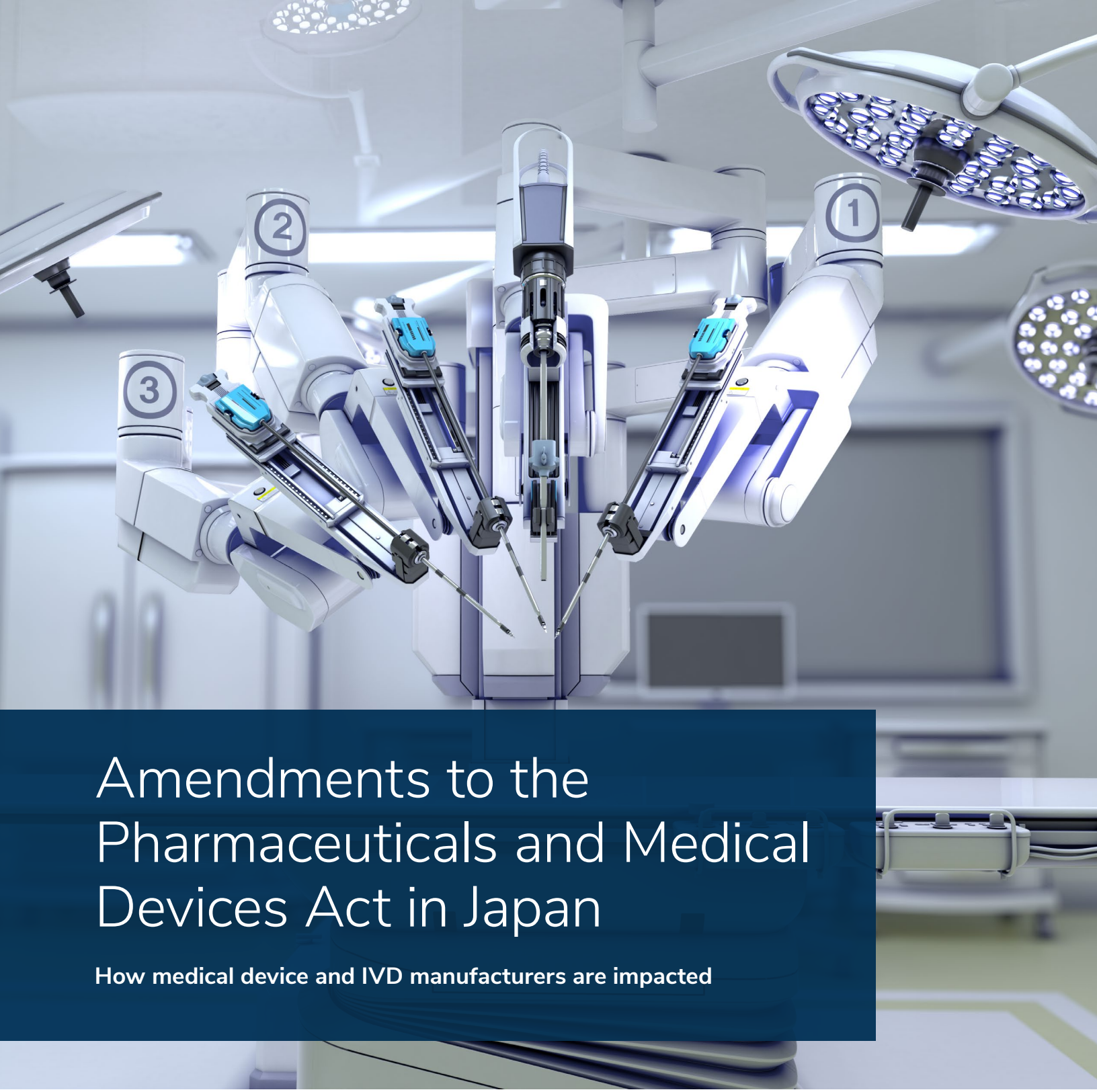

Amendments to the Pharmaceuticals and Medical Devices Act in Japan

How medical device and IVD manufacturers are impacted

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Executive summary

In Japan, the Ministry of Health, Labour and Welfare (MHLW) regulates healthcare products, including medical devices and in-vitro diagnostics (IVD), under the Pharmaceuticals and Medical Devices Act (PMD Act) which replaced the previous regulation, the Pharmaceutical Affairs Law (PAL), in 2014.

Many manufacturers with healthcare business experience in Japan may already be familiar with the PMD Act and current regulatory framework. However, the PMD Act has undergone several amendments since the regulation first took effect in 2014. This white paper will discuss key takeaways from the latest amendments, which include the launch of new review processes and labeling requirements.

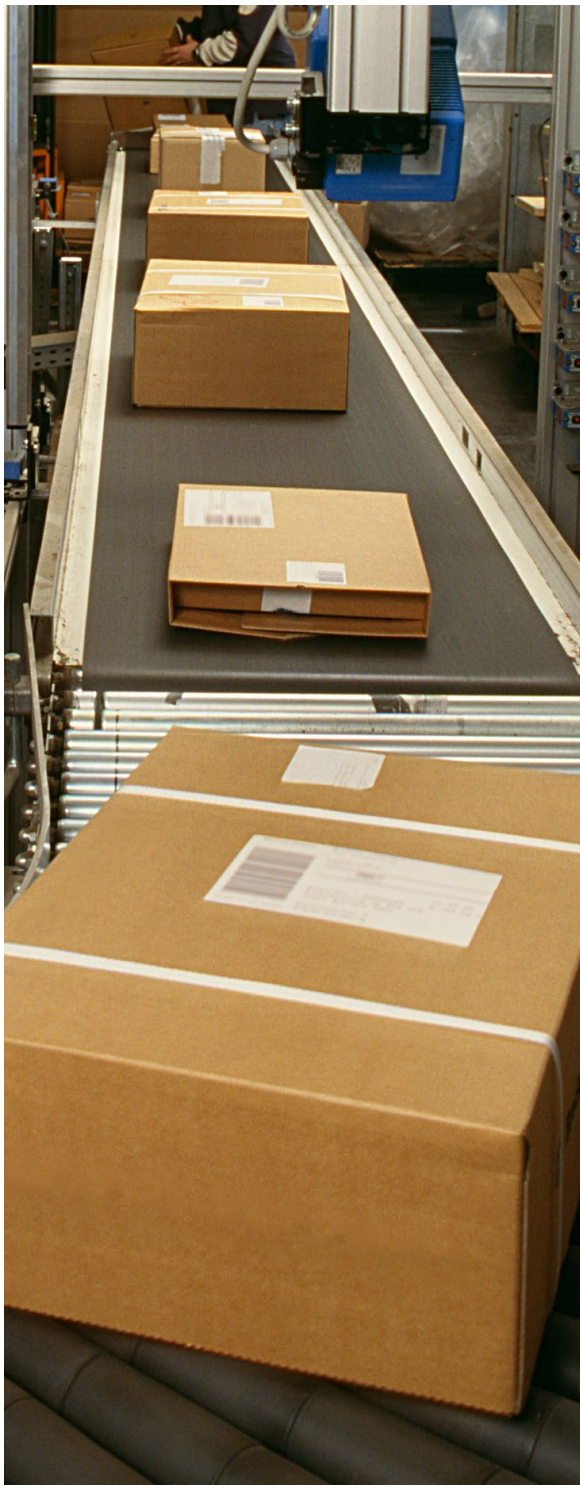
Introduction

The PMD Act establishes the regulatory framework for medical devices and IVDs in Japan. It came into effect in 2014, replacing the previous legislation, the Pharmaceutical Affairs Law (PAL), which had regulated healthcare products since 1960. The PMD Act has undergone several modest amendments since its introduction, including a significant amendment in 2019, which was activated in phases from 2020 through 2022.

2019 PMDA Act amendment objectives include:

i. Changes involving pharmacists and pharmacies — addition of duties and responsibilities of pharmacies and pharmacists and introduction of the accreditation system for specific-function pharmacies
ii. Introduction of new fast-track review systems
iii. Unique device identifier (UDI) requirements
iv. Additional requirements and duties for business license holders and increased penalties for violations of the PMD Act

This white paper will focus on objectives ii and iii related to manufacturers outside Japan.

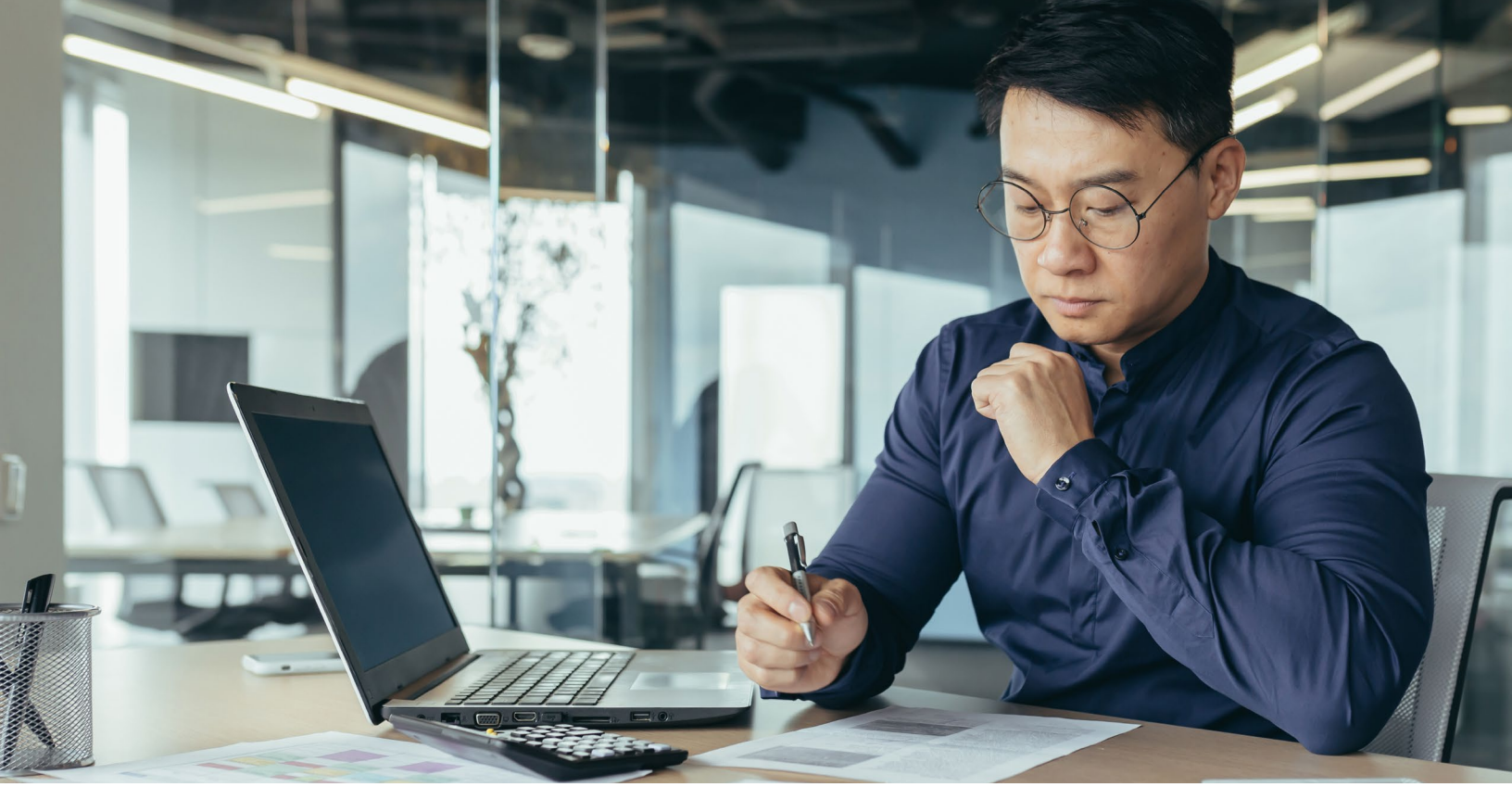


New fast-track review systems

Even before the 2019 amendment, the PMD Act stipulated a fast-track review system for orphan pharmaceuticals and medical devices in Japan. This empowered the use of connective technology and software programs to improve the lives of patients with uncommon, unmet healthcare needs. The 2019 PMD Act amendment stipulates additional fast-track review systems to support this mission:

a. Fast-track review for precursor healthcare products
b. Fast-track review for conditional premarket authorization
c. Improvement Design within Approval for Timely Evaluation and Notice (IDATEN)

Fast-track review systems are independent and have different target devices and uses.



Fast-track review for precursor healthcare products

This opportunity is best considered during the early stages of product development. It is designed to facilitate innovative pharmaceuticals, medical devices, IVDs and regenerative healthcare products (hereafter, healthcare products) in Japan. Eligible manufacturers meet every condition listed below:

- **Breakthrough treatment and diagnostic techniques**
  This includes healthcare products with significantly different principles and mechanisms or modes of action from existing healthcare products in Japan and other markets.
- **Severity of target disease**
  Your precursor healthcare products are indicated for patients enduring conditions with symptoms that make daily life difficult due to a lack of available treatments.
- **High efficacy or safety for target diseases**
  Either no treatments or diagnostic techniques exist, or your healthcare products can drastically improve current treatments and diagnostic techniques, making them safer.
- **Realization strategy**
  Is the manufacturer willing to carry out development and product registration activities earlier than the rest of the world? Or will the product be registered in a foreign market within 30 days of a pre-market submission in Japan, referred to as a simultaneous registration?

How it works

Fast-track review for precursor healthcare products is an open application system hosted by the MHLW twice a year (April and October). To get started, manufacturers must apply and be accepted before proceeding to healthcare product designation. The MHLW will review these applications and determine which healthcare products are eligible for fast-track review. Highly urgent healthcare products may be selected ahead of others. The official list of precursor healthcare products designated for fast-track review can be found on the MHLW website

Standard regulatory path

Step 1

Consult with the MHLW and PMDA to determine whether your precursor healthcare product is eligible for fast-track review.

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Step 2

Apply to the MHLW for a precursor healthcare product designation. The MHLW holds the Pharmaceutical Affairs and Food Sanitation Council and determines whether the device is eligible.

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Step 3

Complete product development and validation.

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Step 4

Request Precursor healthcare product general consultation meetings with the PMDA for guidance on the sufficiency and validity of the manufacturer's data package, including non-clinical and clinical data.

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Step 5

File a PMA application under the fast-track review system.

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Step 6

Once the PMDA review is complete, the MHLW holds the Pharmaceutical Affairs and Food Sanitation Council to make the final determination.

Advantages

- The average review timeline for new medical devices and IVDs is 14 months, while the fast-track review period is approximately six months.
- Precursor healthcare products designated for fast-track review will be prioritized when arranging a date for the PMDA pre-submission consultation.
- Once designated to the fast-track review system, PMDA assigns a concierge to the manufacturer. The concierge works as a liaison and coordinator between the MHLW, the PMDA Review Department and the manufacturer to manage inquiries about product development progress and issues that arise during development.
- By utilizing the fast-track review, manufacturers can build and maintain interaction with PMDA from the early stages of development to facilitate design and development. Considering specifications and verification items expected by PMDA and MHLW from the beginning helps reduce the risk of differences in requirements between Japan and overseas after development.

Disadvantages

- Precursor healthcare product general consultation meetings must be requested before the pre-market submission. These consultations include several modules:
  - Quality
  - (QMS)
  - Non-clinical
  - Clinical
  - Reliability
- The manufacturer must request some of these modules according to PMDA instructions, and consultation fees range from $2,000 to $11,000. These consultations are not required for new medical devices or IVDs that do not use fast-track review.
- While fast-track review is expected to shorten your regulatory path by approximately eight months, Precursor healthcare product general consultation meeting requirements may cause deviations from this timeline.
- For manufacturers focused on other markets, it may not be realistic to submit pre-market submissions overseas and in Japan at the same time.
- Once the MHLW designates a precursor healthcare product for fast-track review, device information will be published along with the manufacturer's name on the ministry's website. Therefore, the fast-track review may not be suitable for manufacturers who want to keep their development confidential.

Fast-track review for conditional premarket authorization

Conditional pre-market authorization is designed to facilitate the introduction of medical devices and IVDs indicated for crucial rare diseases to the Japanese market. In particular, manufacturers can use this fast-track review system in cases where it is challenging to conduct new clinical trials due to the small number of patients. For example, suppose there is clinical data from an exploratory clinical trial, but conducting a large-scale trial again is unrealistic. In such cases, the device is approved based on the clinical data from an exploratory clinical trial and then re-reviewed based on the results from post-market surveillance (PMS) conducted over a certain period. Eligible manufacturers meet every condition listed in either case one or case two below:

Case one: Your medical device or IVD is based on new technologies.

- **Severity of target disease**
  Medical devices and IVDs are indicated for crucial diseases affecting a patient's life or diseases whose progression is irreversible.
- **High efficacy or safety for target diseases**
  Medical devices and IVDs that are indicated for diseases with no existing treatment or diagnostic techniques, which address unmet needs, medical devices and IVDs that can improve existing treatment or diagnostic techniques drastically, or medical devices and IVDs that can improve safety drastically.
- **Clinical data**
  Appropriate clinical data is available. At least the results of GCP-compliant exploratory trials are available.
- **Justification**
  Manufacturers can justify why it is challenging to conduct new clinical trials or clinical performance tests.
- **Criteria for proper use**
  Manufacturers, in collaboration with academic societies, can develop criteria for using the medical devices/IVDs properly. Also, the manufacturers can submit a specific plan for post-marketing surveillance.

Case two: Involves the application of existing technologies to other indications.

- **Expand indications**
  Extending indications of existing medical devices or technology that affect the structure or function of the human body, such as ablation devices to other indications where the need is high.

  Example: When expanding the application of an ablation catheter for paroxysmal atrial fibrillation to persistent atrial fibrillation.
- **Clinical data**
  There is no clinical data from large-scale clinical trials for the additional indications. However, other clinical data can be extrapolated to support the new indications.

  Example: Clinical data from GCP-compliant investigator-initiated exploratory trials is available.
- **Justification**
  Manufacturers can confirm the proper use of additional indications without new clinical trials.
- **Criteria for proper use**
  Manufacturers can develop criteria for properly using medical devices in collaboration with academic societies and submit a specific plan for post-marketing surveillance.

How it works

Manufacturers must consult with the PMDA before submitting a pre-market application to utilize the fast-track review for conditional pre-market authorization.

Standard regulatory path

Step 1

The manufacturer will have PMDA pre-submission consultation meetings with the PMDA, which may include a Pre-development consultation and an Additional Clinical Trial Necessity consultation to determine whether the existing data package and clinical data can proceed with fast-track review for conditional pre-market authorization.

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Step 2

The manufacturer applies for a PMA application under the fast-track review system and submits it with the PMS protocol.

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Step 3

Once the MHLW approves the medical device, the manufacturer will conduct a PMS for a period agreed with the PMDA. During the PMS, use for additional indications is limited to medical facilities specified in the PMS protocol.

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Step 4

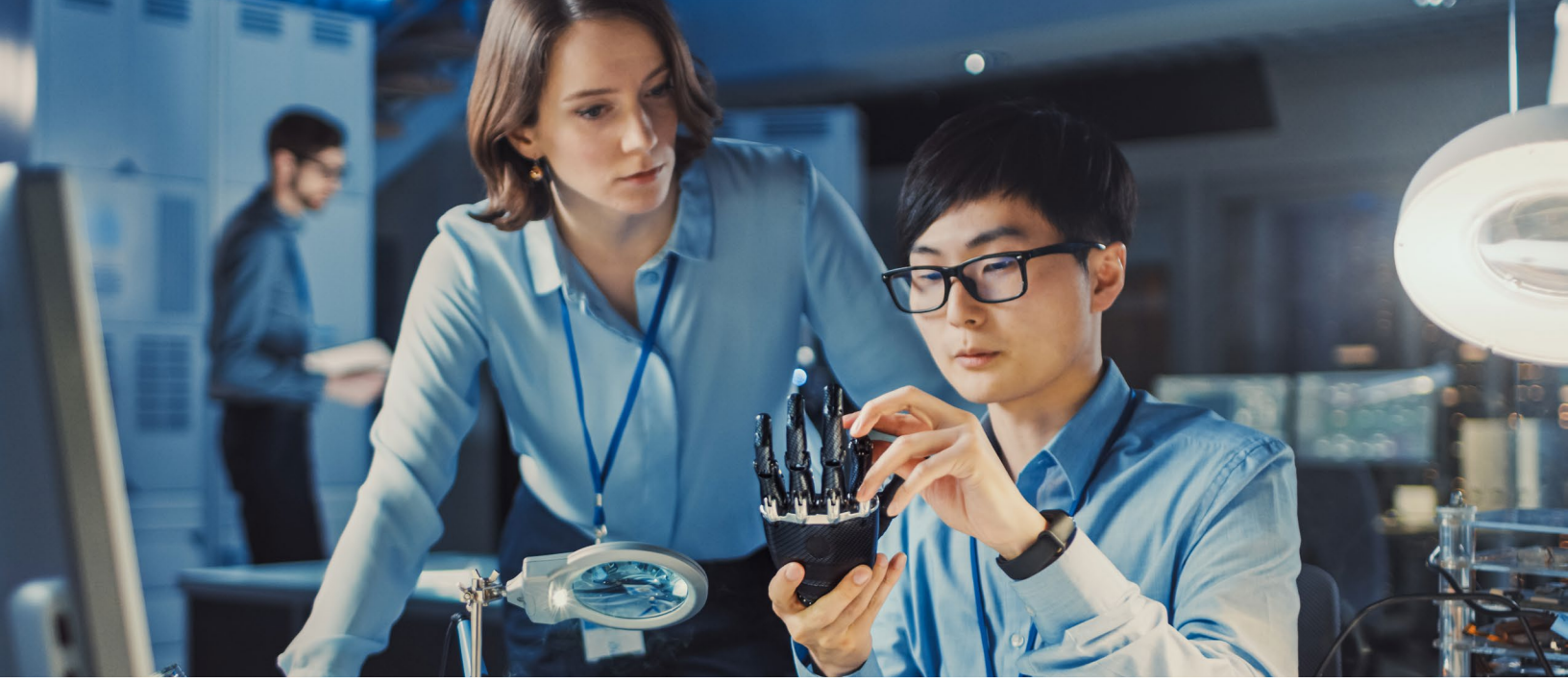
After completing the PMS, the PMDA will review the results and determine whether to allow use outside of specified medical facilities.

Advantages

- Fast-track review for conditional pre-market authorization is effective in cases where large-scale clinical trials are challenging, such as for rare diseases, or when clinical data is only available from exploratory trials.
- The average review timeline for new medical devices and IVDs that do not use fast-track review is 14 months, while the target review period of fast-track review for conditional pre-market authorization is 10 months.
- Even new medical devices and IVDs that do not use fast-track review for conditional pre-market authorization are required to request PMDA pre-submission consultation meetings. Therefore, unlike fast-track reviews for precursor healthcare products, this review expects to reduce timelines by four months throughout the regulatory pathway, including PMDA pre-sub consultation.

Disadvantages

- Costs for the PMS can be high.
- If the PMS does not achieve the intended results, the MHLW might provide direction to modify the intended use or indications.
- If an adverse event, etc., occurs in PMS, the MHLW might rule to discontinue the PMS.



Improvement Design within Approval for Timely Evaluation and Notice (IDATEN) application system

The IDATEN application system is not technically a fast-track review. However, it is designed to simplify post-approval submission for devices that expect to undergo frequent design changes in post-approval phases. The IDATEN application system is slightly similar to the Post-Approval Change Management Protocol (PACMP) offered by the U.S. Food and Drug Administration (FDA). It could also simplify associated post-approval submissions and reduce the associated regulatory burden. In particular, the IDATEN system might be beneficial for medical devices, such as Artificial Intelligence (AI) and Machine Learning (ML)-based Software as Medical Devices (SaMD), which may undergo frequent improvements in the post-approval phase.

The PMD Act prescribes two types of post-approval change paths, i.e., change applications and change notifications. While change applications require review by the PMDA, change notifications are completed by the manufacturers. Note there is a difference between change notifications and change notifications in IDATEN. The impact of the changes on device effectiveness and safety determines whether it is a change application or a change notification. For example, for SaMD, the diagnostic algorithm changes based on AI learning or ML are generally subject to a change application.

When using the IDATEN system, manufacturers develop design change plans and submit them to the PMDA in parallel with pre-market submissions. In the design change plans, manufacturers must define the design change schedule and the criteria for evaluating the modified devices in advance. The PMDA will confirm the validity of the evaluation criteria during the review of pre-market submissions. They will also decide whether the modification requires a change application or a change notification. In addition, during QMS audits, the PMDA reviews the validity of design, development and design change processes. For example, when developing a device using AI technology, the PMDA reviews how manufacturers use AI learning in the design and development.

When using the IDATEN system, most of the modifications planned in design change plans will only be subject to change notifications. Note there is a difference between regular change notifications and change notifications in IDATEN. While PMDA does not review regular change notifications, they review change notifications submitted under the IDATEN system. However, the review timeline is within 30 days. The PMDA will confirm whether the modifications can be realized following the design change plans and the criteria submitted in advance.

In addition, even if modifications are planned in the design change plans, updates regarding the indications might require a change application. Whether a change notification or a change application is required, each planned change must be agreed upon with PMDA during the review of design change plans.

How it works

To utilize the IDATEN application system, manufacturers must consult with the PMDA before the premarket submission.

Standard regulatory path

Step 1

A manufacturer considering the IDATEN system will have PMDA Pre-submission consultation meetings with PMDA (Pre-development consultation) to seek their opinion on whether the medical device is eligible for the IDATEN system.

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Step 2

The manufacturer applies with a PMA application and submits a design change plan under the IDATEN system.

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Step 3

Once the MHLW approves the medical device, the manufacturer will continue improving the design (such as AI or ML) and make close design changes in each planned phase.

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Step 4

If needed, the manufacturer can request a pre-sub meeting for change notifications or applications under the IDATEN system. This is especially important in cases where there are concerns about verification and validation data related to changes or where planned goals have yet to be achieved.

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Step 5

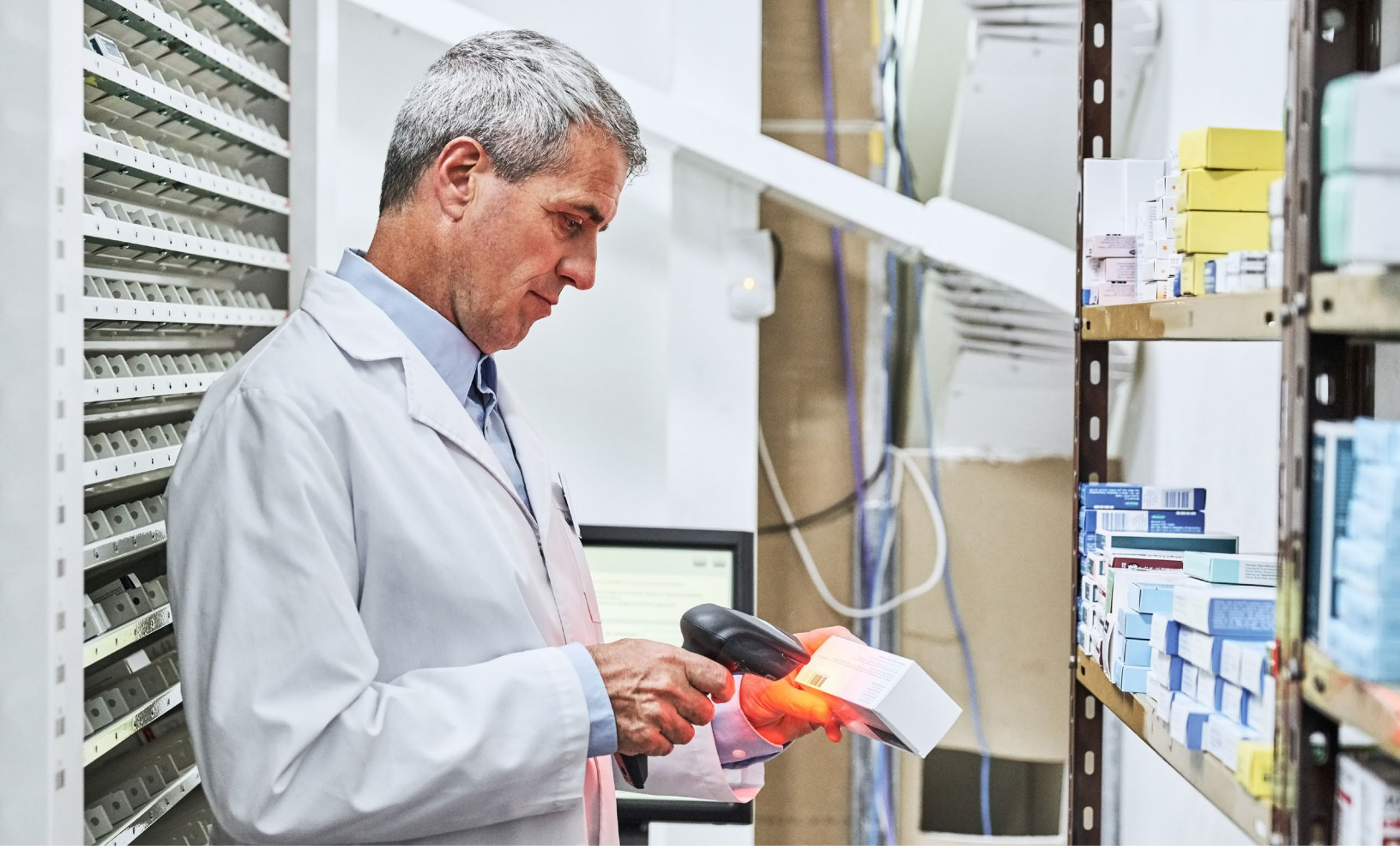
The manufacturer submits a change notification to the PMDA, which will review the verification or validation data supporting the change within 30 days.

Advantages

- While critical modifications, such as new indications, still require a change application, most updates can now be completed with a change notification, allowing manufacturers to bring design improvements to market faster than before.

Disadvantages

- Manufacturers must set future change plans, including schedules and criteria when submitting a pre-market submission. However, setting a change plan during pre-market submission may be challenging for AI and ML using real-world data.



Mandatory Unique Device Identifier (UDI)

Since 2008, the MHLW has asked manufacturers to include UDI on device labels and packages. However, that was voluntary for manufacturers. After that, the MHLW built and operated the database of healthcare products[1] that allows access to product registration information and IFU from UDI.

With the amendment in 2019, UDI on device labels and packages is mandatory, except where the rule provides an exception or alternative. In addition to registering UDIs in the MHLW database, the labeling and IFU of healthcare products, including those distributed in Japan before the 2019 amendment, will now require the following:

- Every healthcare product must have UDI (GS1-128 format) on device labels and packages.
- Every UDI must be registered to the database of healthcare products.
- Every IFU, excluding ones for home-use devices that do not require prescriptions, must be registered to the database on the PMDA website as an electronic file and be published.

Many manufacturers outside Japan probably outsource the management of UDIs, Japanese product labels, and Japanese IFUs to their Marketing Authorization Holder (MAH) and Designated MAH (DMAH). The deadline for registering UDIs and Japanese IFUs was August 2021.

We often review registered devices and have occasionally found that Japanese IFUs still need to be registered on the PMDA website. Please take this opportunity to confirm with your MAH or DMAH if the UDIs and IFUs of your products have been appropriately registered.

1. https://www.kikidb.jp

Learn more

Need help with Japan's Amendments to the Pharmaceuticals and Medical Devices Act? Emergo by UL supports regulatory compliance and market access for device manufacturers worldwide. Here's how we help:

- PMDA medical device registration and approval
- PMDA registration for IVDs
- 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 Senior Regulatory Consultant at Emergo Japan Consulting. Kenji 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.

Kenji 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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