Clinical Data Requirements in Japan

Understanding how and when PMDA requires clinical data in premarket submissions

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Introduction: When is clinical data required?

The Pharmaceuticals and Medical Devices Act (PMD Act), which is the primary law regulating healthcare products in Japan, provides three registration routes for medical device market authorization: Pre-market Approval (PMA), Pre-market Certification (PMC), and Pre-market Notification (PMN).

The PMD Act classifies medical devices by device risk classes from Class I through IV and Japan Medical Device Nomenclature (JMDN). Similar to the U.S. product codes, each JMDN corresponds to a device risk class and a registration route. Therefore, once an applicable JMDN is identified, an associated registration route can be identified.

The differences between registration routes are beyond the scope of this white paper. The registration routes, depending on device class, can be summarized as follows.

Device risk class	Registration route	Submitted to
Class I	PMN	PMDA (self-declaration)
Almost Class II and some Class III	PMC	A Registered Certification Body (RCB)
Some Class II, almost Class III, and Class V	PMA	PMDA

The PMD Act requires clinical data for some devices subject to the PMA route. Unlike U.S. Food and Drug Administration (FDA) Pre-market Approval and European CE marking certification, PMAs in Japan do not always require clinical data. Also, PMN and PMC routes do not require clinical data.

The PMD Act prescribes the three-track review system, generic device, improved device, and new device, including one sub-review track (improved device with clinical data), under the PMA route, depending on equivalence with similar devices.

Equivalency

Review track (sub track)	Description	Clinical data
Generic (me-too) device	Substantial equivalence (SE) with predicate devices	Not required
Improved device	Gaps with predicate devices and non-clinical data alone needs to support the gaps	Not required
- Improved device with clinical data	Significant gaps with predicate devices and clinical data need to support the gaps	Required
New device	No applicable JMDN and no predicate devices, e.g., new indications, new principle, new mode of action, etc.	Required

Devices are eligible for the review track based on the degree of equivalence and gaps with similar devices in the Japanese market. Amongst the review tracks, new devices without similar devices and improved devices that have similar devices but also have gaps that need clinical data supporting their validity require clinical data as a part of the PMA data package. Please note that whether clinical data is required for devices subject to the PMA route does not depend on the classification (device risk class and JMDN).

The Ministry of Health and Welfare (MHLW) issued the notice for 'Guidance for the scope of medical devices requiring clinical data (Yakushokukihatsu No.0804001)' dated Aug. 4, 2009. The MHLW notice mentions that clinical data is required if a medical device's clinical effectiveness and safety cannot be demonstrated only by non-clinical data, such as non-clinical performance and safety tests, including animal tests, bench tests or existing literature.

The MHLW notice also mentions that the PMDA comprehensively determines whether clinical data is required for a medical device PMA depending on the manufacturer's existing non-clinical data and equivalence with similar devices. The MHLW notice also recommends that manufacturers request a PMDA Pre-submission consultation to seek the PMDA's determination of whether clinical data is required.

Manufacturers can quickly determine that devices subject to the new device review track always require clinical data, however for devices subject to the Improved device review track, which have gaps with similar devices, it may not be easy to anticipate whether clinical data is required, i.e., "improved device" or "improved device with clinical data." For improved devices, whether clinical data is required is determined by the degree of gaps with similar devices, manufacturers must consider differences between markets in the gap assessment. For example:

- Gap assessments must be based on similar devices registered in Japan.
- The standard care in which the device is used may differ between Japan and overseas markets.
- For devices intended to be used with drugs, the concomitant drugs may differ between Japan and overseas markets.

Also, PMDA comprehensively determines whether clinical data is required depending on the manufacturer's existing non-clinical data and equivalence with similar devices from PMDA's perspective, considering the above differences with other markets. Consequently, it may be difficult for manufacturers to determine whether clinical data is required for their PMA submissions.

PMDA pre-submission consultation

The MHLW notice recommends that PMDA's decision at the pre-submission (pre-sub) consultation is sought before submission when it is unclear whether clinical data is necessary.

The PMDA offers several types of opportunities for regulatory consultation and advice for manufacturers. The pre-sub consultation is a major component designed to give manufacturers PMDA feedback on pre-market submissions such as PMA 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.

Among PMDA pre-sub programs, whether clinical data is required can be discussed with the PMDA at a Pre-development consultation (Kaihatsumae-Sodan) designed to discuss the anticipated entire data package for PMA at a high level, or at a Clinical Trial Necessity consultation (Rinshoshiken Yohi-Sodan) designed to discuss the necessity of additional clinical data based on the existing clinical data gathered outside Japan.

At a Pre-development consultation and Clinical Trial Necessity consultation, a manufacturer must expound upon the device description, characteristics, equivalence with predicates and the existing data package, including literature and non-clinical data. If manufacturers want to avoid submitting clinical data for the PMA, they will justify that at a Pre-development consultation. Also, if manufacturers want to avoid acquiring additional clinical data, they will justify that at a Clinical Trial Necessity consultation that the existing clinical data is sufficient.

A Pre-development consultation is suitable for discussing the necessity of clinical data and the non-clinical data package expected for a PMA by the PMDA at the early design and development phase.

On the other hand, a clinical trial necessity consultation is suitable for discussing the acceptability of clinical data for completed devices, as is the case with many imported devices, and whether additional clinical trials are required.

For devices subject to the review track requiring clinical data, i.e., new device and improved device with clinical data, whether clinical data gathered outside Japan, or a Clinical Evaluation Report (CER) can be used will be challenging to determine. In this case, a clinical trial necessity consultation can discuss whether additional clinical trials are required.

The PMDA pre-sub programs are beyond the scope of this white paper. For more information on the PMDA pre-sub, please refer to **the Emergo white paper on the PMDA pre-sub** process.

Utilization of clinical trial data gathered outside Japan

Devices subject to PMA in the U.S. or devices requiring clinical study for CE marking certification almost always require clinical data for Japan PMA. The manufacturers of those devices are assumed to have usually already started or completed a U.S. FDA PMA or European CE marking certification before undertaking medical device registration in Japan. Also, the manufacturers expect to utilize the clinical data for Japan.

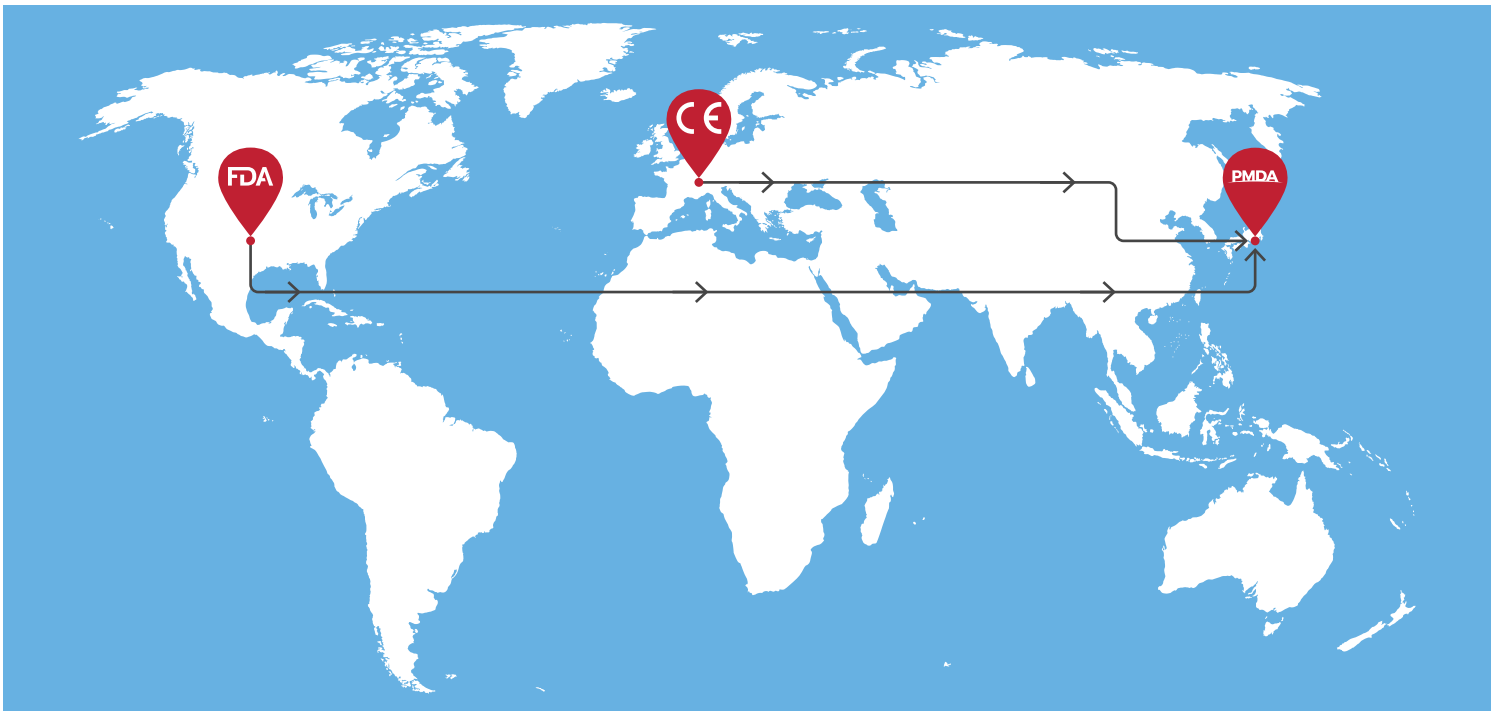
At the same time, PMDA assigns weights to clinical data as follows and places the highest importance on clinical trial results gathered in Japan:

1. Clinical trial results in Japan
2. Clinical trial results outside Japan
3. CER

PMDA allows clinical trial results gathered outside Japan or CER for PMAs in Japan; however, PMDA does not always accept them due to the differences between Japan and other countries or regions. In particular, additional clinical trial results might be required due to the racial composition of the study subjects, differences in control devices, concomitant drugs and standard of care. Even if the clinical trial design is reasonable and appropriate and the results support the validity of the device, the manufacturer can only use it if it supports its effectiveness and safety in the Japanese market (Japanese people).

That said, if manufacturers plan to utilize clinical trial results gathered outside Japan for Japan PMA, it is essential to determine in advance whether the clinical trial results are also sufficient through a gap assessment. Also, as mentioned above, it is recommended to discuss the acceptability of trial results gathered outside Japan, and whether additional clinical trials are required at a clinical trial necessity consultation with the PMDA before submission.

There is another perspective to determine the accessibility of clinical trial results gathered outside Japan, which is compliance with Good Clinical Practice (GCP requirements). Clinical trials conducted outside Japan generally comply with GCP standards such as ICH E6 GCP and ISO 14155. The MHLW has established Japan's GCP requirements based on ICH E6 GCP and has promulgated them as MHLW Ministerial Ordinance (MO) #36. Accordingly, MO #36 requirements are almost identical to ICH E6 GCP; however, there are some differences between both. Therefore, for clinical trials complying with ICH E6 GCP or ISO 14155, the manufacturers must demonstrate compliance with MO #36 before submission. PMDA will audit compliance with MO #36 in its reliability investigation, which will be conducted in parallel with the PMA application review. In addition, individual CRFs will be subject to the audit. Therefore, if there are any incomplete records, manufacturers must have a reason to justify them before submission.



GCP compliance investigation

A GCP compliance investigation (GCP audit) by the PMDA consists of off-site audits (document review) and on-site audits of investigational sites.

In an off-site audit, the PMDA investigates evidence of clinical trials, including raw data such as contract with investigational site and investigator, Institutional Review Board (IRB) documents, Case Report form (CRF), etc., and determines compliance with MO #36 first. If PMDA doubts the compliance through the evidence investigations and the manufacturer cannot submit further evidence to dispel doubts, the PMDA might conduct an on-site audit on the selected investigational site(s). To avoid on-site audits, it is critical to have evidence supporting the compliance before submission.

The following are the standard steps of the Good Clinical Practice (GCP) audits:

Step 1
Once the PMDA begins a reliability investigation, they issue a request to draft a list and description of evidence documents subject to GCP audit (“Siryo Shosai Mokuroku”) to the manufacturer. The manufacturer drafts and submits it to the PMDA correspondingly.

Step 2
The PMDA reviews the drafted index and description of evidence documents and determines if this is sufficient for the audit. If the PMDA determines this is sufficient, it requests the finalized index and description of evidence documents and also arranges the dates of the GCP audit (off-site audit).

Step 3
The manufacturer submits the following evidence documents with the finalized index and description of evidence documents

- Clinical Trial Protocol (“Chiken Jissi Keikakusyo”)
- Clinical Trial Report (“Chiken Sokatu Hokokusyo”)
- List of Cases (“Shorei Ichiranhyo”)
- Status of Clinical Trial (“Chiken Jissi Jyokyohyo”) — per investigational site
- List of Deviation (“Itsudatsu Ichiransho”)
- Minutes of Case Conference etc.
- Template of Informed Consent Form
- Template of Case Report Form
- Summary of QA/QC Organization

Step 4
PMDA conducts a GCP off-site audit on the evidence documents and determines compliance with MO #36.

Step 5
Only if the PMDA determines that an on-site audit is needed will on-site audits of selected investigational site(s) be conducted. If there are no findings or observations, the PMDA will close the audit and issue a letter of GCP conformity.

Is Clinical Evaluation Report available?

Clinical Evaluation Report(s) (CERs) can be used only for devices for which clinical effectiveness and safety can be demonstrated based on existing clinical literature, non-clinical data and post-market information without conducting new clinical trials. Japan's Ministry of Health, Labor and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) regard that CERs created by manufacturers cannot be completely ruled out as being biased by the manufacturers or authors, e.g., biases in literature searches, selection, and evaluation, etc. Also, there are uncertainties about the reliability of the data in the cited literature.

Of course, almost all CERs may not be biased; however, it cannot deny the existence of biased CERs. Also uncertainties about the data reliability in cited literature are beyond the control of the manufacturers and authors. Therefore, CERs are more likely to be accepted in the following cases tactically:

- Even if bias exists, it can be objectively determined that the evaluation results do not vary significantly or that the effectiveness and safety do not vary significantly, e.g., low-risk to mid-risk devices, CER supported by publicly known literature with a high level of evidence, etc.
- A device provides benefits to unmet clinical needs
- Benefit of the device outweighs the risks
- Difficult to conduct clinical trials, e.g., device for rare diseases
- A device qualified in diagnostic/treatment guidelines outside Japan

CERs submitted to PMDA are required to meet the following guidelines. CERs only based on MEDDEV 2.7/1 Rev. 4 is insufficient.

The Japan Federation of Medical Devices Association issued “Guidance for Clinical Evaluation Report and Submissions for Clinical Trial Necessity Consultation, part 1,” which PMDA has confirmed. Since there are some gaps in the requirements between the guidance and MEDDEV 2.7/1 Rev. 4, manufacturers must prepare CERs according to the guidance. The CERs must include information related to the design and development of the device, particularly, the purpose and history of developing the device, the background of the technology used, the clinical significance, improvements compared with existing devices, etc.

Also, CERs must support clinical effectiveness and safety in Japan. Suppose the cited literature depends on non-Japanese races, medical environment, standard care, etc. In that case, manufacturers must re-evaluate the effectiveness and safety considering the Japanese race, medical environment, standard care, etc. If needed, manufacturers will search Japanese literature and conduct evaluations, including Japanese literature.

According to “Guidance for Clinical Evaluation Report and Submissions for Clinical Trial Necessity Consultation, part 2” issued in 2023, since 2009, the number of devices approved only by CER has been increasing. Notably, since 2011, the number of devices approved based on clinical trial results and those approved based on CER are almost the same. Specifically, among the annual average 71 PMAs (filed from 2009 to 2021) required clinical data, 26 PMAs submitted only clinical trial results gathered outside Japan, and 24 PMAs submitted only CERs. There is a shift in the clinical data requirements and a greater acceptance of CERs.

Conclusion

Clinical data requirements for medical device registrations in Japan do not necessarily mean added costs and delayed market entry for manufacturers. Options, including Clinical Evaluation Reports and PMDA pre-sub consultation meetings, provide potentially more efficient Japanese market pathways than conducting clinical trials. Manufacturers are recommended to familiarize themselves with PMDA clinical data requirements and the various approaches and paths of those requirements to commercialize in the large and complex Japanese device market.

Learn more

Need help with Japan compliance? Emergo by UL helps medical device companies with regulatory compliance and market access in Japan and other markets worldwide. Here's how we can help:

- PMDA medical device registration
- Foreign Manufacturer Registration application
- Japanese Marketing Authorization Holder (D-MAH)

Learn more about how we can help you with Japan medical device compliance at **EmergobyUL.com**.

About the author

Kenji Yashiro has more than 20 years of medical device regulatory knowledge, combined with extensive technical experience in device development, manufacturing and quality control. His background includes 40+ medical device registration submissions in Japan, pre-submission consultations with the PMDA, more than 10 years of experience with risk management files compliant with ISO 14971, more than 10 years of regulatory strategy research in Japan, and more than three years managing MAH responsibilities.

Yashiro manages Emergo Japan's Regulatory Affairs consulting team. In this role, he has peer-reviewed numerous regulatory filings and reports. Prior to Emergo, he held device development, manufacturing and quality control positions in the medical device industry as well as roles in regulatory affairs consulting.

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