

# Marketing Authorization Process of New Drugs in Japan

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**Abstract:** The process for obtaining marketing authorization for new pharmaceuticals in Japan is a comprehensive and methodical regulatory system managed by the Pharmaceuticals and Medical Devices Agency (PMDA) in partnership with the Ministry of Health, Labour and Welfare (MHLW). This framework is designed to guarantee the safety, effectiveness, and quality of drugs prior to their introduction into the Japanese market. The process initiates with pre-submission consultations, followed by the submission of an Investigational New Drug (IND) application along with clinical trial data. After the completion of clinical trials, a New Drug Application (NDA) is submitted in the Common Technical Document (CTD) format. The PMDA undertakes scientific evaluations, while the MHLW provides the final approval. Additionally, Japan has expedited pathways, including the SAKIGAKE designation and priority review for innovative treatments or those addressing life-threatening conditions. Ongoing safety and efficacy are further monitored through post-marketing surveillance and re-examination periods. Recent updates to regulations are focused on enhancing the development process and expediting access to new therapies. This document offers a detailed overview of the marketing authorization process in Japan, the regulatory agencies involved, and the latest trends in drug approval.

**Keywords:** PMDA – Pharmaceuticals and Medical Devices Agency, MHLW – Ministry of Health, Labour and Welfare, CTD – Common Technical Document, NDA – New Drug Application, IND – Investigational New Drug, SAKIGAKE – SAKIGAKE Designation System (Japanese fast-track approval system), Japan Drug Approval Process, Expedited Approval Pathways, Clinical Trial Phases, Marketing Authorization.

**Introduction:** [1][2]

Japan remains the third-largest pharmaceutical market in the world, following the United States and China, and continues to be a critical export destination for U.S. pharmaceutical products. Since 2013, the Government of Japan (GOJ) has actively promoted the healthcare and life sciences sector as a strategic growth engine under its national economic revitalization strategy. This has been supported by regulatory reforms aimed at accelerating drug approvals and improving access to innovative therapies.

According to the Ministry of Health, Labour and Welfare (MHLW), Japan's pharmaceutical market—including both prescription and over-the-counter (OTC) products—was valued at approximately USD 109 billion in 2020. While market size saw modest shifts due to post-pandemic dynamics, it remains stable and is projected to reach around USD 95.87 billion by 2025, driven by an aging population and high healthcare standards.

The U.S. Commercial Service Japan (CS Japan), using MHLW monthly production reports and historical import trends, estimated the 2021 local production and import figures. Their research indicates that the market share of U.S. pharmaceutical imports is significantly underreported in official Japanese statistics, suggesting a stronger U.S. presence in the Japanese pharmaceutical market than formally reflected.

**Introduction to PMDA (Pharmaceutical Medical Device Agency):**[3]

Pharmaceutical and Medical Device Agency (PMDA) was established and came into services on April 1, 2004 under the law for the Pharmaceuticals and Medical Device Agency, as a consolidation of the services of the PMDA Evaluation Centre of the National Institute of Health Science (PMDEC), the organization for pharmaceutical safety and research and part of the Japan Association for the advancement of medical Equipment. Head office of PMDA was located in Kasumigaseki, Chiyodaku, Tokyo.

Information provision (via the internet) Pharmaceutical Consultation for Consumers.

Updated Pharmaceutical Regulations in Japan (2024-2025)

**Departments of PMDA (Pharmaceuticals and Medical Devices Agency)**

The PMDA is Japan's regulatory authority responsible for ensuring the safety, efficacy, and quality of pharmaceuticals and medical devices. It operates under the Ministry of Health, Labour and Welfare (MHLW) and consists of various specialized departments handling drug reviews, post-marketing surveillance, and relief services for adverse drug reactions (ADRs).

## Japanese Pharmaceutical Laws [4] [5]

Pharmaceutical regulation in Japan is governed by multiple laws and regulations, including:

- **Pharmaceutical and Medical Device Act (PMD Act) (formerly the Pharmaceutical Affairs Law)** – Primary law governing drug and medical device approval, marketing, and safety.
- **Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization** – Defines the structure and role of PMDA.
- **Law Concerning Securing a Stable Supply of Blood Products** – Ensures the availability of blood-derived medical products.
- **Poisonous and Deleterious Substances Control Law** – Regulates the handling of toxic substances.
- **Narcotics and Psychotropic Control Law** – Controls the production, distribution, and use of narcotic and psychotropic drugs.
- **Opium Law** – Governs the production and distribution of opium and related products.
- **Stimulants Control Law** – Regulates the use of stimulants to prevent misuse and abuse.

## Recent Changes in the PMD Act (2024 Updates) [4] [6]

The Pharmaceutical and Medical Device Act (PMD Act) underwent key amendments in 2024 to enhance Japan's regulatory framework:

1. **Strengthening Conditional Approvals**
  - Conditional approvals can now be revoked if post-marketing data fails to demonstrate adequate efficacy and safety.
  - The scope of conditional approvals has been expanded to facilitate the faster approval of innovative drugs, particularly those targeting rare diseases.
2. **Incentives for Pediatric Drug Development**
  - The re-examination period for pediatric drugs has been **extended by two years** to encourage research and development.
  - Pharmaceutical companies are given regulatory support for conducting clinical trials in children.
3. **Integration of Real-World Data (RWD) in Drug Approvals**
  - The PMDA has **clarified the acceptance of real-world data (RWD)** in regulatory submissions to accelerate the approval process.

- This aligns Japan's regulations with global trends, where RWD from electronic health records and patient registries is increasingly used to support drug safety and efficacy evaluations.

#### 4. Drug Shortage Management System

- New measures allow **expedited approval and importation** of alternative drugs from international markets during critical shortages.
- Companies are required to report potential shortages in advance to prevent supply disruptions.
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#### **Japanese Pharmaceutical Affairs Law (Structure and Chapters) [5] [8]**

The **Pharmaceutical Affairs Law** (now part of the PMD Act) consists of 11 chapters and 91 articles, regulating pharmaceutical administration, drug approvals, and safety measures. Key chapters include:

- **Chapter 1: General Provisions (Article 1 & 2)** – Defines drugs, quasi-drugs, cosmetics, and medical devices, along with the purpose of pharmaceutical regulations.
- **Chapter 2: Prefectural Pharmaceutical Affairs Councils (Article 3)** – Establishes regional regulatory bodies for drug safety oversight.
- **Chapter 7: Handling of Drugs** – Governs manufacturing, distribution, and quality control of pharmaceutical products.
- **Chapter 9-2: Handling of Designated Drug Substances** – Covers regulations on specific substances that require special handling due to potential health risks.
- **Chapter 9-3: Designation of Orphan Drugs** – Outlines the approval process and incentives for orphan drugs (medications for rare diseases).

#### **Functions of PMDA**

PMDA plays a critical role in Japan's pharmaceutical regulatory system, focusing on three major areas:

##### **1) Review and Audit for Drug/Medical Device Efficacy and Safety [7]**

- **Clinical Trial Consultation:** Provides scientific and regulatory guidance to pharmaceutical companies before clinical trials begin.
- **Efficacy and Safety Review:** Assesses new drug applications based on clinical trial data to ensure safety and therapeutic benefits.

- **Conformity Audits:** Evaluates adherence to **Good Laboratory Practice (GLP)**, **Good Clinical Practice (GCP)**, and **Good Manufacturing Practice (GMP/QMS)** standards.

## 2) Post-Marketing Safety Operations for Drugs/Medical Devices [3] [6]

- **Reinforced Safety Monitoring:** Tracks adverse drug reactions (ADRs) and medical device incidents.
- **Scientific Review of Safety Data:** Continuously assesses post-marketing safety information and updates precautionary measures.
- **Public Information and Pharmaceutical Consultation Services:** Disseminates safety updates via official websites and provides guidance to healthcare professionals and consumers.

## 3) Relief Services for Adverse Drug Reactions (ADR) and Infectious Diseases [3]

- **Financial Support:** Provides medical expenses, disability pensions, and compensation to patients affected by severe ADRs.
- **Relief for Severe Myoclonic Epilepsy of Infancy (SMON), HIV, and AIDS Patients:** Special compensation programs for individuals affected by specific drug-related health issues.

## Types of Pharmaceutical Products in Japan

Japan classifies pharmaceuticals into two major categories:

### 1. New Drugs (Innovator Drugs) [3] [6]

- Defined as drugs with **new active ingredients, dosages, administration routes, or indications** that differ from previously approved medications in the **Japanese Pharmacopoeia (JP)**.
- These drugs undergo a **strict review process**, including preclinical studies, clinical trials, and post-marketing surveillance.

### 2. Generic Drugs [3] [6]

- A generic drug is a **bioequivalent** version of an innovator drug, containing the same active ingredient, strength, dosage form, and route of administration.
- Japan has been promoting **generic drug adoption** to reduce healthcare costs, with a government target of **80% generic drug usage by 2025**.

### **Orphan Drug Designation in Japan [10]**

Under Article 77 of the Pharmaceutical and Medical Device Act (PMD Act), the Ministry of Health, Labour and Welfare (MHLW) designates a drug or medical device as an orphan product based on the Act on Securing Safety, Efficacy, and Quality of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. To receive orphan drug designation, a product must meet the following criteria:

It is intended to treat a rare disease affecting fewer than 50,000 patients in Japan. There is a high medical need, meaning no existing satisfactory treatment is available. The development plan is scientifically feasible and has a reasonable prospect for commercialization.

**SAKIGAKE Designation System:** Japan has implemented the SAKIGAKE system to accelerate the approval of innovative and orphan drugs, reducing review timelines and encouraging early market access.

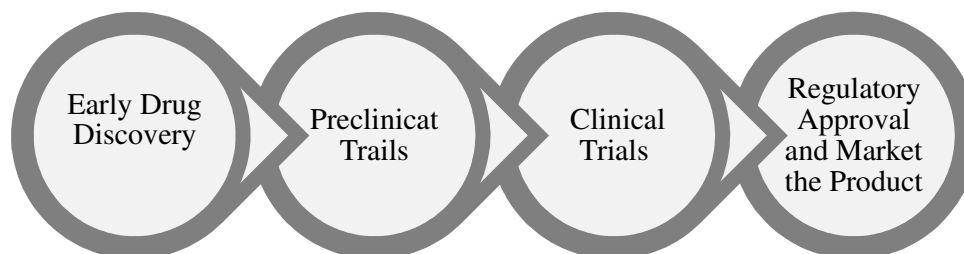
**Expedited Approval Pathways:** Orphan drugs with strong real-world evidence (RWD) may qualify for conditional early approval, allowing patients access while additional clinical data is gathered.

**Funding and R&D Incentives:** Japan has expanded financial incentives and regulatory support for orphan drug developers to promote research in rare diseases.

### **Drug Development Procedure: [11]**

The drug discovery and development process is a complex and lengthy journey, typically taking **10 to 15 years**. It begins with identifying potential active compounds that exhibit therapeutic effects on the intended disease. After selection, these compounds undergo extensive testing to evaluate their safety and effectiveness before advancing through further stages

The drug development process are as follows:



**Figure No 3: Drug Development Procedure**

The drug development process involved many different stages and series of actions. Typically, it can be divided into four main stages like Early Drug Discovery, Pre-Clinical Phase, Clinical Phase and Regulatory Approval and Market the Product.

- a. Early Drug Discovery:** Early drug discovery process is required for desirable effect on a specific biological target implicated in a particular disease, in the hope for treating the disease.
- b. Pre – Clinical Phase:** Pre-clinical studies may carry out by the researcher in experimental animals. The main objectives of these studies to provide sufficient evidence of safety and efficacy before clinical trials start in human beings.
- c. Clinical Phase:** In Clinical phase composed of four phases Phase I, Phase II, Phase III, Phase IV, in clinical phase trial should be conducted on human subject the main objective for clinical phase is to identify the Quality, Safety and Efficacy of the product.

Phases of clinical trial are as follow:

- I. Phase I:** A phase I clinical trial is performed for testing the safety of drug, in phase I healthy human subject are enrolled but some exception like trial for cancer therapy or recombinant DNA technology.
  - II. Phase II:** A Phase II clinical trial is performed for testing the efficacy of the drug, in Phase II trial are carried out in patient population.
  - III. Phase III:** A Phase III clinical trial that proves the safety and how well a new treatment works compared with a standard treatment, in Phase III trial are carried out in patient population
  - IV. Phase IV:** A Phase IV type of clinical trial is carried out for determination of side effects caused over time by a new treatment after the product approved in the market.
- d. Regulatory Approval and Market the Product:** After completion of clinical trials the data is generated from clinical trial is collected and analysed. Then it can be submitted to the appropriate regulatory authority for review. Before drug approved for sold in market.

### **Regulatory Submission [12]**

The applicant must submit a regulatory dossier in the preferred format for new marketing authorization. All regulatory documents must comply with the Common Technical Document (CTD) format, which consists of five key modules.

## CTD Modules

### 1. **Module I: Region-Specific Information**

- This module includes country-specific regulatory and administrative information submitted to the **Pharmaceuticals and Medical Devices Agency (PMDA)**.
- It includes **prescribing information**, such as labeling and package inserts, based on Japan's regulatory guidelines.

### 2. **Module II: Quality Overall Summary**

- Provides an overview and summary of **Chemistry, Manufacturing, and Controls (CMC), non-clinical, and clinical study results**.
- Summarizes **Modules III, IV, and V** to demonstrate drug quality, safety, and efficacy.

### 3. **Module III: Quality (Pharmaceutical Document)**

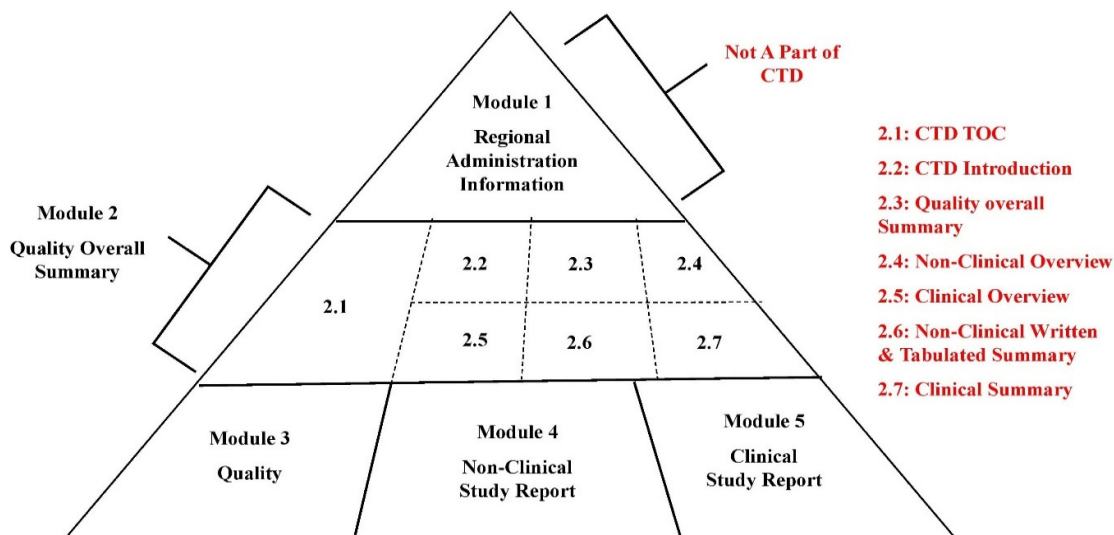
- Covers **formulation development, manufacturing (GMP), analysis and testing (GLP), packaging, stability studies, and storage conditions**.
- This module ensures that pharmaceutical and technical aspects maintain the drug's quality.

### 4. **Module IV: Non-Clinical Study Report**

- Includes **pharmacological and toxicological study reports**.
- Demonstrates **preclinical safety data** to support clinical trials.

### 5. **Module V: Clinical Study Report**

- Contains **clinical trial data conducted on human subjects**.
- Demonstrates **efficacy and safety** of the drug for regulatory approval.
- For **generic drugs**, the applicant only needs to **prove bioequivalence** to the reference (innovator) drug.



**Figure No 4: CTD Triangle**

### **Types of Regulatory Applications in Japan**

The primary types of drug applications in Japan include:

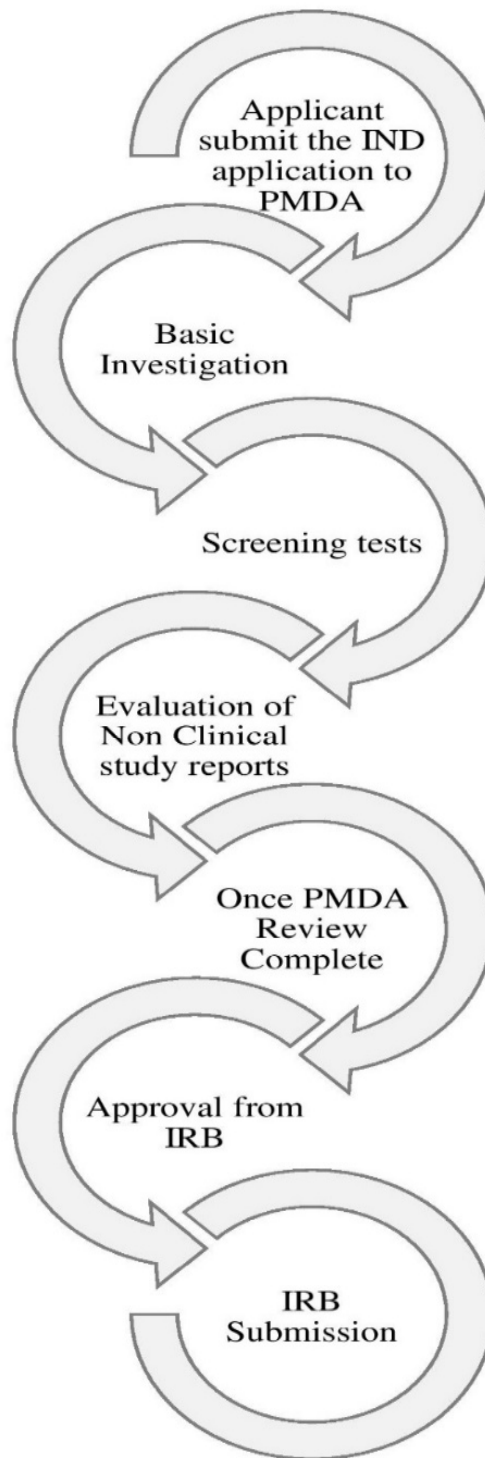
1. Investigational New Drug (IND) Application
2. New Drug Application (NDA)

#### **A. Investigational New Drug (IND) Application [13]**

An IND application is submitted to the PMDA to request approval for initiating clinical studies of a new drug in Japan [2].

Filing Process for IND Application in Japan

- All documents must follow the ICH CTD format.
- A pre-IND consultation meeting with PMDA is recommended to streamline the application process.
- The initial IND consultation may take up to 30 days, while subsequent meetings require only 14 days.
- The applicant submits an IND application to PMDA, including preclinical data, protocols, toxicity reports, investigator brochures, and other necessary documents.
- During PMDA evaluation, the applicant must promptly address any queries.
- Upon PMDA review completion, the application is sent for Institutional Review Board (RB) approval, which typically takes 1-4 weeks. Once IRB approval is granted, the sponsor may commence clinical trials on human



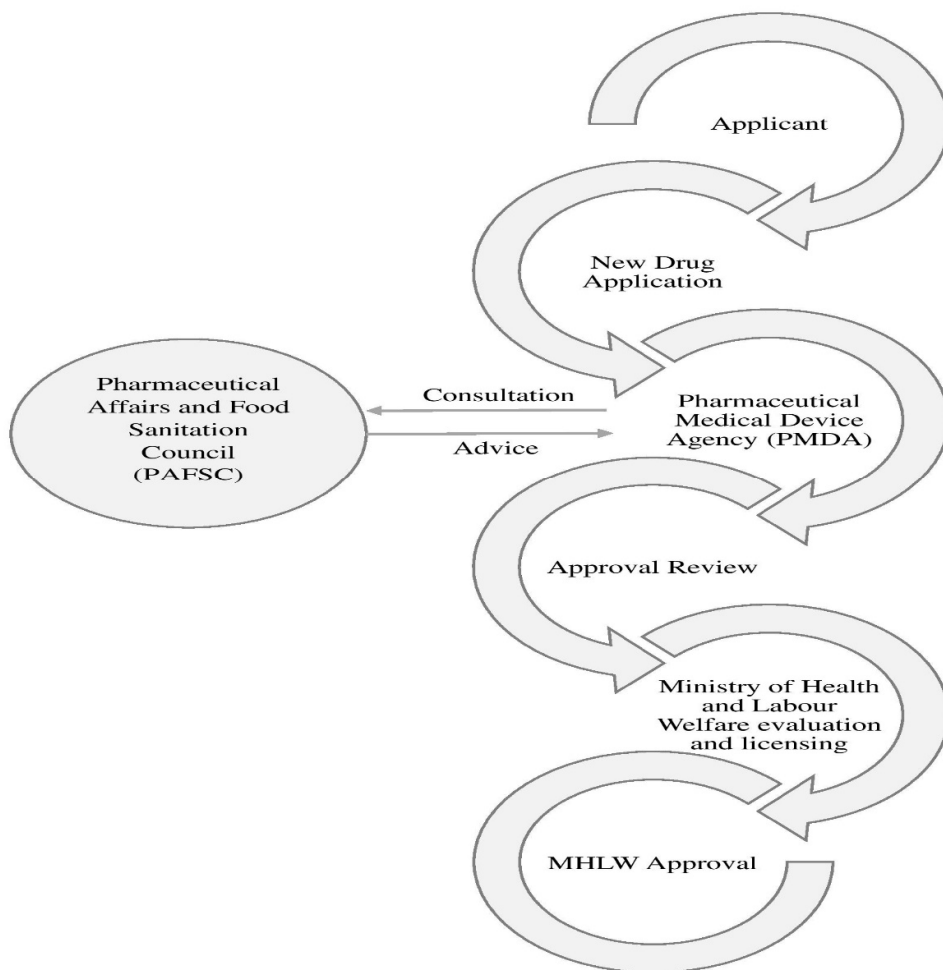
**Figure No 5: INDA Approval Process**

**A. New Drug Application: [13]**

New Drug Application (NDA) is submitted by the manufacture of drug to the regulatory authority after clinical trials have been completed for a licensed to market the drug product.

**Filing Procedure of NDA:**

- Applicant submit the NDA application to PMDA for marketing authorization of new entity.
- PMDA review the application, and if they feel necessary, may arrange the face – to – face meeting with the applicant.
- During meeting the applicant needs to discuss and answer the queries from PMDA, and after the face-to-face meeting, the PMDA reviewer prepare the review report.
- If the PMDA finds any serious issue during the review, it organizes the expert discussion.
- On this discussion between applicant, PMDA and external experts on proposed serious issues.
- After review, the experts submit the results along with GMP conformity investigation reports to MHLW.
- The MHLW upon consultation with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) the Ministry of Health and Labor Welfare (MHLW) may approved the NDA.
- After approval, the MHLW's evaluation and licensing division issues the approval certificate.
- The PMDA delivers the approval certification for the drug reviewed by the bureau.



**Figure No 6: NDA approval Process**

**Fees Structure:**

Approval Type	Fees (MHLW)	Fees (PMDA)
<b>New Product Manufacturing Approval</b>	¥533,800	¥30,535,100
<b>Generic Product Marketing Approval</b>	¥28,100	¥632,200
<b>Marketing Business License</b>	¥28,100	¥110,300

**Conclusion:** Japan remains a highly regulated and demanding market for drug approvals due to its strict regulatory framework and demographic value. The PMDA and MHLW ensure that all pharmaceutical products manufactured and marketed in Japan are safe, effective, and of high quality. These agencies continuously monitor regulatory changes and enforce compliance with Pharmaceutical Medical Device Agency (PMDA) and Ministry of Health, Labour, and Welfare (MHLW) guidelines to maintain public health safety.

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