Japan's PMDA pre-submission consultation program for medical devices

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Executive summary

This white paper provides an overview of Japan's Pharmaceuticals and Medical Devices Agency (PMDA) pre-submission consultation program, a mechanism available to manufacturers through which they can request feedback from, or a consultation meeting with, the PMDA. These communications may pertain to a potential or planned medical device premarket approval (PMA), a notification of a clinical study plan, regulatory strategy and approach or other facets of the market access process.

What type of agency is the PMDA?

Japan's PMDA is an incorporated administrative agency controlled by the Ministry of Health, Labour and Welfare (MHLW), established in April 2004. The Pharmaceuticals and Medical Devices Agency Act (PMDA Act) prescribes the agency's roles and duties commissioned by the MHLW. The primary roles and mission of the PMDA are to review and administer pre-market submissions of medical products, including pharmaceuticals, medical devices, tissue-engineered medical products, in vitro diagnostic devices (IVDs) and quasi-drugs to confirm their effectiveness and safety for the Japanese market. The PMDA also assumes responsibility for the implementation of relief systems such as the Relief System for Sufferers from Adverse Drug Reactions, safety measures such as the delivery of information on hazardous medical products on the market, information about recall and field actions and the Japanese IFU database and more.

How are medical devices authorized in Japan?

The PMD Act requires all medical products placed on the Japanese market to be authorized before commercial distribution. Medical device authorizations outside of Japan are not operative in Japan, and medical products placed on the Japanese market must be authorized through an appropriate registration route defined by the PMD Act.

There are three authorization routes for medical devices in Japan: Pre-Market Approval (PMA), Pre-Market Certification (PMC) and Pre-Market Notification (PMN). The appropriate authorization route is determined based on the applicable device class (Class I through Class IV), Japan Medical Device Nomenclature (JMDN), and equivalence with predicate devices registered in Japan. Among the routes, the PMDA administers the PMA and PMN.

The PMA route is mainly designed for high-risk (Class IV, most Class III, and some Class II) medical devices, including generic "me- too" devices, and it caters to products that have a lesser degree of equivalence with predicate devices registered in Japan, such as those that are particularly novel or have unique characteristics. The PMA route is also used for new devices that have no precedents and no applicable JMDNs or that require clinical data to demonstrate validity.

What challenges do foreign manufacturers face when seeking to register products in Japan?

A foreign manufacturer considering introducing a medical device to the Japanese market may have already placed the same device on the market in their home country and/or major markets such as the U.S. and EU. They may, therefore, anticipate that the same (clinical or non-clinical) data sets submitted for registrations outside of Japan would be sufficient to fulfill requirements in Japan without adding or modifying anything.

The MHLW has established and maintained not all but many requirements, standards and criteria applied to medical devices, referring to standards and guidance documents found outside of Japan, such as ISO, IEC, ASTM, FDA guidance, GHTF, IMDRF and ICH guidance, and others, in keeping with the global harmonization policy. For example, the MHLW established the Essential Requirements for Medical Devices based on Annex I of EU Directive 93/42/EEC. The requirements for biocompatibility and electrical safety and most fundamental safety requirements are mostly compatible with the requirements of the ISO 10993 and IEC 60601 standards, etc. Furthermore, the requirements for clinical trials and studies are generally compatible with the requirements of ICH E6 GCP. Accordingly, the data sets foreign manufacturers already possess may meet requirements in Japan, especially regarding generic "me-too" devices, which are designed based on compatible standards and requirements. Additionally, since clinical data gathered outside of Japan is sometimes admissible, such data gathered inside Japan is not necessarily required even if the presence of clinical data is mandatory.

Nevertheless, the data sets held by foreign manufacturers are not guaranteed to meet requirements in Japan. For devices that show a lower equivalence with predicate devices registered in Japan, such as those that are particularly novel or have unique characteristics, additional or supplemental data or evidence may be required. Below are typical examples:

- The MHLW has established rigorous or unique requirements for some medical devices, and the PMDA might require compliance with them even for generic "me-too" devices (e.g., unique requirements for fatigue tests for spinal implants).
- For a novel technology that has no precedents in Japan, the PMDA might require supplemental evidence to justify and demonstrate the device's performance and safety (e.g., animal tests supporting metabolic excretion and/or disposition for new bioabsorbable material).
- Medical devices likely to be impacted by racial anatomical differences might require clinical data representing primarily East Asian subjects.

The MHLW and PMDA assume that the healthcare environment, the standard of care, combinations of medical devices and pharmaceuticals used, techniques, technologies and patient demographics in Japan are not identical to those in other countries. Consequently, they do not consider a medical device to be safe and effective in Japan even when the device itself, its technology and its clinical effectiveness and safety have been qualified in other countries. Acknowledging those differences, the PMDA might require additional or supplemental data or evidence to bridge the gaps. However, the PMDA does not always require additional/supplemental testing data and instead might admit rationales and justifications based on objective evidence, such as clinical publications.

The bottom line here is that manufacturers are required to submit a complete application package, including a rigorous presentation of the data sets that are believed to be necessary. The PMDA condones provision of supplemental information and justification supporting the submitted application and data following the submission; however, it does not tolerate significant replacement or addition of data after the fact. For instance, if a manufacturer does not submit any clinical data for a PMA objectively requiring additional clinical data, the PMDA would recommend the manufacturer withdraw the PMA application.

For a generic "me-too" device that only requires conformance with standardized requirements and has substantial equivalence with predicate devices, the manufacturers might easily assemble sufficient data sets and complete the application package prior to the submission, even if there are minor differences in the requirements. On the other hand, with novel medical devices or those with unique characteristics, it may not be feasible for manufacturers to identify which data sets are required by the PMDA and prepare them in advance.

These challenges are not unique to PMA submissions and can be found in other pathways. For instance, they also apply to data sets submitted with an obligatory notification of clinical trials. If the sponsor of a clinical trial in Japan does not submit a sufficient verification data set or essential documents (investigator's brochure, etc.), with the obligatory notification of clinical trials (which does not fulfill the requirements laid out by the MHLW or meet the MHLW and PMDA expectations), the notification would be rejected by the MHLW and the clinical trials would not be allowed to begin.

Sometimes, a manufacturer attempting to prioritize their business plan and timeline tries to submit a package with incomplete data sets to authorities. This way, a record would be created to show that the manufacturer has submitted an application. However, it might further delay the business plan if authorities deem the data sets to be incomplete and either reject the application or recommend that the manufacturer withdraw it. Additionally, submitting incomplete data sets might give the authorities an unfavorable impression of the manufacturer and tighten the review of the manufacturer's subsequent submissions. To avoid such worst-case scenarios, manufacturers are advised to consult with regulatory authorities prior to the submission and assemble sufficient data sets based on these discussions.

The PMDA offers opportunities to advise on these challenges for manufacturers through the pre-submission consultation program, which any manufacturer may request regardless of nationality.

What is the PMDA pre-submission consultation program?

The PMDA offers several types of opportunities for regulatory consultation and advice for manufacturers, the pre-submission (pre-sub) consultation being a major component designed to give manufacturers PMDA feedback on pre-market submissions such as pre-market approval (PMA), notification of clinical study plan and others.

The pre-sub program offered by the PMDA is a bit like the Pre-Submission in the **Q-Sub program** offered by the U.S. Food and Drug Administration (FDA) and allows for various types of consultation depending on the manufacturer's agenda. The program also allows a manufacturer to discuss specific aspects of the regulatory process and requirements with PMDA experts. Although this white paper does not have space to address the alternatives in detail, the PMDA also offers opportunities to address simple questions on regulations and regulatory procedures from manufacturers other than the pre-sub consultation program. These alternatives do not generate official meeting minutes.

Requesting participation in the pre-sub consultation program is voluntary on the part of manufacturers; however, early interaction with PMDA on planned design and development, including non-clinical and clinical studies and careful consideration of PMDA's feedback might improve the quality of subsequent submissions, such as a PMA application and a notification of clinical study plan, and might shorten overall review times of subsequent submissions. The PMDA believes that interactions provided by the pre-sub consultations are likely to enable a more transparent review process for PMDA and the manufacturer alike.

At the same time, pre-sub consultations can be an essential step for facilitating subsequent submissions and discussions with the PMDA. Pre-sub consultations might help to reduce unexpected risks in subsequent submissions. In particular, interactions with the PMDA provided by the pre-sub consultations are essential for a successful planned PMA with clinical data and a successful notification of clinical study plan. With the revision of the PMD Act, which took effect in September 2020, the MHLW established new registration paths for specific medical devices, i.e., fast-track reviews for precursor medical products, conditional fast-track reviews, and Improvement Design within Approval for Timely Evaluation and Notice (IDATEN). The medical devices subject to one of the new registration pathways are required to request a pre-sub consultation before their submissions.

Types of pre-sub consultation

The MHLW released an implementation guideline for the pre-sub consultations, the MHLW ministerial notice **Yaku- ki-Hatsu #0302072** (link in Japanese) and its amendment notices (final amendment: Dec. 28, 2023), and the PMDA published a list of the consultation types on the website accordingly.

The pre-sub consultation program for medical devices is divided into seven major types below, organized by the agenda to be discussed. Furthermore, some of the types ("d. Protocol" and "e. Adequacy of existing data") are segmented by the particular area under consideration.

a. Expanded access study
b. Pre-development
c. Necessity of (additional) clinical study
d. Protocols
e. Adequacy of existing data
f. Submission package
g. Submission compilation
h. IDATEN pre-submission

The pre-sub consultation format basically consists of an in-person meeting with the PMDA experts. Additionally, PMDA feedback will be documented in the meeting minutes issued by the PMDA after the in-person meeting. The PMDA assigns an identification number to each pre-sub consultation meeting. If subsequent submissions are for the same device and indications for use as the Pre-Sub consultation, the subsequent submissions are considered to be related submissions. To help link pre-sub consultations to the subsequent submissions, the manufacturer identifies the identification number in the subsequent submission.

This white paper outlines the following high-use consultation types: "b. Pre-development," "c. Necessity of (additional) clinical study," and "d. Protocols."

b. Pre-development

Pre-development consultation is appropriate when PMDA's feedback on specific questions is necessary to guide product development and/or submission preparation.

This consultation type consists of a request for PMDA (high-level) feedback on the data framework anticipated for a PMA. The PMDA feedback helps a manufacturer identify what non-clinical data would be required for a medical device PMA, and whether clinical data would be required for a medical device PMA as a part of the data sets. For medical devices in the development stage, PMDA feedback can help to establish design inputs and verification and validation items. For completed medical devices, it can help to confirm the adequacy of existing data sets and the necessity or lack thereof of additional non-clinical data such as animal models and clinical data.

Pre-development consultation is suggested for medical devices featuring a new technology that is difficult to evaluate according to widely recognized (e.g., ISO and IEC) standards and that may cause the PMDA to request additional clinical or non-clinical study data. Pre-development consultation is also required particularly for medical devices that will use the Fast-Track Review system and IDATEN Review system. Manufacturers will discuss the eligibility of using these review systems in pre-development consultation.

c. Necessity of (additional) clinical study

Necessity of (additional) clinical study consultation is appropriate when PMDA's feedback on specific questions is necessary to determine the sufficiency of the manufacturer's existing non-clinical and clinical data and the necessity of (additional) clinical data for a PMA.

This consultation type consists of a request for PMDA feedback on an existing data package including non-clinical and clinical data anticipated for a PMA. The PMDA feedback especially helps a manufacturer to determine the sufficiency of existing clinical data gathered outside of Japan. As an example, a manufacturer could request PMDA's feedback on the sufficiency of clinical study data that does not include many East Asian subjects and confirm the necessity of additional clinical study data to bridge any gaps. Furthermore, a manufacturer could request PMDA's feedback on the sufficiency of Clinical Evaluation Reports (CERs) as an alternative to clinical study data and confirm the necessity of clinical study data.

As another example, with medical devices for which it is unclear whether clinical data is required, a manufacturer could request PMDA's feedback on its necessity, based on the sufficiency of existing non-clinical data, clinical literature, data from PMS, etc.

d. Protocols

Protocols consultation has five segments depending on the endpoint of a study or test: safety test, quality test, performance test, preclinical study and clinical study. Protocols consultation is appropriate when PMDA's feedback on specific questions is necessary to determine the design of a particular test or study.

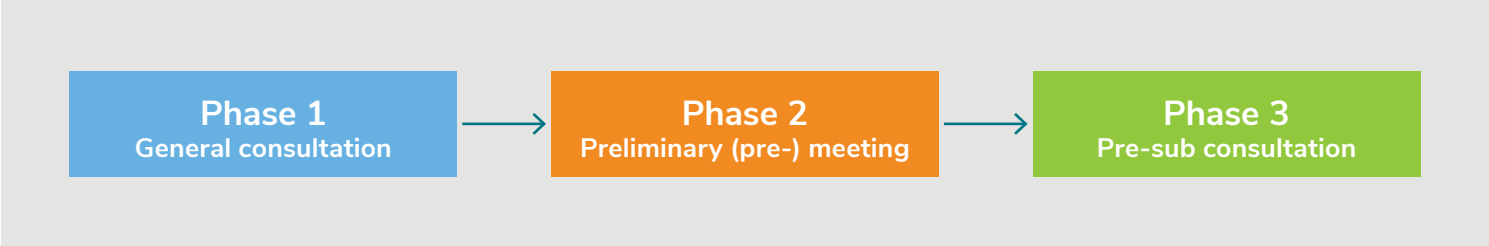
PMDA feedback at the protocols consultation for the safety test, quality test and performance test helps a manufacturer determine the design and the criteria for a non-clinical study or quality test that is not standardized, such as an animal test supporting unique technology. On the other hand, PMDA feedback at the protocols consultation for preclinical study and clinical study helps a manufacturer determine the design, clinical endpoints, performance of criteria, and acceptance criteria for these activities. In these last two segments, the PMDA also confirms the sufficiency of a package of non-clinical data sets. PMDA feedback can especially help a manufacturer determine the design of a planned study conducted to support a PMA.

As mentioned above, the request of the pre-sub consultation program is voluntary for manufacturers. However, the request of the consultation types associated with clinical data and clinical study (i.e., "c. Necessity of (additional) clinical study" and "d. Protocols") is virtually a necessary step in this regulatory process.

The pre-sub consultation process

The pre-sub consultation process may be a little complicated for first-time users, requiring every participant to follow a phased process approach through to a pre-sub consultation meeting. The general processes for the pre-sub consultation program are outlined below.

Participants should expect to request at least three meetings, including the pre-sub consultation. To facilitate each phase, it is important to be aware of their purposes, roles and goals.



Phase 1 – General consultation

The general consultation is a 30-minute free consultation meeting and a versatile opportunity to present PMDA experts with questions on regulations and regulatory procedures face-to-face. The PMDA provides oral feedback only, and the feedback will not be documented. General consultation is not designed solely for pre-sub consultation and is the most accessible opportunity to consult with the PMDA experts.

As the initial step in the path toward a pre-sub consultation, the PMDA requires the user to request a general consultation first. The purpose of the general consultation meeting is to organize and clarify the questions and agendas that are awaiting feedback from the PMDA at the pre-sub consultation meeting. Once the questions and agendas are organized, the PMDA advises on the types of pre-sub consultation appropriate for the user agendas.

If the questions and agenda include both clinical and non-clinical aspects, the PMDA may recommend to request two pre-sub consultations separately: pre-development and necessity of (additional) clinical study. Also, if the product is a more complicated one, such as a combination device or a companion diagnostic, the PMDA experts belonging to the pharmaceutical or IVD review divisions may become involved at this early stage and direct the user to request a pre-sub consultation for pharmaceuticals or IVDs, separately from that for medical devices.

Appointment for general consultation

Participants submit a general consultation request form to the PMDA by e-mail. Since the request form must be completed in Japanese, a foreign manufacturer may ask its Japanese representative to make the appointment with the PMDA. The user requests multiple desired dates for a general consultation meeting on the form. A meeting date will be decided through a phone conversation between the PMDA and the participating company (or its Japanese representative).

A general consultation request form includes the following items:

- Applicant company name and contact information
- Information of primary contact of the user (i.e., the Japanese representative)
- Attendees
- Name of subject product (or identification number, in the case of prototypes)
- Anticipated classification (defined by the MHLW) applicable to the subject product
- Questions and agendas to be consulted at a pre-sub consultation, and
- Other administrative information listed as required in the **PMDA guidance** for a general consultation

Once the request is accepted, the PMDA appoints main and assistant experts in charge.

Document submitted

Although the PMDA guidance does not specify documents and formats for presentation at a general consultation meeting, it is recommended to include the following information. Typically, many participants prepare a document for the general consultation meeting in slide presentation form. Considering the short time (30 minutes) allocated for a general consultation meeting, it is crucial to deliver a clear and concise presentation.

- Introduction featuring product description, general information and images
- Short summary of controversial characteristics (e.g., unique intended use, indications for use, clinical significance, mode of action/operating principle, raw materials)
- Description of usage
- List of existing non-clinical data sets
- Short summary of existing clinical data sets, if the participant requests the necessity of (additional) clinical study or a protocols consultation for preclinical study and clinical study, and
- Questions in need of PMDA feedback at a pre-sub consultation

Meeting

The primary PMDA expert in charge leads the meeting. The user usually shows the document for the general consultation meeting to PMDA experts and provides a briefing on the product itself, outlining the questions and agendas in need of PMDA feedback at a pre-sub consultation within around 15 minutes. The remaining 15 minutes is allocated to a question-and-answer session. At the end of the general introduction meeting, the PMDA advises the user to request which pre-sub consultation is appropriate for their questions.

Phase 2 – Preliminary meeting

The preliminary (pre-) meeting is a 30-minute paid consultation providing an opportunity to ask the PMDA experts face-to-face about particular matters leading toward a desired pre-sub consultation, in more depth than is available at a general consultation meeting. The PMDA provides oral feedback only, and the feedback will not be documented.

As the second step in the path toward a pre-sub consultation, the pre-meeting is a mandatory part of the process. The goal of the meeting is to confirm the participating company's readiness for a specific pre-sub consultation.

Appointment for a preliminary meeting

The user submits a pre-meeting request form to the PMDA by e-mail. Since the request form must be completed in Japanese, a foreign manufacturer may ask its representative in Japan to create the appointment with the PMDA. The user requests a few multiple desired dates for a pre-meeting on the form. A meeting date will be decided through phone conversation between the PMDA and the participating company (or its Japanese representative). Once the day for the meeting has been established, the user pays the pre-meeting fee to the PMDA's bank account by the day before the meeting.

The request form includes the following items:

- Applicant company name and contact information
- Information of primary contact of the Japanese representative
- Attendees
- Name of subject product (or identification number, in the case of prototypes)
- Anticipated classification applicable to the subject product
- Anticipated type of pre-sub consultation
- Questions and agendas for pre-meeting
- A list of attachments (e.g., the name of the draft Technical Document), and
- Other administrative information required in the **PMDA guidance** for a pre-meeting

Document submitted

The user submits the following at a pre-meeting:

- A copy of the meeting fee receipt, and
- A Draft for Technical document

Users should draft Technical Documents summarizing the available information regarding the subject product, together with the questions and agendas to be discussed in a pre-sub consultation and submit it to the PMDA experts. Information and content to be presented in the Technical Documents will vary depending on the type of pre-sub consultation the user requests. Generally, users draft a Technical Document for a pre-sub consultation in **Summary Technical Documentation** (STED) format, including anticipated information and content, and submit it for the pre-meeting. Since most users are familiar with STED format, using it can provide a simple and easy way to organize and summarize the information regarding the subject product. For details on the anticipated information and content, see Table 1 below.

Meeting

The primary PMDA expert in charge leads the meeting. The PMDA experts check the user's readiness through discussion and review of the submitted Technical Documents, eventually determining whether the user is ready for a pre-sub consultation. The Technical Documents submitted at a pre-meeting are drafts of Technical Documents that will be officially reviewed at a pre-sub consultation. At a pre-meeting, the PMDA experts quickly review the draft version and determine the degree of completion. Once the PMDA experts determine that the Technical Documents are ready and can move to a pre-sub consultation, the PMDA issues a diploma to the user and directs them to request a pre-sub consultation. Refer to Table 1 below for the information that should be presented in the Technical Document for a pre-sub consultation.

If the PMDA determines that the Technical Documents are not ready, the experts might direct the user to refine the Technical Document before requesting another pre-meeting.

Phase 3 – Pre-sub consultation

The pre-sub consultation meeting is a one- to two-hour (depending upon the type) paid consultation meeting and an opportunity to ask the PMDA experts about questions and agendas face-to-face in a formal setting. The PMDA provides documented feedback in the form of meeting minutes. The PMDA assigns an identification number to each pre-sub consultation in order to link them to subsequent submissions.

Appointment for a pre-sub consultation

The user submits a pre-sub consultation request form to the PMDA by e-mail. Since the request form must be completed in Japanese, a foreign manufacturer may ask its representative in Japan to create the appointment with the PMDA. The user requests a few desired dates for a pre-sub consultation meeting on the form. A meeting date will be decided through a phone conversation between the PMDA and the participating company (or its Japanese representative). Once the day for the meeting is established, the user pays the fee for the pre-sub consultation to the PMDA's bank account within 15 days of the meeting.

The request form should include the following items:

- Applicant company name and contact information
- Information of primary contact of the Japanese representative
- Attendees
- Name of subject product (or identification number, in the case of prototypes)
- Anticipated classification applicable to the subject product
- Anticipated intended use and indications for use
- Registration history outside of Japan, if imported product
- Purpose of clinical study, if applicable
- A list of attachments (e.g., the name of the complete Technical Document)
- Other identification number, if the user previously requested another pre-sub consultation for the same product, and
- Other administrative information required in the **PMDA guidance** for a pre-sub consultation meeting

If the user requests a necessity of (additional) clinical study or a protocols consultation for preclinical study and clinical study, the request should also include the name and affiliation of any medical expert(s) the user received advice from in regard to designing the study protocol.

Document submitted

The user must submit the following to the PMDA by the deadline defined for each pre-sub consultation program.

- A copy of the meeting fee receipt, and
- The complete Technical Document summarizing the information regarding the subject product (for details, see Table 1 below).

The user must complete the Technical Document following the guidance and PMDA suggestions given at the pre-meeting and submit it to the PMDA. The anticipated information and contents for the Technical Document are as described in Table 1 below. Note that the Technical Document must be compiled in the Japanese language. Additionally, some of the critical attachments for the Technical Document (the clinical study report, its protocol and others) written in languages other than Japanese must be translated into Japanese.

Once the PMDA accepts the Technical Document from the user, the PMDA experts review it within around one week of receiving the submission.

If the PMDA experts have questions and concerns, they direct inquiries to the user via phone call(s) or e-mail(s). The user should respond to any inquiries promptly (typically within three to four days).

The PMDA experts will determine the direction of the feedback prior to the consultation meeting through discussion with the user. Therefore, these conversations leading up to the meeting are of essential importance. The bottom line of predetermined feedback might be adjusted due to the outcome of the discussion at the pre-sub consultation meeting; however, any change is unlikely to be drastic. Therefore, if the user expects substantive and constructive feedback from the PMDA experts, it is recommended to respond to their inquiries promptly and precisely.

Table 1. The contents in Technical Documents

Type of pre-sub	Pre-development consultation
Submission deadline	By 3 p.m. on Monday two weeks before the day of the meeting.
Contents required	For products in the early development or pre-development stage: • Outline of the product and its characteristics, including planned intended use, indications for use, mode of action, configurations, etc. • A list of similar products on market • Information provided by publications, such as clinical studies of similar products • Summary of data from basic research • A list of planned design input and verification and validation items For completed products such as imported products: • Product description, including intended use, indications for use, mode of action, configurations, specifications, etc. • Design history, design concept, and the basis of device specifications (device performance and safety) • Comparison with predicate devices • A list of applied standards and related data sets (per test) that the manufacturer can submit with a PMA application • Data of actual clinical use, including vigilance and adverse event information • Safety data for predicate devices in Japan, if any

Type of pre-sub	Necessity of (additional) clinical study
Submission deadline	By 3 p.m. on Monday three weeks before the day of the meeting.
Contents required	• Product description, including intended use, indications for use, mode of action, configurations, specifications, etc. • Design history, design concept, and the basis of device specifications (device performance and safety) • Comparison with predicate devices • Summary of the results of design verification, including applied standards and related data set (per test), plus non-clinical data set (per test), that the manufacturer can submit with a PMA application, such as animal data, including in vivo and in vitro data • Data of actual clinical use (real-world), including vigilance and adverse event information • Safety data for predicate devices in Japan, if any • Summary of any clinical data the manufacturer has • The translated clinical study report and its protocol (or CER), along with publications related to the product, should be attached to the Technical Document

Type of pre-sub	Protocols consultation for preclinical study (Phase II study)
Submission deadline	By 3 p.m. on Monday three weeks before the day of the meeting.
Contents required	• Product description, including intended use, indications for use, mode of action, configurations, specifications, etc. • Design history, design concept, and the basis of device specifications (device performance and safety) • Comparison with predicate devices or standard care for the targeted disease • Summary of the results of design verification, including applied standards and related data set (per test), plus non-clinical data set (per test), that the manufacturer can submit with a PMA application, such as animal data, including in vivo and in vitro data • Safety data for predicate devices in Japan, if any • Summary of the results of the preclinical study, if any • Summary of planned study protocol, including the design, such as the disease being treated and the patient population, inclusion/exclusion criteria, clinical endpoints, clinical site, etc. • Drafted essential documents, such as the Investigator's Brochure (IB) and Informed Consent Form (ICF) • Planned study protocol and publications related to the product should be attached to the Technical Document

Type of pre-sub	Protocols consultation for clinical study
Submission deadline	By 3 p.m. on Monday three weeks before the day of the meeting.
Contents required	• Product description, including intended use, indications for use, mode of action, configurations, specifications, etc. • Design history, design concept, and the basis of device specifications (device performance and safety) • Comparison with predicate devices, or standard care for the targeted disease inside and outside of Japan • Clinical implications and benefits of the product • Summary of the results of design verification, including applied standards and related data set (per test), plus non-clinical data set (per test), that the manufacturer can submit with a PMA application, such as animal data, including in vivo and in vitro data • Data of actual clinical use (real-world), including vigilance and adverse event information if the product is already placed on markets outside of Japan • Safety data for predicate devices in Japan, if any • Summary of the results of the preclinical study, if any • Summary of planned study protocol, including the design, such as the disease being treated and the patient population, inclusion/exclusion criteria, clinical endpoints, clinical site, etc. • The basis for the study design, such as the probability statistical basis for determining the number of subjects, etc. The following (translated into Japanese) should be attached to the Technical Document: • Planned study protocol • Publications related to the product • Drafted essential documents, such as the Investigator's Brochure (IB) and Informed Consent Form (ICF) • A copy of the meeting minutes if the user requested another pre-sub consultation for the same product before

Consultation meeting
The main expert in charge leads the meeting. For a Necessity of (additional) clinical study or protocols consultation for pre-clinical study, clinical experts may attend from the PMDA side.

The user gives a 30-minute presentation summarizing the contents of the submitted Technical Document first. If the user can integrate the previous conversation with the PMDA experts into the presentation, this is ideal. The remaining time is allocated to technical discussion with the PMDA experts. After the discussion, the main expert in charge will provide oral feedback from the PMDA.

Around one week after the consultation meeting, the user will get a draft of written feedback, along with an audio recording of the meeting. If the user has an objection to the written feedback, it is possible to bring a challenge to the PMDA within generally one week. The PMDA may adjust the feedback if the challenge is deemed to be justified.

Once the user decides to accept the feedback, the PMDA will issue the regularized feedback as the meeting minutes. The user will attach a copy of the written feedback to subsequent submissions and should keep the original on hand.

Complementary phase – Follow-up consultation

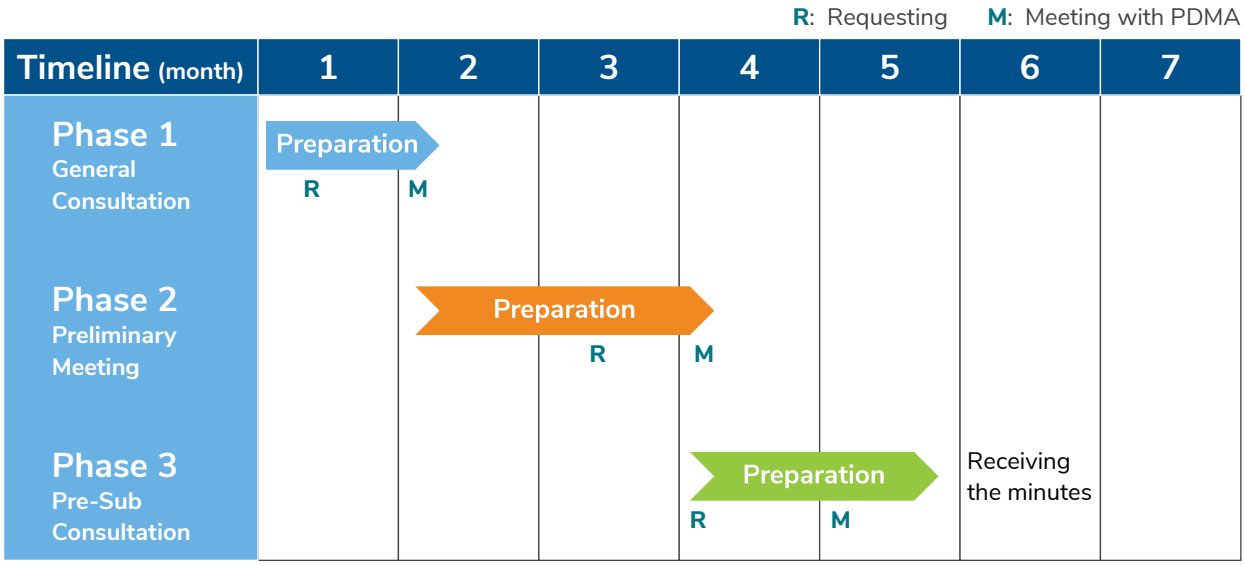
If any questions remain following a pre-sub consultation, the user can request a pre-sub follow-up meeting with the PMDA experts. A pre-sub follow-up meeting consists of a 30-minute meeting/telephone call and an opportunity to discuss questions with the PMDA experts. The PMDA provides oral feedback only, and the feedback will not be documented. The method for requesting a pre-sub follow-up meeting is the same as for the general consultation.

Timeline for a pre-sub consultation

The anticipated timeline for a pre-sub consultation might vary depending on the questions and agendas to be discussed, the sufficiency of data sets possessed by the manufacturer, preparation time for the Technical Document, and PMDA's bandwidth.

As mentioned above, the Technical Document needs to be drafted and compiled in Japanese, and key evidence and essential documents, including the clinical study report, its protocol, draft Investigator's Brochure (IB), and Informed Consent Form (ICF), written in languages other than Japanese must be translated into Japanese. When planning a timeline for a pre-sub, it is important to consider the time to be allotted to translation. Table 2 shows a typical timeline for a pre-sub consultation.

Table 2. The contents in Technical Documents



Other pre-sub consultation programs

Including pre-sub consultation programs mentioned above, the PMDA also offers the following pre-sub consultation programs, using the same phased process approach as the pre-sub consultation programs mentioned above (See Table 3).

Table 3. Pre-Sub consultation programs

Consultation program	Agendas	Consultation fee/Meeting hours
General consultation	• A meeting to consult with PMDA experts for advice on general questions about regulations, guidance notification, regulation, and product registration. • An opportunity for the PMDA experts to select a specific pre-sub consultation program appropriate for the agenda.	Free/0.5 hour
Preliminary (Pre-) meeting	• A meeting to consult with PMDA experts about the points and agendas of a specific pre-sub consultation. • An opportunity to check the readiness of requester by the PMDA experts. A pre-check toward a particular pre-sub consultation.	JPY29,400 per meeting/0.5 hour
Pre-Sub consultation programs		
1. Expanded Access Study Phase 2 - Preliminary (Pre-) meeting can be skipped.	• Consultation with PMDA experts for advice on a study design intended for an Expanded Access Study.	JPY249,000/1 hour
2. Pre-Development	• Consultation with PMDA experts for advice (high-level) on the framework of the data sets for submission. • Pre-development/development stage: advice on design inputs and specifications considering subsequent submissions such as PMA application. • Completed product: advice on the sufficiency of the package with existing data sets for a subsequent submission such as a PMA application. • Consultation with PMDA experts for advice on the eligibility for the fast-track review/IDATEN Review system	JPY294,100/1 hour
3. Necessity of (additional) clinical study	• Consultation with PMDA experts for advice on the necessity of an additional clinical study, based on the existing clinical and non-clinical data sets. • Consultation with PMDA experts for advice on the necessity of a clinical study, based on the sufficiency of existing non-clinical data, clinical literature, post-market data from PMS, etc.	JPY1,960,900/2 hours JPY980,300/2 hours

Consultation program	Agendas	Consultation fee/Meeting hours
4. Protocols	a. Safety test: Consultation with PMDA experts for advice on safety specifications, such as biocompatibility and electrical safety, etc. Ex.: appropriateness of testing design for unstandardized electrical safety.	JPY98,000*1 per protocol/1.5 hours
	b. Quality test: Consultation with PMDA experts for advice on quality specifications, stability and test design.	JPY390,100/1.5 hours
	c. Performance test: Consultation with PMDA experts for advice on non-clinical performance testing, such as animal testing, bench testsand test design relevant to device performance.	JPY98,000*1 per protocol/1.5 hours
	d. Preclinical study: Consultation with PMDA experts for advice on validity of a pilot study and its design conducted before pivotal study.	JPY1,076,200/2 hours
	e. Clinical study: Consultation with PMDA experts for advice on validity of study protocol for pivotal study and its study design, including number of patients, necessity of controlled study, clinical endpoints, etc. (like pre-IDE offered by the U.S. FDA).	JPY2,353,100/2 hours
5. Adequacy of existing data This consultation is intended to facilitate PMDA's expert analysis of individual test/study data.	a. Consultation with PMDA experts for advice on validity and sufficiency of existing data set of a safety test.	JPY147,700*2 per test/1.5 hours
	b. Consultation with PMDA experts for advice on validity and sufficiency of existing data set of a quality test.	JPY588,200*3/1.5 hours
	c. Consultation with PMDA experts for advice on validity and sufficiency of existing data set of a performance test.	JPY147,000*2 per test/1.5 hours
	d. Consultation with PMDA experts for advice on validity and sufficiency of existing data set of preclinical study.	JPY1,519,700*3/2 hours
	e. Consultation with PMDA experts for advice on validity and sufficiency of existing data set for a clinical study.	JPY2,647,200*3/2 hours
	f. Consultation with PMDA experts for advice on validity and sufficiency of existing data set of evaluations of the results of usage in the real world (PMS).	JPY2,647,200/2 hours
6. Submission package Phase 2 - Preliminary (Pre) meeting can be skipped.	Consultation with PMDA experts for advice on the sufficiency of PMA application package and completeness of the application documents.	JPY390,100 Only document check and documented feedback
7. Submission compilation Phase 2 - Preliminary (Pre-) meeting can be skipped.	Consultation with PMDA experts for advice on validity and sufficiency of PMA application package and completeness of the application documents.	JPY134,800 Only document check and documented feedback

*1. Consultation fee will vary depending on the number of protocols.
*2. Consultation fee will vary depending on the number of tests. The fee will be reduced if the user utilized 4) Protocols consultation for the same test before the testing.
*3. The fee will be reduced if the user utilized 4) Protocols consultation for the same test before the testing.

Benefits of requesting pre-sub consultation

Requesting a pre-sub is not mandatory, and from the standpoint of business, manufacturers may think that it is a waste of time. However, there are several advantages of using a pre-sub consultation program, and the advantages often outweigh the disadvantages.

Advantages	Disadvantages
• Prevents subsequent submissions from running into problems and prolonging the review period • Increases the possibility that the product is authorized within the "Time Clock," allowing the manufacturer to plan accordingly	• Extends the timeline for the overall regulatory pathway • Increases the cost (consultation fee)

Unlike the U.S. FDA, the MHLW and PMDA do not set a specific period for review of a PMA application, such as 180 days. The PMDA also will not forcibly refuse a PMA application accepted during the review. Instead, they set numerical targets for the PMA review period, called a "Time Clock." If a manufacturer submits the complete PMA application, it would be extremely likely to be authorized within the Time Clock; however, an incomplete PMA application might prolong the review period beyond the Time Clock.

For manufacturers, it may not be challenging to prepare a complete PMA application for generic devices and improved devices without clinical data. However, for manufacturers who have limited experience in medical device registration in Japan, it may not be easy to prepare a complete PMA application without feedback from the PMDA. Also, for medical devices with unique characteristics or requiring clinical data, feedback from the PMDA may be essential to prepare a complete PMA application. In any of these cases, if a manufacturer submits an incomplete PMA application, the review period might be extended, it would make it difficult to estimate when commercial distribution in Japan could be started.

The delay created by requesting a pre-sub consultation may actually be small. For instance, the contents and information required for Technical Documents of necessity of (additional) clinical study and protocol consultation for pre-/clinical study are similar to the requirements of subsequent submission (PMA application documents), and around 60% to 70% of the Technical Document can be used for the compilation of the PMA application. Considering the time required for translation of critical documents such as the clinical report, the compilation of a PMA application package usually takes a few months even if not requesting a pre-sub consultation. If the manufacturer compiles the PMA application package in parallel with the preparation of the Technical Document, the delay caused by requesting a pre-sub consultation may be kept within a few months. If manufacturers set a timeline for the Japan regulatory pathway including the request of pre-sub consultation from the beginning, a few months' extension might be absorbed.

Major past examples of advice from the PMDA at a pre-sub consultation

The following is a non-comprehensive list of significant past examples that Emergo by UL has experienced:

Scenario and cause	Required additional data
Scenario: The device was based on relatively new technology, and the technology itself had not been sufficiently qualified even in markets outside of Japan yet. The manufacturer only had a Clinical Evaluation Report (CER) of the device, based solely on literature and non-clinical data. **Cause:** The literature cited in the CER evaluated only similar devices based on conventional technology, and non-clinical data could not support the mode of action sufficiently.	At a necessity of (additional) clinical study consultation, the PMDA concluded that the CER alone was not enough and clinical study data was necessary for the PMA.
Scenario: Since the U.S. FDA regarded the device as a new one requiring clinical data through the 513(g) consultation, the manufacturer conducted a clinical study in the U.S. for PMA. Since the PMDA also regarded it as a new one, the manufacturer expected to use the same clinical data as in the U.S. for Japan registration. **Cause:** The effectiveness and safety of the investigational device were susceptible to anatomical differences; however, the subjects of the clinical study did not include many Japanese or other East Asian subjects.	At a necessity of (additional) clinical study consultation, the PMDA concluded that additional clinical study data covering East Asian subjects was necessary for the PMA.
Scenario: The manufacturer had clinical study data of a controlled study, gathered outside of Japan. Since the subjects of the clinical study included the Asian population as well, the manufacturer expected to use the same clinical data for Japan registration. **Cause:** The device (or pharmaceutical) used in the control group had not been authorized in Japan yet.	At a necessity of (additional) clinical study consultation, the PMDA concluded that additional clinical study data (a controlled study with device/ pharmaceutical authorized in Japan) was necessary for the PMA.
Scenario: The manufacturer had clinical study data of a surgical device, gathered outside of Japan. Since the clinical study data supported its effectiveness and safety in Asian populations, the manufacturer expected to use the same data for Japan registration. **Cause:** Since there were slight differences in (gold) standard care, concomitant medications, and the surgical technique applied to the indications between Japan and other countries, the safety and usability of the investigational device had not been evaluated sufficiently for use in Japan.	At a necessity of (additional) clinical study consultation, the PMDA concluded that additional clinical study data (a small study in Japan) was necessary for the PMA.

Scenario and cause	Required additional data
Scenario: The manufacturer had the results of a controlled study (crossover) for the diagnostic device, gathered outside of Japan. Since the clinical study data supported the effectiveness and safety in Asian populations, the manufacturer expected to use the same data for Japan registration. **Cause:** The device employed a new technology for lesion detection and the clinical study data supported its effectiveness and safety; however, the manufacturer lacked sufficient scientific evidence supporting the detection principle and could not present the justification.	At a necessity of (additional) clinical study consultation, the PMDA concluded that additional clinical study data (a small study in Japan) was not necessary for the PMA; however, scientific and objective evidence supporting the detection principle was essential.
Scenario: The manufacturer had clinical study data of a bioabsorbable device, and the raw material was new, although there was a similar existing device. The clinical study data supported effectiveness and safety. **Cause:** The manufacturer had animal data demonstrating that the raw material would be biodegraded and expelled from the body. However, the manufacturer had no scientific rationale supporting the metabolic pathway.	At a necessity of (additional) clinical study consultation, the PMDA concluded that additional clinical data was unnecessary but additional data supporting the metabolic pathway, such as pharmacokinetics and pharmacodynamics of the raw materials, were necessary for the PMA.
Scenario: The manufacturer had data from fatigue tests for an implantable device, such as dental or orthopedic implants. Since the data showed that the device met the requirements set by the U.S. FDA, the manufacturer expected to use the same data for Japan registration. **Cause:** There were differences in the requirements for some implantable devices between the U.S. and Japan, and the U.S. data did not support conformance with the requirements in Japan sufficiently.	At a pre-development consultation, the PMDA concluded that the manufacturer needed to conduct fatigue tests according to the guidelines in Japan and submit the results for the PMA.

Subsequent submissions

Once a pre-sub consultation is closed, the user will obtain the meeting minutes. If any questions or challenges remain from the discussion at the pre-sub consultation, those would be stated in the minutes. Before the submission of a subsequent submission, the manufacturer would take the questions or challenges carefully into account and address those (e.g., conducting an additional test, gathering additional evidence or enhancing the justification for an existing data set).
If the manufacturer needs feedback on the sufficiency and validity of responses to the questions or challenges, the manufacturer can request a pre-sub follow-up meeting with the PMDA experts.

When preparing a subsequent submission, such as a PMA application, the manufacturer would include the responses to the questions stated in the minutes. Also, the manufacturer would include the identification number assigned to the pre-sub consultation in the submission documents and attach the meeting minutes to the submission.

Supplementary information

Before the COVID-19 pandemic, pre-sub was based on face-to-face meetings.
In the wake of the COVID-19 pandemic, PMDA has moved most pre-sub meetings online.
The WebEx from CISCO is available for a meeting with the PMDA online.

Learn more

Need help with Japan's PMDA pre-submission consultation program for medical devices? Emergo by UL supports regulatory compliance and market access for device manufacturers worldwide. Here's how we help:

- Medical device registration and approval
- IVDs registration and approval
- Medical device classification consulting and JMDN code research
- Clinical data evaluation and GCP compliance
- Foreign manufacturer registration in Japan

Learn more about global market access for medical devices at **EmergobyUL.com**.

About the author

Kenji Yashiro is managing director and lead senior regulatory consultant at Emergo Japan Consulting. Kenji has more than seven years of experience in the design and development of medical devices in Japan, and more than 17 years of experience managing quality assurance and regulatory issues facing medical device manufacturers selling in Japan and other markets.

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