients has been reported with similar drug • Intrinsic / extrinsic ethnic differences not anticipated • Safety measures ✓Well qualified institution specializing in cancer treatment ✓ Measures to ensure the safety of Japanese participants ✓ Periodic reviews in data monitoring ✓ Definition of dose modification criteria in case of adverse events • Unmet medical needs and delays in the development in Japan
Not agreed-upon (2 projects)	• Data from foreign clinical studies ✓ Good tolerability and manageable safety profile ✓ No ethnic difference observed between the Asian and non-Asian populations • Safety measures ✓ Plan to include a small number of Japanese participants and closely monitor their safety • Foreign clinical data can be extrapolated to Japanese population

Please describe the MRCT you planned to participate.

Have you reached an agreement with the PMDA to participate in the MRCT without conducting a Phase I study in Japanese?

Have you implemented any safety measures specific to Japanese during the MRCT?

Non-oncology: 7 projects, Vaccines etc.: 3 projects

Therapeutic area	Agreement to participate in MRCT	Planned MRCT	Safety measures specific to the Japanese participants at MRCT
Non-oncology (7)	Agreed-upon (5)	Dose-finding study (2) Pivotal study (3)	The safety of the overall population in MRCT has been established, and it has been agreed upon. (3) It was agreed that no specific safety measures for Japanese participants will be implemented. (1) There was no proposal from either the company or the PMDA (1).
	Not agreed-upon (2) *	Dose-finding study (2)	NA
Vaccines etc. (3)	Agreed-upon (3)	Pivotal study (3)	The safety measures for the overall population in MRCT has been established, and it has been agreed upon. (3)

(number of projects)

＊including one case that had a preliminary meeting but did not have a PMDA consultation due to a change in the company's plan.

Please specify the main rationale provided by the company during the consultation for claiming that "the safety of Japanese participants in MRCT is clinically acceptable/ manageable."

Non-oncology: 7 projects

Agreement to participate in MRCT	Rationale
Agreed-upon (5 projects)	• Combination drug ✓ No particular safety concerns in Japanese patients was suggested based on the results of each single agent. • Drug characteristics • Data from non-clinical studies • Data from foreign clinical studies • Information on similar drugs ✓ No major safety concerns • Intrinsic / extrinsic ethnic differences not anticipated • No major differences in safety and/or PK are anticipated between Japanese and non-Japanese participants. • Safety measures ✓ Adequate safety measures are in place for MRCT
Not agreed-upon (2 projects)	• Consultation materials have not been submitted because only preliminary meeting was held. • New biological entity, Linearity, Enough safety margin, Safety of drug with the same mode of action

Please specify the main rationale provided by the company during the consultation for claiming that “the safety of Japanese participants in MRCT is clinically acceptable/ manageable."

Vaccines etc.: 3 projects

Agreement to participate in MRCT	Rationale
Agreed-upon (5 projects)	• Products for pediatrics ✓ Data from Japanese adult Phase 1 study do not suggest ethnic differences ✓ Since the foreign Phase 1/2 study is conducted in the pediatric population, the safety in Japanese children considered to be acceptable and manageable even if the Phase 1 study in Japanese is not conducted. • Data from foreign clinical studies ✓ No major safety concerns • Information on similar drugs • No ethnic difference observed • No obvious ethnic factors

In cases where it was agreed to participate in the MRCT without conducting the Phase 1 study in Japanese, what are your plans for collecting PK and PD data in Japanese population?

number of projects

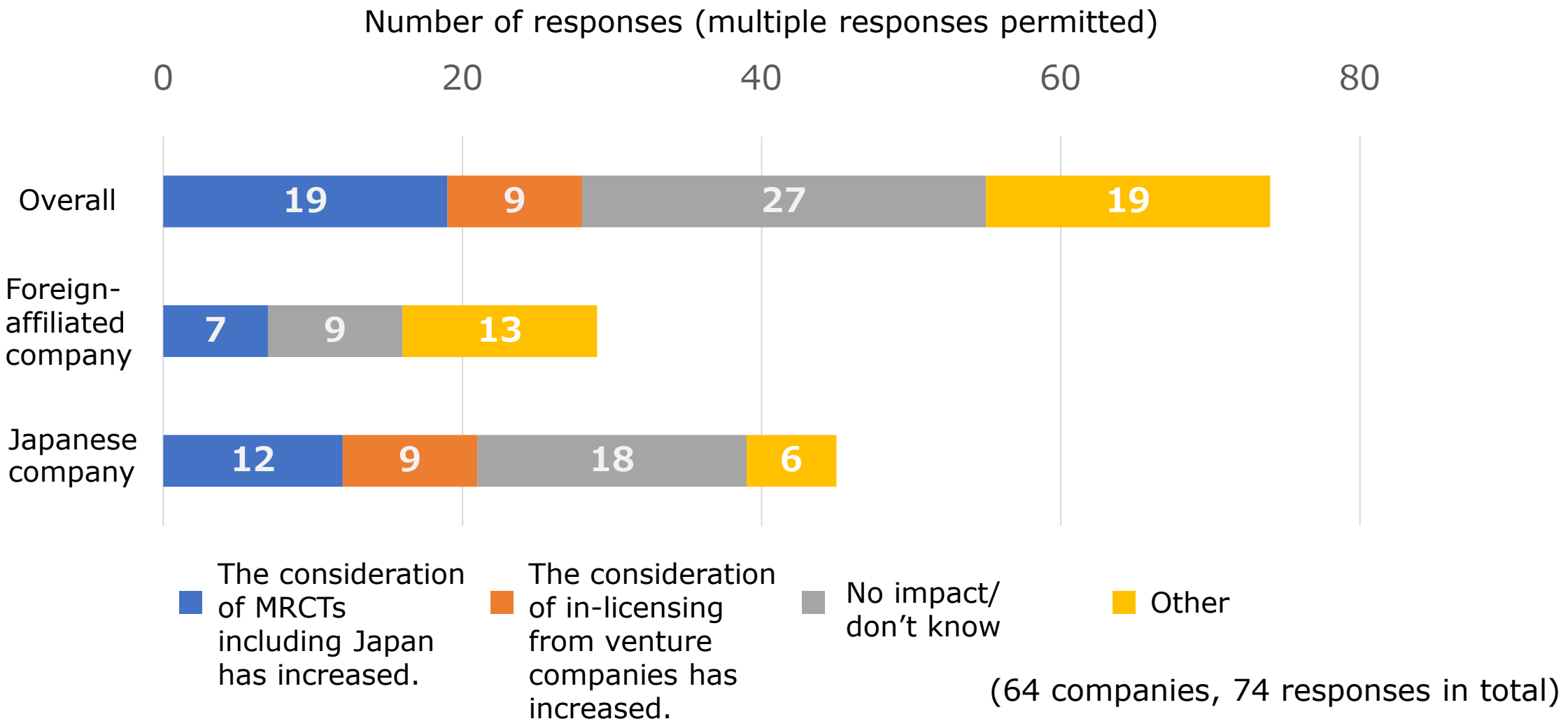
Therapeutic area	1. The same data as in the overall population will be collected through this MRCT.	2. Data will be collected with settings specific to the Japanese in this MRCT.	3. Other
Oncology (3)	1	1 (The data are the same as for the overall population in this MRCT, but collected at a different frequency.)	1 (A Phase 1 study in Japanese is ongoing in parallel.)
Non-oncology (5)	4	1	0
Vaccines etc. (3)	1	0	2 (There is no plan to evaluate PK and PD for this project, as it involves vaccine products: 2 projects)
Total (11)	6	2	3

Projects in which a Phase I study in Japanese was not conducted, and a CTN for a MRCT was submitted without a PMDA consultation regarding the Phase I study in Japanese after January 2024.

Experience reported by two companies
(both foreign-affiliated, one case per company, total of two)

Therapeutic area	Reasons for not conducting the PMDA consultation	Acceptance of PMDA regarding participation in MRCT
Oncology	• The company judged that 'the safety of Japanese participants is clinically acceptable/manageable' could be sufficiently explained. • The participating MRCT was a Phase 1b combination therapy study, which involved a dose-escalation from a low dose.	Participation in the MRCT was approved by PMDA without any changes to the plan.
Non-oncology	• The company judged that 'the safety of Japanese participants is clinically acceptable/manageable' could be sufficiently explained. • There was not sufficient time to conduct the PMDA consultation.	Participation in the MRCT was approved by PMDA without any changes to the plan.

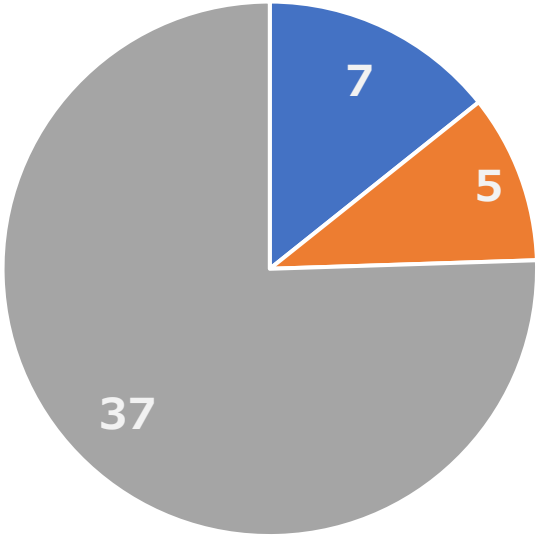
Did you perceive any impact on your development strategy due to the issuance of the notification? If so, please specify the impact.



(64 companies, 74 responses in total)

Does the notification influence your development decisions in Japan? If so, please specify the main changes.

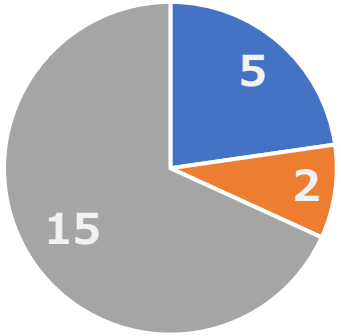
Oncology (49 companies)*



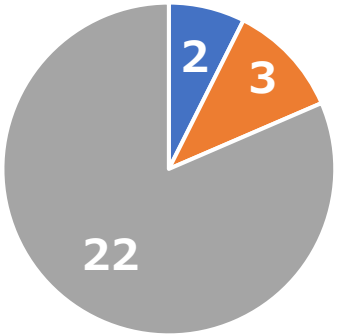
■ Yes ■ Under consideration ■ No influence at present

(multiple responses permitted)

Foreign-affiliated company (22 companies)



Japanese company (27 companies)



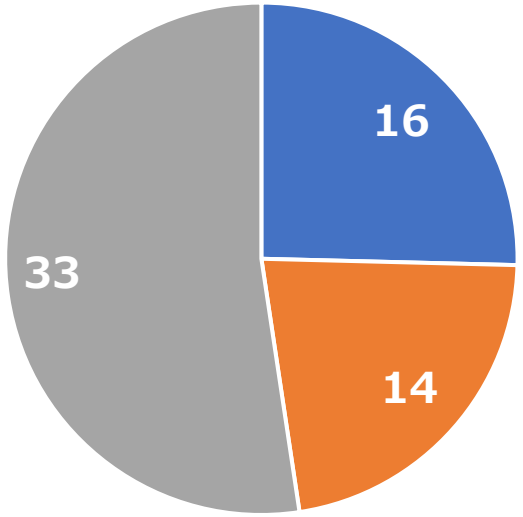
1. Increased consideration of participation in MRCTs despite delays in development in Japan (8).
2. Increased consideration of the necessity for Phase 1 studies in Japanese prior to MRCTs (11).
3. An increase in PMDA consultation regarding Phase 1 studies in Japanese (5).
4. Difficulties within the company in conducting Phase 1 studies in Japanese or Japanese cohort before MRCTs (e.g., fewer number of participants) (2).
5. Others (2).

(number of responses)

*Excluding companies that are not developing oncology (15 companies, 3 foreign-affiliated companies, 12 Japanese companies)

Does the notification influence your development decisions in Japan? If so, please specify the main changes.

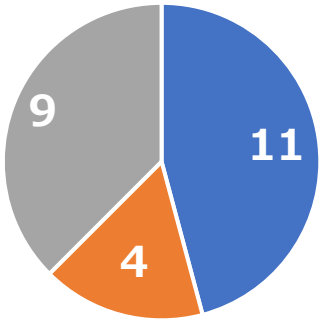
Non-oncology (63 companies)*



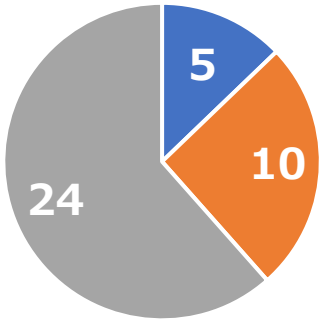
■Yes ■Under consideration ■No influence at present

(multiple responses permitted)

Foreign-affiliated company (24 companies)



Japanese company (39 companies)



1. Increased consideration of participation in MRCTs despite delays in development in Japan (16).
2. Increased consideration of the necessity for Phase 1 studies in Japanese prior to MRCTs (25).
3. An increase in PMDA consultation regarding Phase 1 studies in Japanese (9).
4. Difficulties within the company in conducting Phase 1 studies in Japanese or Japanese cohort before MRCTs (e.g., fewer number of participants) (4).
5. Others (7).

(number of responses)

*Excluding a company that is not developing non-oncology (1 foreign-affiliated company)

Did the notification influence the preparation of the PMDA consultation briefing documents or the documents for Clinical Trial Notification related to MRCTs? If so, please specify the impact.

Number of responses (multiple responses permitted)

- Preparation of documents became easier by referencing notices and Q&A
- Preparation of documents for clinical trial notification became easier, resulting in fewer inquiries.
- No relevant experience with PMDA consultation or clinical trial notification submission.
- No influence.
- Others (One comment: Consultation materials have already been submitted)

(64 companies, 80 responses in total)

Points difficult to interpret, requests for additional explanation, and operational challenges concerning the notifications and Q&A (Part 1/2)

Many requests for supplementary explanations and sharing of case examples were made:

- A supplemental explanation on what kinds of cases would not require additional Phase 1 studies in Japan, anticipating future case accumulation.
- Specification of the minimum requirements that must be satisfied, following indications from a preliminary consultation meeting that some form of tolerability assessment is necessary due to the absence of information on similar drugs.
- The basis and cases that justify a high unmet medical need, as well as evidence and examples supporting the judgment that the safety of Japanese participants can be clinically acceptable/ manageable. Consideration of the necessity and approach regarding the inclusion of "multiple ethnicities" and "information on similar drugs".
- Examples of safety measures for Japanese participants and/or design modifications related to ensuring safety when including Japanese participants in an MRCT without prior Phase 1 studies in Japan.
- Appropriate trial designs if phase 1 studies in Japanese are deemed necessary.
- Additional explanation regarding the documentation to be submitted at the CTN (document for scientific justification of the MRCT), when a Phase 1 study in Japanese is not conducted prior to an MRCT.
- Clarification on the extent of PK and ethnicity difference data required at the time of NDA submission, when Phase 1 studies in Japanese are not performed and participation in the MRCT is enabled.

Points difficult to interpret, requests for additional explanation, and operational challenges concerning the notifications and Q&A (Part 2/2)

Questions and comments regarding the scope of the notification were also raised:

- It is understood that the notification also applies to drugs developed through simultaneous global development. However, if this is not the case, expanding the scope in the future should be considered.
- In cases where clinical development has been advanced overseas and a Japan-specific bridging study is planned, whether the same considerations for determining the necessity of a Phase 1 study in Japan can be applied is questioned.
- Even 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”, if existing data support a clinical judgment that “the safety of Japanese participants can be judged to be clinically acceptable/manageable”, then the decision to conduct a Phase 1 study in Japanese should ultimately be at the discretion of the company. Is this understanding correct?
- Regarding anticancer drug development, comments from PMDA suggest that, in principle, skipping Phase 1 studies in Japanese is generally not permitted. Consideration of rephrasing this aspect in the notification is requested.

Several opinions emphasized the importance of flexible operational approaches.

- While the term "consultation" was used, case-by-case flexibility—such as utilizing preliminary meetings—was requested to accommodate different situations.

Summary

- Cases were confirmed where participation in an MRCT without conducting Phase 1 studies in Japanese was agreed upon with PMDA.
  - ✓ The differences in the rationale supporting whether cases were agreed upon or not could not be clearly identified from this survey.
  - ✓ Numerous requests were made for sharing evidence and examples supporting the judgment that “the safety of Japanese participants can be clinically acceptable/manageable”.
  - ✓ In the oncology area, Japan-specific safety measures were implemented when participating in MRCTs without phase 1 studies in Japanese .
- An increase was observed in considerations for MRCTs including Japan and in the potential for in-licensing from venture companies, although many responses indicated no perceived impact from issuing notifications at the time of the survey.
- Both in oncology and non-oncology areas, there is a growing trend to examine the necessity of Phase 1 studies in Japanese prior to MRCT.
- Multiple requests were made for expanding the scope of the notification and for adopting more flexible operational practices.

Thank You

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August 4, 2025

CRO Perspective on the Notification for Phase I Study with Japanese

Noriyuki Takai

President and CEO

EPS Corporation

Disclaimer

This content has been prepared based on the author's personal views and insights obtained through participation in international conferences and routine business discussions. It does not represent the official position or opinion of any affiliated organization or institution.

Agenda

- **Current Status** of the Notification
  (From issuance to 1.5 years later)
- **Examples** of Perspectives on the Notification
  (From overseas EBPs/CROs without a Japan presence)
- **Case Examples** in the CRO Response to the Notification
- **Operational Challenges** Arising from the Notification
- **Recommendations** from the CRO Regarding the Notification

Current Status of the Notification
(From issuance to 1.5 years later)

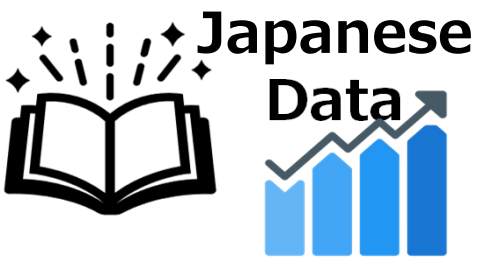
<Immediately after issuance>

- Following the regulatory changes regarding the necessity of conducting Phase 1 studies with Japanese and the requirements for conducting MRCTs including Japan, inquiries from overseas companies without Japan development bases increased.
- At the same time, only the phrase “Phase 1 study with Japanese not required” began circulating as a standalone message, leading to many cases where ethnic factors under ICH E5 were not sufficiently considered.
- There were also inquiries from overseas companies that do have development operations in Japan, including during international conferences.

Current Status of the Notification
(From issuance to 1.5 years later)

<1.5 years after issuance>

- There has been a gradual increase in cases where development plans with skipping domestic Phase 1 studies in Japan, based on Phase 1 data obtained overseas that include Asian and Japanese subjects.
- Awareness of this notification is now being raised through various channels, including:
  - Information sharing and communication from pharmaceutical companies and CROs with operations in Japan
  - Insights provided through conferences and websites



Examples of Perspectives on the Notification
(From overseas EBPs/CROs without a Japan presence)

- The perception that "Japanese Phase 1 studies are no longer required" has gained traction on its own, while ethnic differences specific to the Japanese population are not being sufficiently considered.
  - Only the first sentence of the “2. Basic Principles” section in the English version of the notification is widely recognized, while the second sentence remains largely overlooked - particularly among U.S. and European biotech companies, where accurate information has not been adequately conveyed.

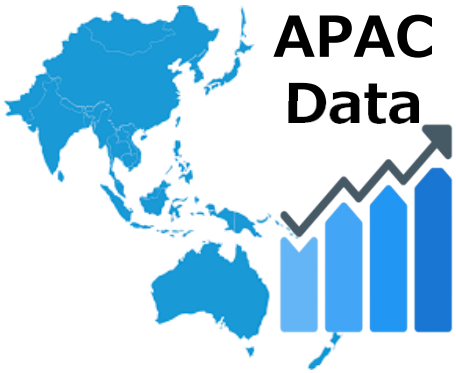
2. Basic principles

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.

Examples of Perspectives on the Notification
(From overseas EBPs/CROs without a Japan presence)

- There have been cases where the following perceptions were observed even before the issuance of the notification:
  - Since Japan is an ICH member country, it can participate in global clinical trials without population-specific data limited to Japanese subjects, just like other ICH countries.
  - Studies focusing primarily on East Asian populations are considered sufficient, and additional studies specifically involving Japanese subjects are deemed unnecessary.

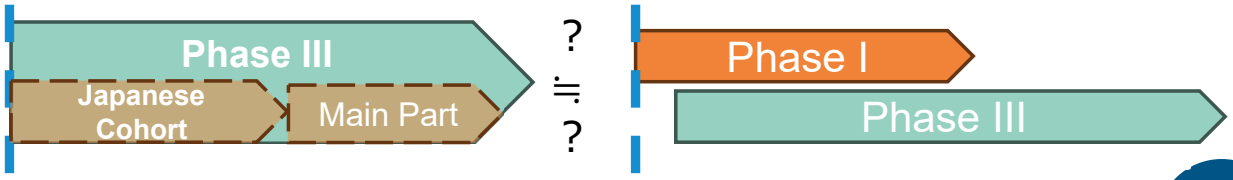
- Based on the Q&A section, some have questioned whether the regulatory framework now allows simultaneous conduct of Phase 1 and Phase 3 studies in Japan - similar to the approach in China.



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

(Answer)

- 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.



Case Examples in the CRO Response to the Notification

<Case 1>

- Feedback gathered at international conferences regarding impressions of the notification.
  - Many commented positively, expressing the view that this regulatory change reflects progress in regulatory flexibility and is a highly welcome development.

<Case 2>

- Interviews were conducted (both Japan domestic and international) regarding changes in development plans and thinking before and after the issuance of the notification.
  - In most cases, there have been no major changes in approach - such as including a Japanese profiling cohort or determining the number of Japanese subjects in MRCTs. Many continue to follow development plans consistent with previous practices.

Case Examples in the CRO Response to the Notification

＜Case 3＞

- While a Phase 1 study including Japanese subjects was underway overseas, the notification was issued.
- The U.S.-based EBP representative understood this to mean that a separate Japanese Phase 1 was no longer required and began considering moving to the next phase based on the current existing data.
- A PMDA consultation is planned using the results of non-clinical studies conducted overseas and an overseas Phase 1 study that included a small number of Japanese subjects. The development plan does not include a standalone Japanese Phase 1 or a Japanese cohort in Phase 2/3.

＜Case 4＞

- A Global Phase 2 study including Japanese subjects was conducted without a preceding Japanese Phase 1.
- Additional PK/PD assessments for Japanese subjects were incorporated within the Global Phase 2 study.

Operational Challenges Arising from the Notification

＜Current Status＞

- 1.5 years have passed since the issuance of the notification, and a certain level of understanding has been promoted—mainly through information sharing by regulatory staff at the Japanese offices of global companies and CRO representatives.

However, in some cases:

- **Discussions have been limited to only whether Japanese Phase 1 is required or not**, without addressing the essential points of the notification - such as its purpose or the evaluation of ethnic differences.
- In such cases, little to no consideration has been given to ethnic differences.

While the principle of case-by-case evaluation is assumed:

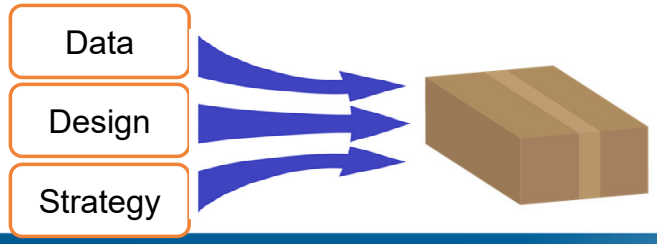
- It remains unclear in what types of cases Japanese Phase 1 can be deemed unnecessary, or what additional assessments might be required in Phase 3 MRCT if Japanese Phase 1 is skipped. As examples are still limited, there is a risk of missing the appropriate timing to participate in Phase 2 or Phase 3 MRCTs.
- There are varying interpretations not only among overseas companies but also among Japan based companies.
- Unlike Japan, in other countries, **regulatory officials often introduce case examples at seminars and symposia - even if only as personal opinions** - in addition to what is described in notifications, guidelines, or other official documents.

Recommendations from the CROs Regarding the Notification

While it is understood that, as PMDA representatives said, decisions must be made on a case-by-case basis, for overseas EBPs, it is important to consider timelines and associated costs as they relate to business and investment planning.

- From this perspective, ambiguous expressions such as “a certain number of subjects” are not helpful. Instead, it would be preferable to provide numerical examples that clearly demonstrate the absence of ethnic differences affecting pharmacokinetics and the ability to ensure safety.

- The discussion should shift away from whether a Japanese Phase 1 study is required, and toward whether safety assurance measures can be sufficiently validated within the broader development package - including Phase 3 studies and the utilization of real-world data (RWD).
  - It is also important to recognize that safety data is typically insufficient at the Phase 1 stage, making it unproductive to debate its adequacy at that early point.



Recommendations from the CROs Regarding the Notification

- There is not yet a unified understanding, either domestically or internationally. It is increasingly important to create forums for discussion involving stakeholders from various perspectives and areas of expertise, and to actively share the outcomes of these discussions - especially in English - across multiple platforms.

- At international conferences, it would be beneficial to make greater use of speaking sessions and panel discussions organized through collaboration between organizations and companies.

- From the perspective of EBPs/biotech companies:
  - Rather than conducting Japanese Phase 1 simply because there is sufficient time,
  - there is a strong preference for conducting development using the smallest, fastest, and most efficient package that still ensures safety.
- It would be ideal to evaluate concrete, case-based examples from the perspectives of efficacy, safety, cost, and speed.

EPS Corporation

Thank You

Symposium on "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“
August 4, 2025

PMDA
Making everyone’s lives brighter together

Expectations for explanations in consultation materials and dossiers for clinical trial notifications based on the new notification

Yosuke Kobayashi

Multi-regional clinical trials Working Group (MRCT WG)
Pharmaceuticals and Medical Devices Agency (PMDA)

There are no companies with a COI relationship that should be disclosed related this presentation.

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

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Agenda

- PMDA's perspective and current status before and after the issuance of the new notification*
- Points to consider when examining the necessity of Japanese Phase 1 studies (J-Ph1) prior to initiating MRCTs including Japan
- Points to note when preparing consultation materials and dossiers for clinical trial notifications
- Summary

* "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 (PSB/PED Notification No. 1225-2, December 25, 2023)"

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PMDA's perspective before and after the issuance of the new notification

- PMDA has not always requested Japanese phase 1 studies (J-Ph1) prior to initiating multi-regional clinical trials (MRCTs) including Japan for drugs in which early clinical development is preceding outside Japan. PMDA has made a comprehensive judgement based on the information available at that time.

- Although there has been no change in the PMDA's perspective of making a decision on a case-by-case basis, the number of products for which J-Ph1 is required prior to initiating MRCTs has been decreasing since the issuance of the former notification (the 2007 notification) due to the accumulation of knowledge on MRCTs and ethnic differences.

- Although the principle regarding the conduct of J-Ph1 prior to initiating MRCTs has been changed from "necessary" to "unnecessary", PMDA's perspective of making a decision on a case-by-case basis remains unchanged.

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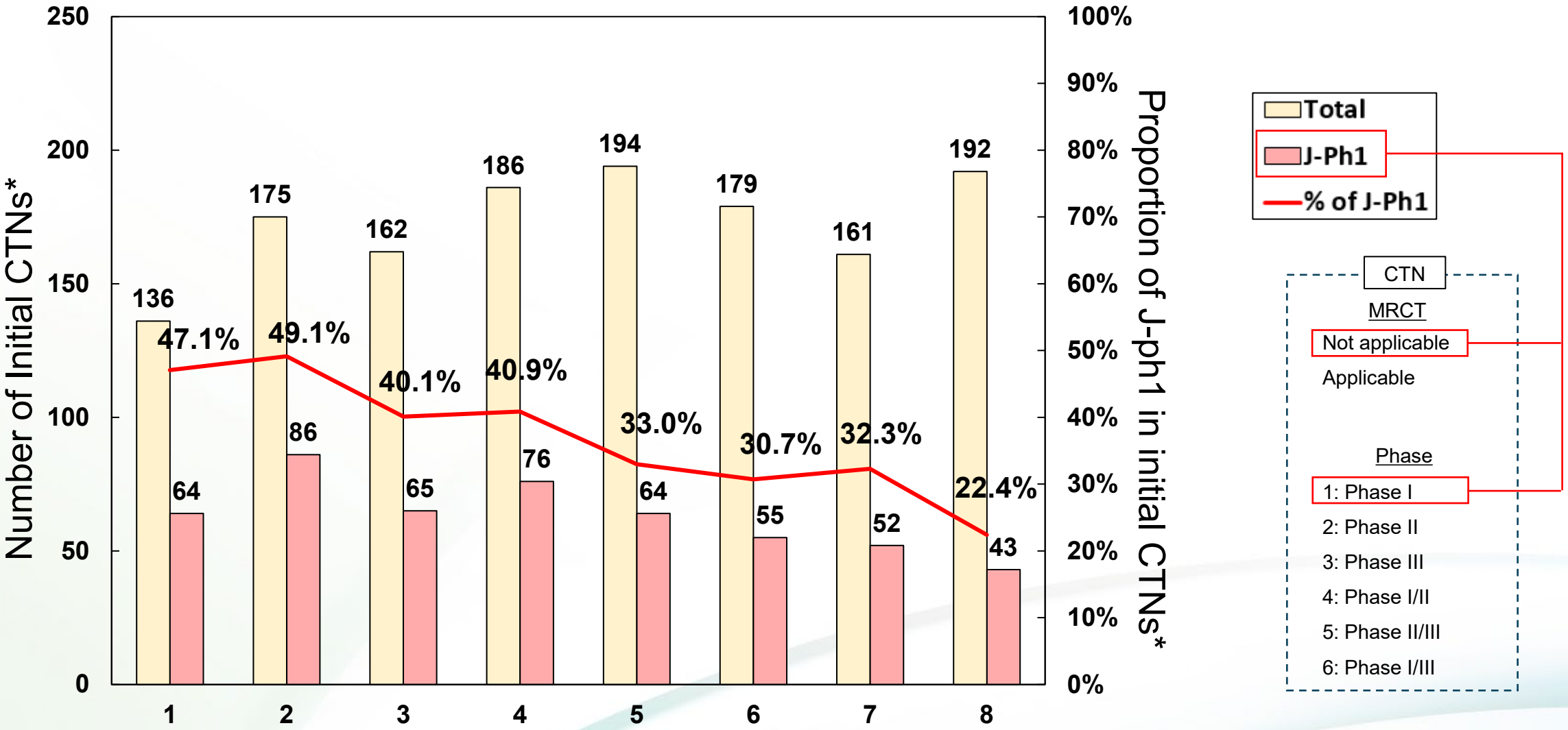
Current status of Japanese Phase 1 studies in the initial clinical trial notifications in Japan



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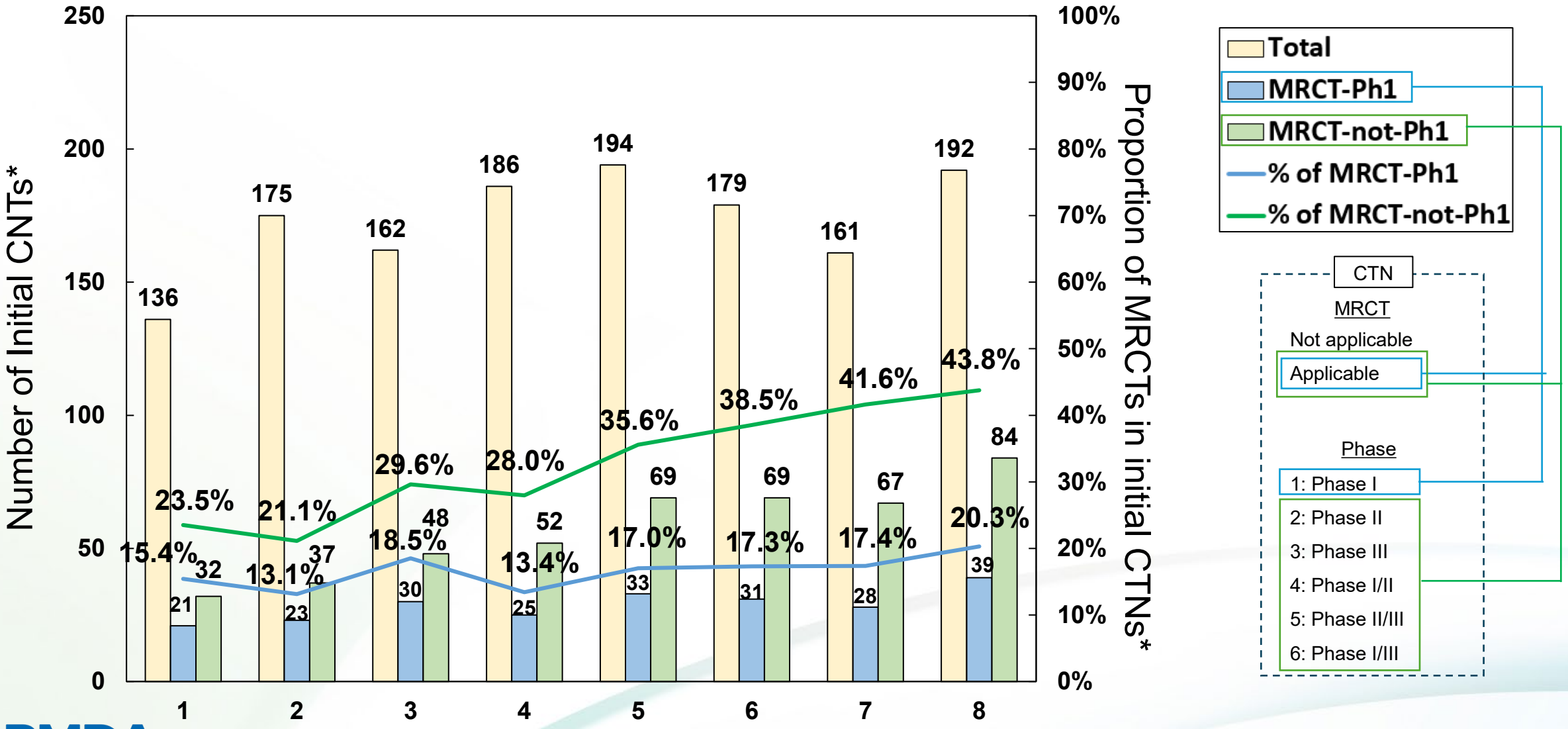
* Initial CTN of a drug that falls under any of the following categories; drug with a new active ingredient, drug with a new route of administration or new combination drug.

Current status of MRCTs in the initial clinical trial notifications in Japan



* Initial CTN of a drug that falls under any of the following categories; drug with a new active ingredient, drug with a new route of administration or new combination drug.

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Points to consider when examining the necessity of Japanese Phase 1 studies prior to initiating MRCTs including Japan

Whether the safety of Japanese participants is clinically acceptable and manageable in the MRCT

- Magnitude of the risk of the study drug
- Sensitivity of the study drug to ethnic factors

Disadvantages of not participating in the MRCT from Japan

- Rare disease
- Medical needs (seriousness, existing treatments, etc.)

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Magnitude of the risk of the study drug

- Based on the available information, the anticipated risks of the dosage to be evaluated in the MRCT are discussed.

[Major considerations]

- The results of the nonclinical studies (potential significant risk).
- Safety margin at the maximum dose used in the MRCT.
- Dose-dependent clinically significant risks in foreign clinical trials.
- Occurrence of serious adverse events at the dosing regimen in the MRCT in foreign clinical trials.
- Information from similar drugs.
- Measures and monitoring methods for mitigating risks in the MRCT.

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Sensitivity of the study drug to ethnic factors

- Based on the available information, the existence of specific ethnic differences and the degree of impact are discussed.

[Major considerations]

- Mechanism of action (e.g., ethnic differences in the target molecule, and systemic or local effects).
- Pharmacokinetic characteristics (e.g., metabolic pathways).
- Foreign clinical trial data including M&S approach (e.g., linearity, dose-response relationship, sensitivity to body weight or ethnicity).
- Information from similar drugs.

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Disadvantages of not participating in the MRCT from Japan

- Consider whether participation in MRCTs desirable for development in Japan due to high unmet medical needs.

[Major considerations]

- Disease scarcity
- Disease seriousness/refractoriness
- Existing treatments and unmet medical needs
- Significant barriers to clinical development (e.g. pediatric drugs)

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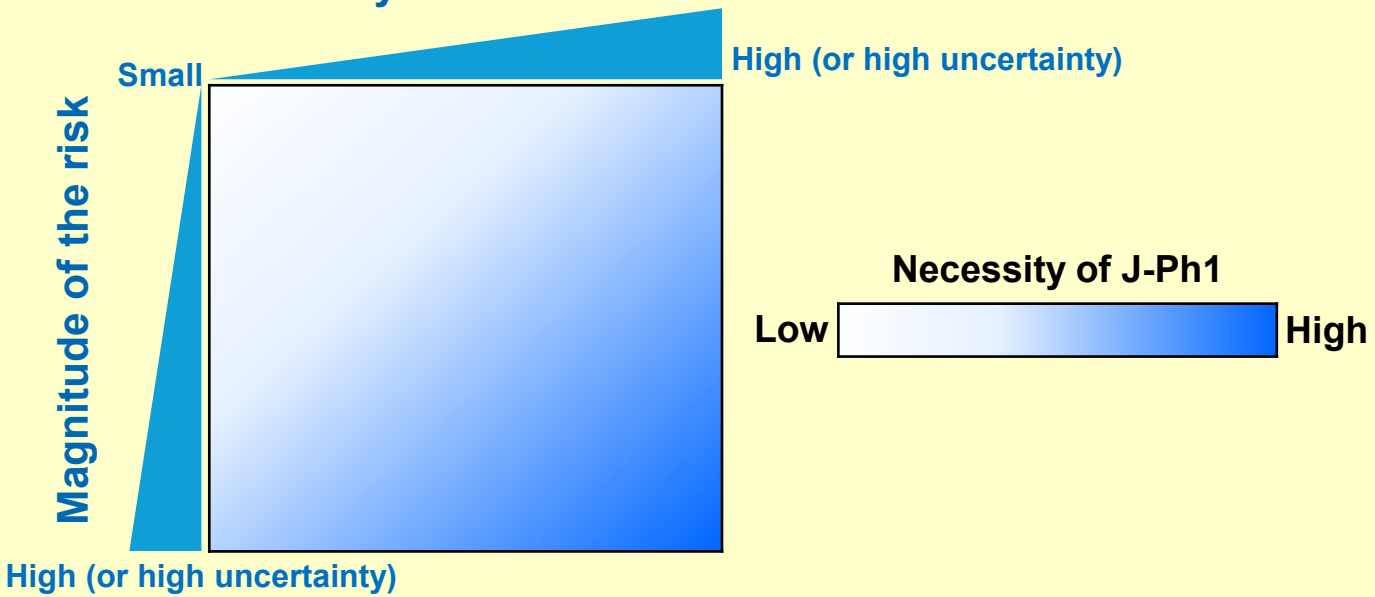
Decision making on whether or not to conduct Japanese phase I studies prior to initiating MRCTs including Japan

- The necessity of J-Ph1 is discussed based on the results of the evaluation on the magnitude of the risk of the study drug and its sensitivity to ethnic factors.

[Image]



- In addition to the above discussion, the sponsor make a decision on whether or not to conduct J-Ph1, considering the disadvantages of not participating in the MRCT from Japan. In some cases, it is considered that J-Ph1 is highly necessary, but participation may be possible by taking additional safety measures in the MRCT.

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Additional safety measures in MRCTs

- For example, the following measures may be taken.

  - 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.

Points to note when preparing consultation materials and dossiers for clinical trial notifications

- Even if J-Ph1 is not conducted based on the new notification, a detailed explanation of the appropriateness of not conducting J-Ph1 is needed.

- It is necessary to explain sponsor's discretion based on the specific data (study results, published papers, etc.).
  - × When only the fact that the conduct of J-Ph1 was judged as unnecessary based on the new notification was stated, and specific details of discussion are not described.
  - × When only data are presented, and the sponsor's thoughts are not described.
  - × When only "there was no problem in the foreign clinical trial" or "there is no safety concern based on the available information" are stated, and data supporting these explanations are not presented.

- Even if J-Ph1 is not conducted, it is necessary to consider the impact of ethnic factors on treatment effects at the time of new drug application based on the results of MRCTs.
  - ➢ Consult with the plan to examine ethnic differences in pharmacokinetics (e.g., plan to obtain Japanese PK data) as needed.

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Summary

- Although the principle regarding the conduct of J-Ph1 prior to initiating MRCTs including Japan has been changed from “necessary” to “unnecessary,” it should not be considered that J-Ph1 before MRCTs is no longer needed.

- The necessity of J-Ph1 before MRCTs should continue to be carefully considered based on scientific basis. Consultations with PMDA should be actively utilized.

- Although the issuance of the new notification is expected to contribute to the reduction of drug loss/lag in Japan, it is important to properly understand the purpose of the new notification and operate it properly.

- In order to prevent future drug loss/lag in Japan, it is important that industry, PMDA/MHLW and academia cooperate to develop the system and infrastructure to enable Japan to participate in clinical development from an early stage, including phase I trials.

Reference

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 (PSB/PED Notification No. 1225-2, December 25, 2023)

Japanese version : https://www.pmda.go.jp/files/000266148.pdf
English version : https://www.pmda.go.jp/files/000266727.pdf

Q&A for 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 (Administrative Notice, December 25, 2023)

Japanese version : https://www.pmda.go.jp/files/000266147.pdf
English version : https://www.pmda.go.jp/files/000266728.pdf

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Thank you for your kind attention

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August 4, 2025

Symposium on "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“

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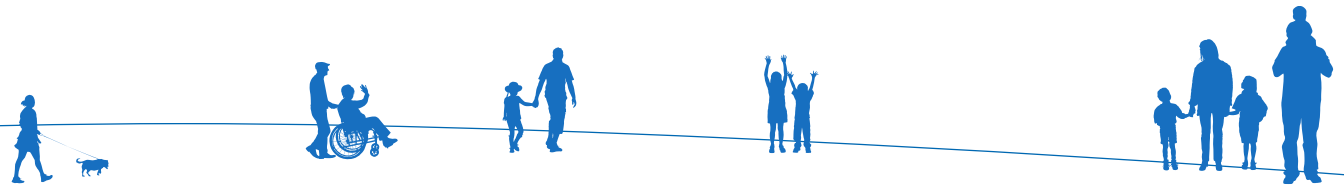
PMDA Washington D.C. Office Initiatives

Pharmaceuticals and Medical Devices Agency
Head, Washington D.C. Office

Akihiro Ishiguro, Ph.D.



PMDA's International Hubs

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Asia Office, Bangkok

PMDA Central Office, Tokyo

Washington D.C. Office

Establishment of PMDA's international hubs
to enhance international contribution/capability for regulatory proposal
PMDA's 5th mid-term plan

Mission of PMDA Washington D.C. Office

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For international contribution/capability to PMDA's regulatory proposal

- Cooperation with U.S. FDA and related administrative agencies, such as
  - to promote further access to innovative human medicines/medical devices/regenerative products
  - to engage in further discussion on marketing authorizations and post-marketing measures

- More opportunities for communication with stakeholders to provide information on Japanese regulation
  - in the same time zone without considering time-zone difference
  - as "General Consultation Service" for small business/start-up companies on early development in Japan

Current collaboration with US FDA in oncology area

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- Oncology Drugs Cluster: Monthly virtual meetings

PMDA FDA EMA HC SMC TGA

- Project Orbis led by U.S. FDA

FDA HC TGA SMC HSA ANVISA MHRA IMOH *PMDA* *EMA*
(observers)

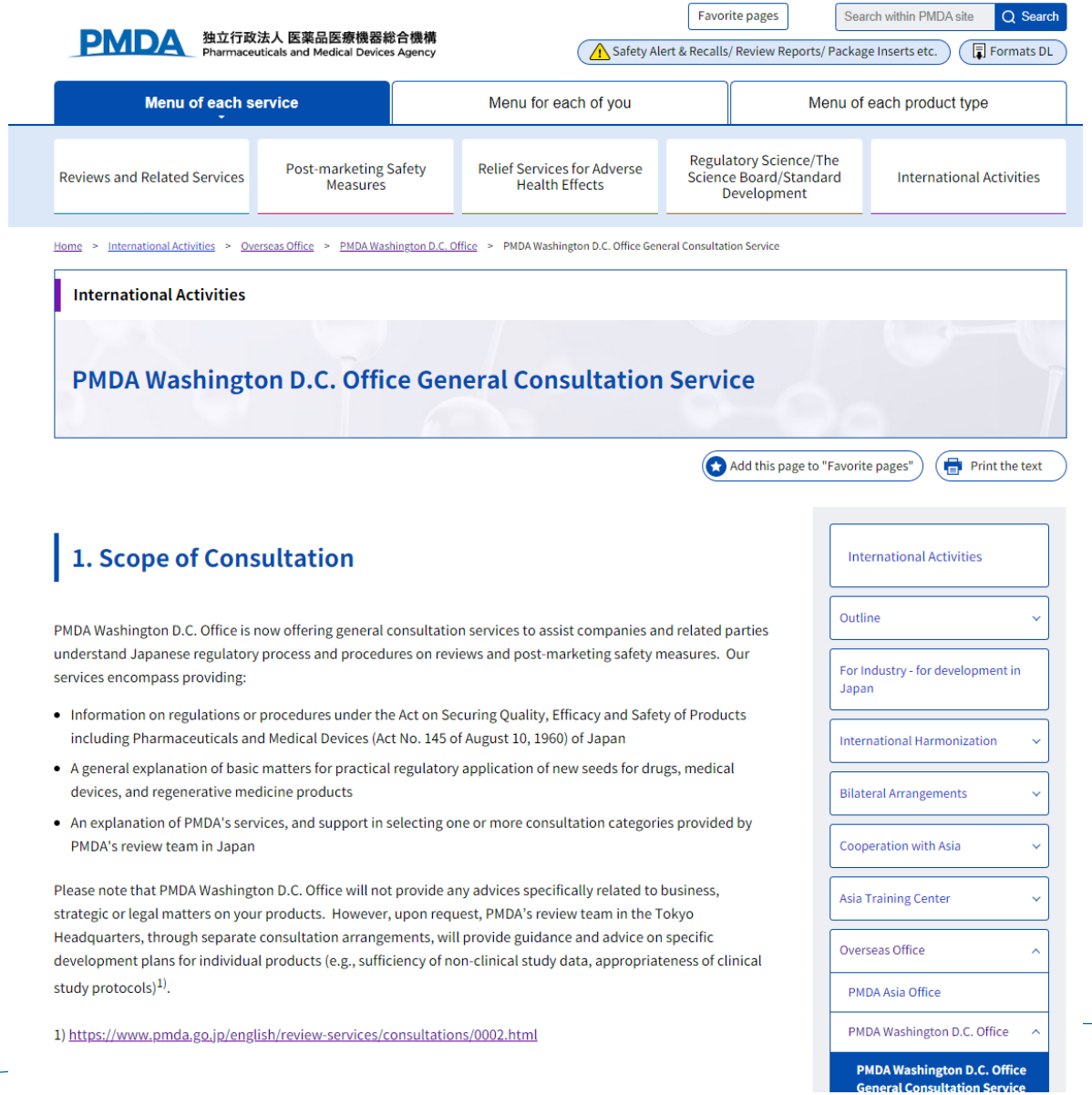
Project Orbis

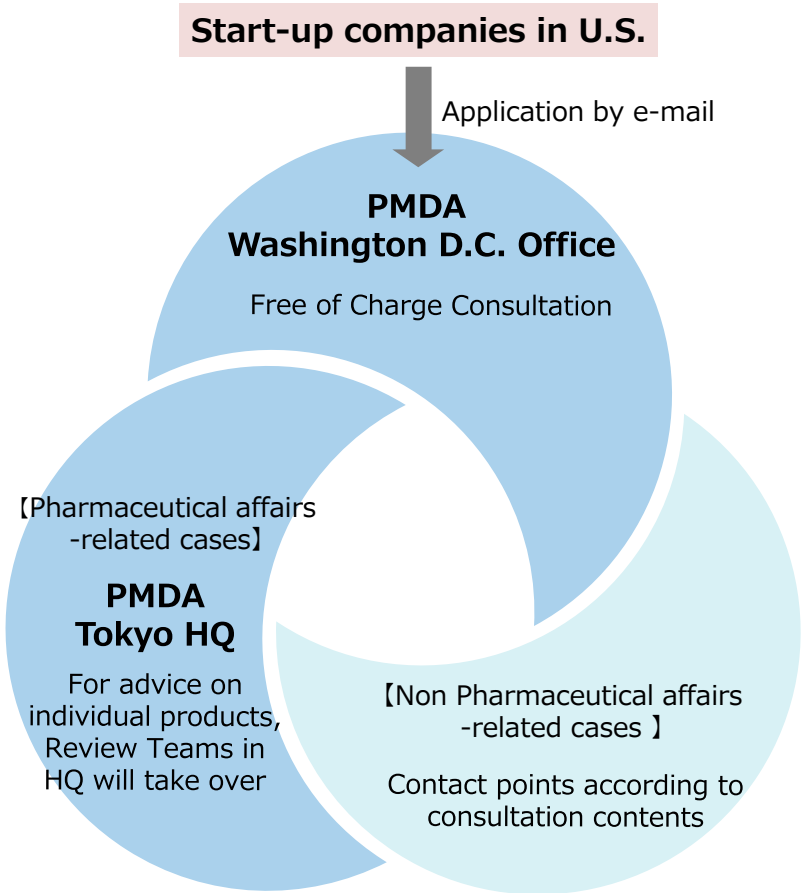
A framework for concurrent submission and review of oncology products

https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis

General Consultation Service at Washington D.C. Office

[Application for General Consultation]





Discussion Points for networking meetings with U.S. organizations

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- How many startups/venture companies (emerging companies), in the U.S. are interested in developing products in Japan?
- If they do develop products in Japan, what do they want to know?
- What are the barriers to entry into Japan?

➢ The smaller the company, the more severe the impact of language barriers (e.g., securing Japanese interpreters, preparing regulatory documents).

➢ Strengthening networking organizations, i.e., Accelerators and Incubators, to enhance drug discovery ecosystem in Japan.

One-Stop Consultation Service led by National Cancer Center Hospital (NCCH)

One-Stop Consultation Platform

Expert functions	Solution provided
KOL pool	Development Strategy (e.g. appropriate path and timing of Japan involvement)
Medical advisor pool for PI mgt	Development Operation (e.g. clinical trial excellence)
Commercial/ Marketing experts	Business Opportunity (e.g. market size, unmet medical needs)
Regulatory/ Market access experts	Regulatory Excellence (e.g. fast track strategy)
Company matching experts	Business Operation (e.g. Post-launch activity in Japan)

Knowledge-sharing

Regulatory Incentive System in Japan

Knowledge-sharing

Financial Incentive System in Japan

Courtesy of Dr. Kenichi Nakamura, NCCH

Future initiatives

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Further collaborations with U.S. FDA in various area

Networking with U.S./JP organizations to enhance development in Japan

Promote better understanding of Japanese regulations that PMDA covers

Thank you

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Check it out !

PMDA Updates 2025 Spring

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