独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulatory updates in Japan

Daisuke TANAKA, Ph.D.
Office Director, Office of International Programs
Pharmaceuticals and Medical Devices Agency, Japan

7th India-Japan Medical Products Regulatory Symposium
10 July 2024

Today's contents

1. PMDA celebrates 20 years

2. Current discussion on Pharmaceutical Regulations

3. Activities with Int'l Harmonisation

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Pharmaceuticals and Medical Devices Agency (PMDA)

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

- Incorporated administrative agency
- Established in April 2004
- Under the Law for the Pharmaceuticals and Medical Devices Agency
- Chief Executive: Dr. FUJIWARA Yasuhiro, MD, PhD (from April 2019)
- Staffs: 1044 (as of April 2023)
- Located in Kasumigaseki, Tokyo (15 min walking distance from MHLW)

PMDA Enters a New Stage on its 20th Anniversary

April, 2004

- Started with 3 main services, Relief Services for Adverse Health Effects, Product Reviews and Post-marketing Safety Measures
- Organization with **about 250 people**

2014

- Initiative to eliminate drug lag or device lag
- Strengthening safety measures
- Prompt relief services for adverse health effects

April, 2024

While connecting with all around the world, realizing a world where everyone lives vividly and healthily

New start of PMDA

- Organization with more than 1000 people
- Every staff faces PMDA' s Purpose in their work

History of PMDA

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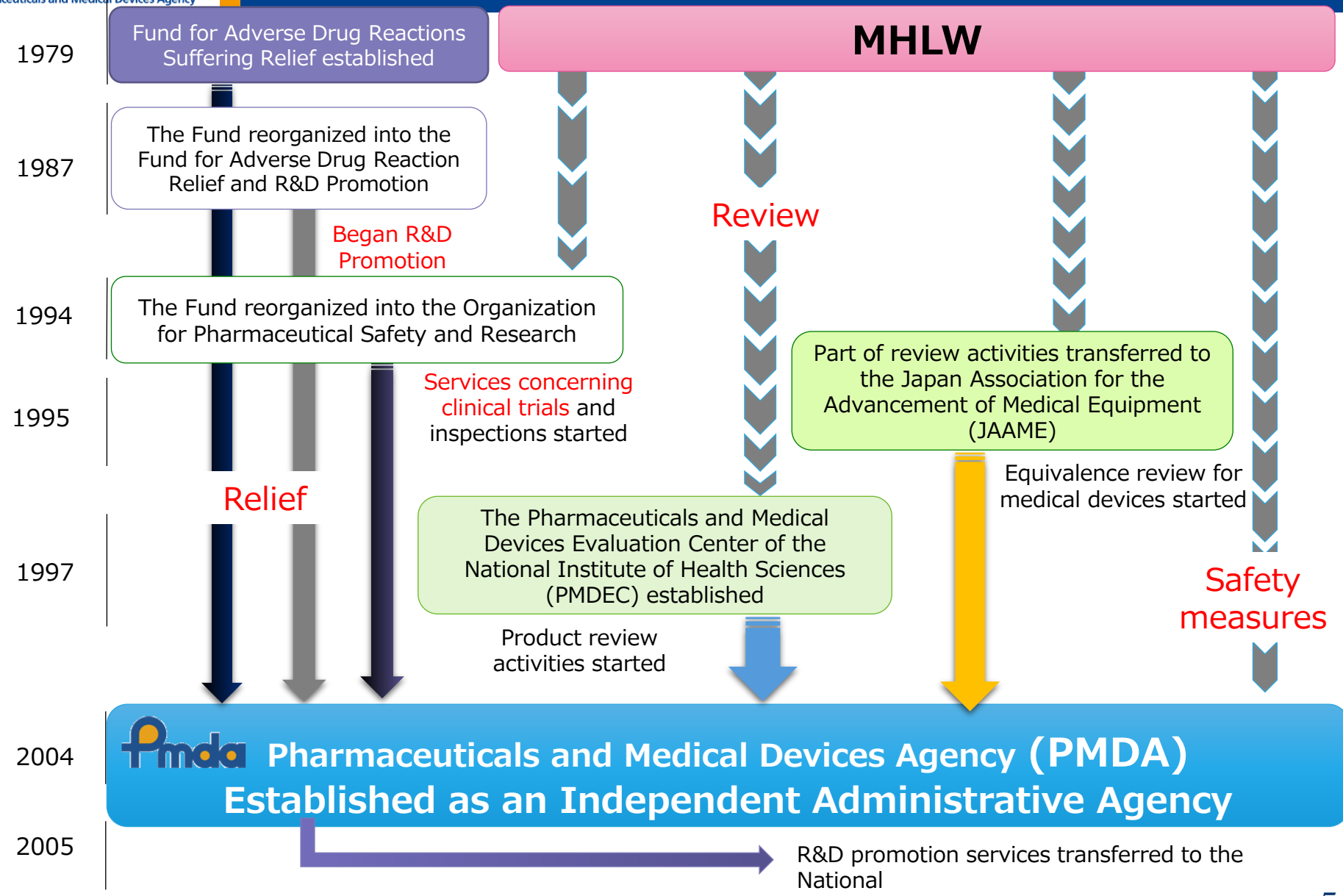
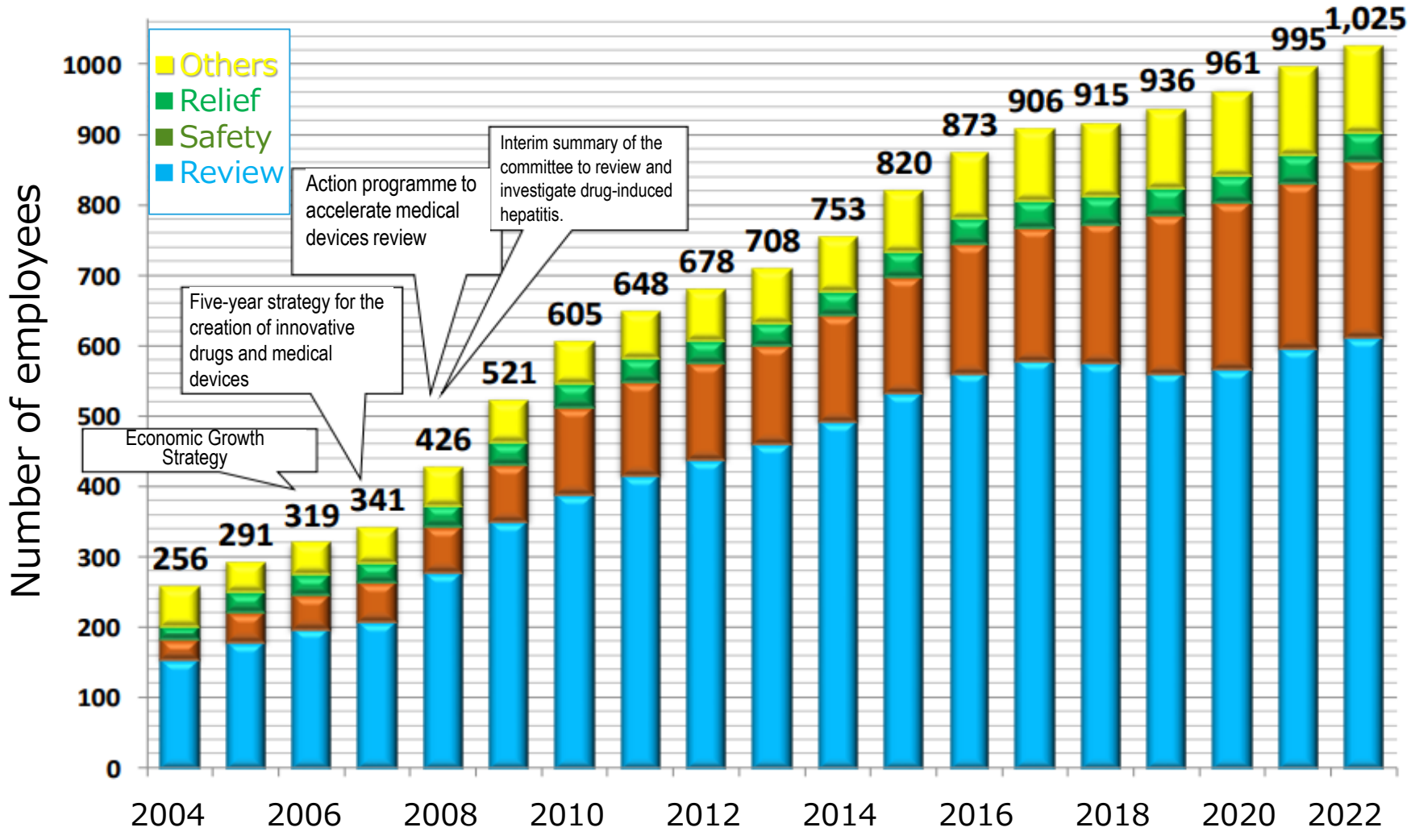
Pharmaceuticals and Medical Devices Agency

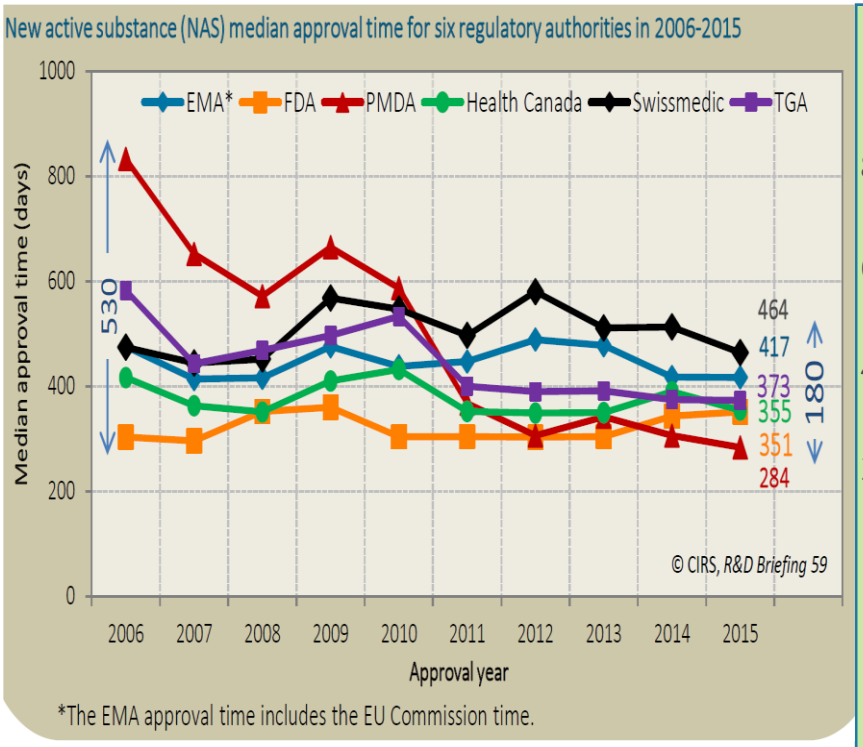


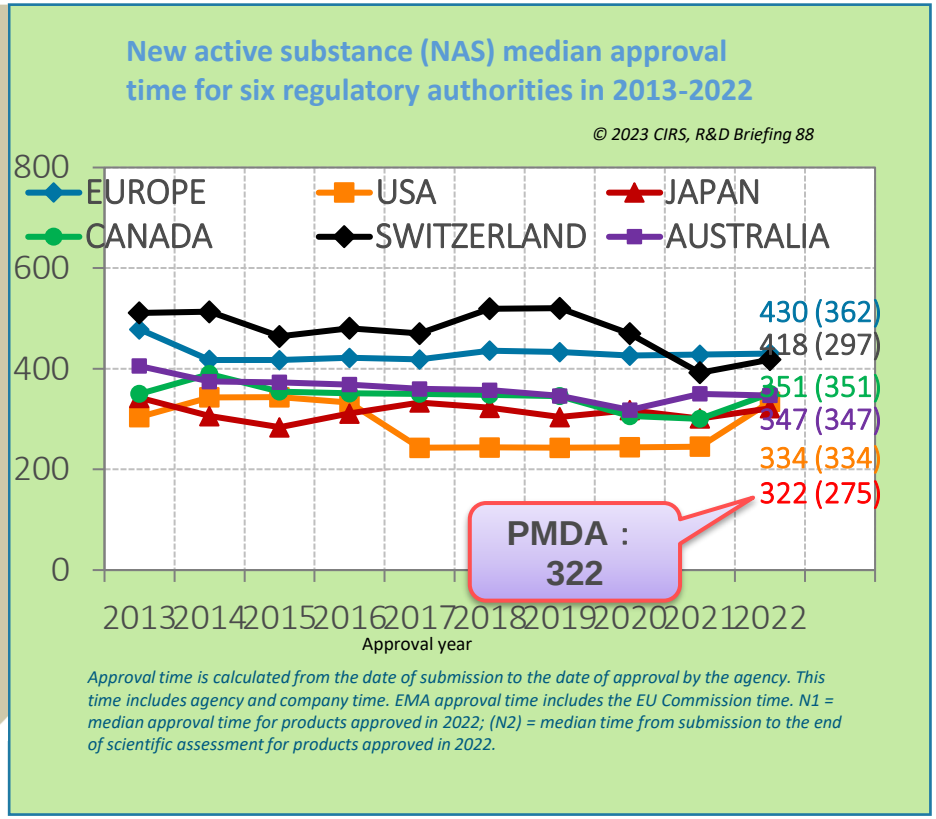
Transition of number of staffs at PMDA



Median review times for new active ingredients in 2006-2022

PMDA has significantly reduced the review period since 2006.
From 2012 to 2022, the review period will remain one of the fastest in the world.





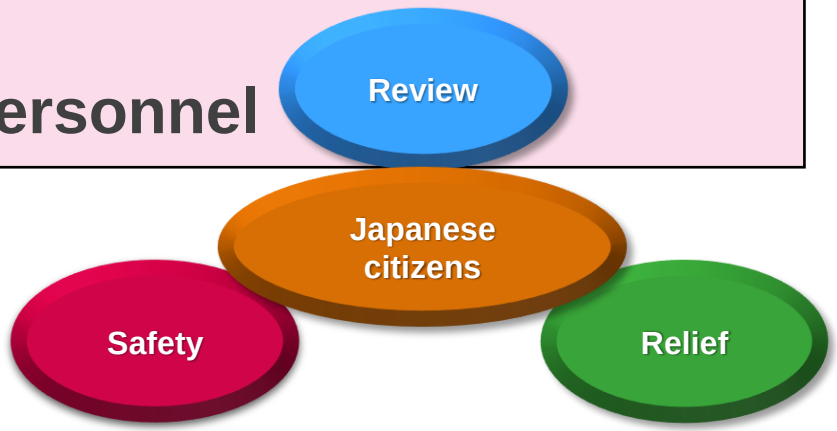
PMDA's Purpose

Making everyone's lives brighter together

We, PMDA, continue to create "Tomorrow's Normal" together,
as a "life platform" that supports everyday life,
where everyone can feel peaceful and can lead vibrant and healthy lives
by PMDA's "Safety Triangle" of review, safety and relief,
with "intelligence" weaved through science and information, and
with "human resourcefulness" accompanying
and bringing the world and the future into harmony.

Direction for 5th Mid-term plan
[FY2024-2028]

- **For further "Quality" through Regulatory Science**
  - **Consultation/review** for pharmaceuticals etc. for *the innovative products*
  - **Proper follow-up of safety measures**
  - **Emergent response system** e.g. Pandemic
- **For strategic international activities**
  - **Regulatory support/Disseminate regulatory information** to overseas companies *to develop innovative products in Japan*
- **Governance and professional personnel**



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Actual situation of drug lag/drug loss

- As of March 2023, there were **86 drugs (60.1% of unapproved drugs)** approved in Europe and the U.S. but not yet developed in Japan. It is said that there is **"Drug loss"** i.e., no companies develop the products in Japan).
- Analysis of 86 products whose development in Japan has yet to start: relatively large proportion of **venture-originated drugs, orphans, and paediatrics.**

Status of drug loss in Japan, Europe, and the United States

	Approved	Unapproved total	Unapproved portion	
			Under development	**Not yet started**
United States	136	7	3	4
Europe	86	57	26	31
Japan	0	**143**	57	**86**

Break-down

Breakdown of items not yet started in Japan

Venture start-up	**Orphan**	**Paediatric**
56 % (48 items)	**47** % (40 items)	**37** % (32 items)

※ Of the 86 loss items, 14 (16%) are not ventures, orphans, nor paediatric.

※Source: Published information from PMDA, FDA, and EMA, prepared by the Pharmaceutical and Industrial Policy Research Institute based on tomorrow's new drugs (Technomic Co., Ltd.), and tabulated by the Ministry of Health, Labour and Welfare.
※1:Of the NMEs approved in Europe and the United States in 2016-2020, those not approved in Japan as of the end of 2022 are counted as unapproved.
※2:As of March 2023, items for which no development information was available are counted as undeveloped products in Japan.
※3:Figures are totaled for development companies with sales of less than US$500 million within 30 years of approval in Europe and the U.S.
※4:Compiled as orphans for items designated as orphan drugs by the time of approval in Europe and the U.S.
※5:2022 Calculated based on pediatric products approved for pediatric use in Europe and the U.S.

Adapted from "Reference Material 4 of the 1st Meeting of the Committee on Regulatory Measures for Strengthening Drug Discovery Capabilities and Securing Stable Supply" implemented by the Pharmaceutical and Environmental Health Bureau, MHLW

Expert Panel on Comprehensive Measures for the rapid and stable supply of pharmaceuticals (MHLW)

(13 meetings from 22 September, 2022 to 6 June, 2023)

Main topics discussed

Securing Stable supply

Many products, mainly generics, are suspended. It is due to the structural problems of the generic industry, such as many companies are small-scale and have limited-capacity, and low-volume with high-diversity production of generic medicines.

Strengthening Pharma R&D

Japan's pharma development capacity has declined, with the global market share of Japanese origin decreasing. The transition to new modalities has been delayed, and a shift to an R&D-oriented business model needs to be accelerated.

Elimination of Drug Lag / Loss

143 products approved in Europe and the US have not been approved in Japan. Of these, 86 have not yet started development in Japan, raising concerns about drug losses. Venture-origin medicines, orphan drugs and paediatric drugs account for a large proportion of these medicines.

https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html

Study Group on Pharmaceutical Regulations to Strengthen Drug Discovery and Ensure Stable Supply (MHLW)

（Jul 10, 2023 – Mar 21, 2024）

Considering the pharmaceutical regulations in order to eliminate drug loss issues, ensure stable supply and accelerate pediatric drugs development

Considerations

Promotion of development	How to designate orphan drugs	*10 Jul, 2023*
	Pharmaceutical reviews that contribute to promote development of pediatric drugs	*7 Aug, 13 Sep,13 Dec, 2023; 8 Feb, 2024*
Clinical trials	Arrangement of necessity of Japanese data for approval review in Japan	*12 Mar, 2024*
	Introduction of further efficiency in trials (ecosystem)	
Post-market safety measures	Post marketing use-results surveys	*12 Jan, 2023; 12 Mar, 2024*
	Use of real world data in regulatory affairs system	
Quality	Regulatory reviews on manufacturing methods of drugs	*13 Oct, 15 Nov, 2023*
Information dissemination	Disseminating the information on Japanese regulatory system around the world	*15 Nov, 2023*

(only in Japanese) https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html

Towards a revision of the requirements for the orphan designation

【Requirements and Issues for Orphan Designation】

Eligibility

The number of patients was **less than 50,000** in Japan

※ Effective April 1, 2015, 50,000 or more cases of designated intractable diseases shall satisfy this requirement.

Medical needs

No appropriate alternative medicines or treatments, or **significant higher** efficacy or safety is expected

If there is an approved drug, it may be judged an alternative is available regardless of its efficacy.

Direct comparison with approved drugs may be required

Possibility of development

With a rationale for the product to use for the disease concerned and with **appropriate development plan**

・Phase II trial completed and Phase III trial plan agreed with PMDA
・Result from a phase III trial

【Points to consider toward revision】

Clarification of “salami slicing" requirements

Clarification of criteria based on medical and pharmaceutical considerations

For example, based on medical and pharmacological considerations, target diseases limited to those for which development has not progressed may not fall under “salami slicing"

Clarification of “medical needs”

Clarification of Concept on Alternative Therapy

Clarification of Concept on Comparison with Existing Therapy

Speeding-up of designation and clarification of withdrawal conditions

Clarification of requirements for acceleration and withdrawal of designations

For the possibility of development, it may be checked the existence of a system and a plan for its development in Japan?

In addition, with acceleration of designation, it is advisable to clarify requirements for withdrawal of designation if requirements are no longer satisfied

Establishment of the PMDA "Center for Regulatory Consultation of Pediatric and Orphan drugs" in 2024

We will work on the following in order to promote introduction of orphan and pediatric drugs to Japan.

1. Earlier and expanded designation of orphan drugs
2. Encouraging companies to develop drug development plans and facilitating PMDA to check them
3. Accelerating evaluation in the MHLW "Study Group on Unapproved and Off-label Drugs of High Medical Need"
4. Assistance to companies for PMDA consultation fees

Center for Regulatory Consultation of Pediatric and Orphan drugs

1 Orphan drugs	2 Pediatric drugs	3 Study group on unapproved drugs
Consultation/review of designation and designation review	Check of development plan and progress management	Accelerating evaluation (e.g. surveys, preparation of evaluation reports)

*To improve efficiency through establishment and operation of the designation and evaluation criteria across disease areas, the center will be separated from each review office.

Cited from MHLW "Main matters on the budget proposal" in 2024

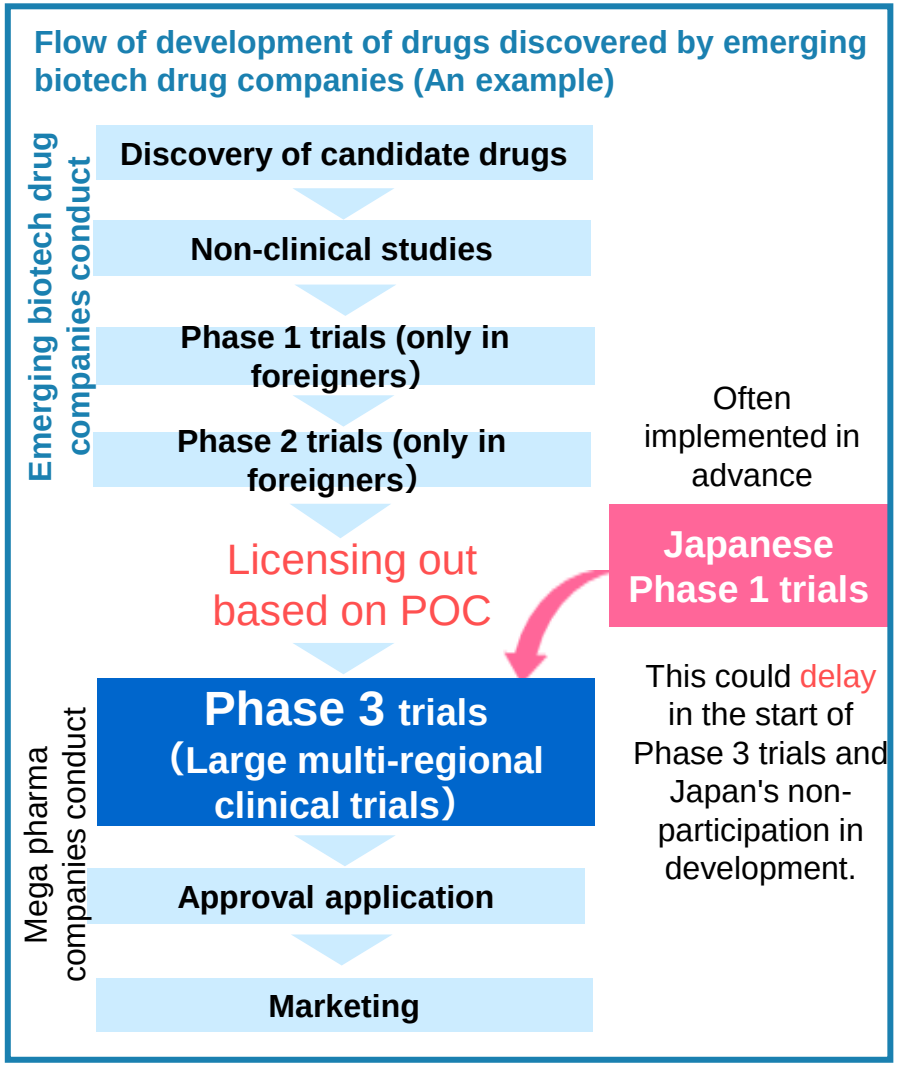
Necessity of Japanese Phase 1 Trial

[PMDA's principle]

- If there are **ethnic differences** between Japanese and foreigners, we recognize that **the Japanese data are important in using drugs safely in Japan**

- **We <u>have not uniformly required</u> Phase 1 trials in Japanese before participating in multi-regional clinical trials**, and determines <u>synthetically by considering multiple perspectives</u>.

- It is desirable that **Japan participates in multi-regional clinical trials from early stage in development and Japanese data are collected**.



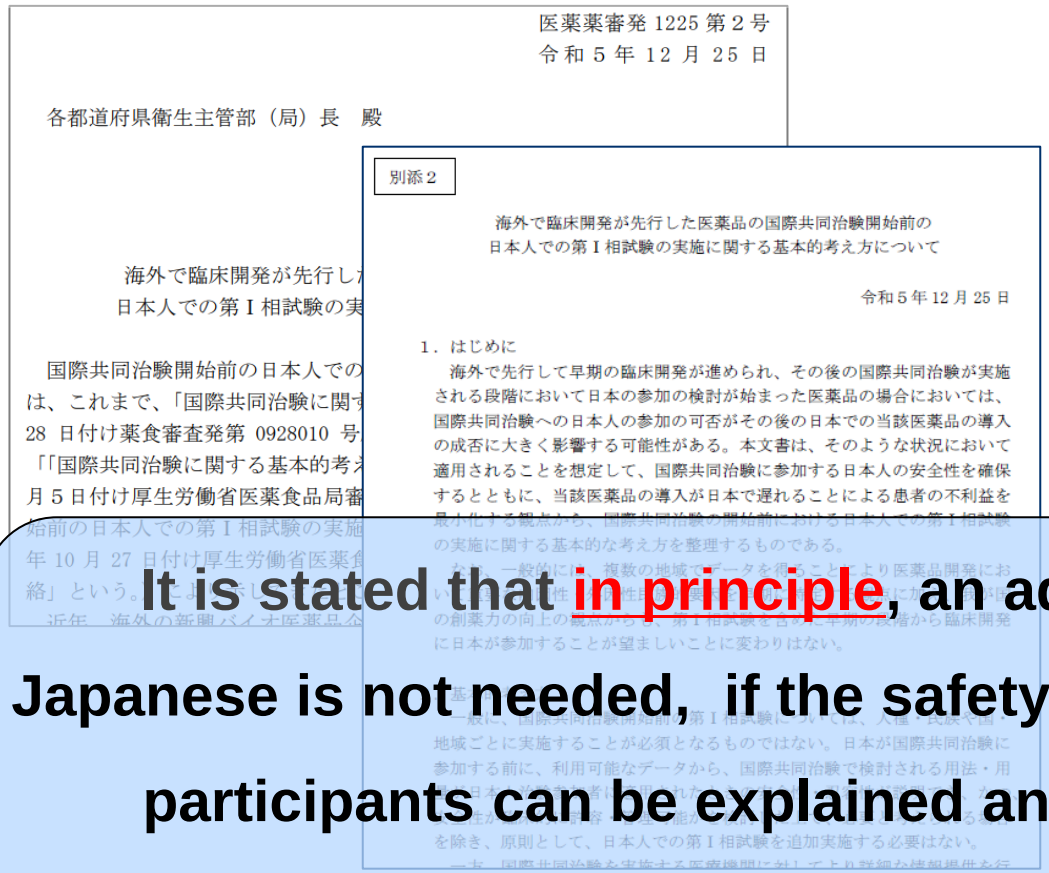
(only in Japanese) https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html

Basic Principles for conducting phase 1 studies in Japanese prior to MRCTs including Japan

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Notification (25 December 2023)

by the Director of the Pharmaceutical Evaluation and Licensing Division, MHLW



医薬薬審発 1225 第２号
令和５年 12 月 25 日

各都道府県衛生主管部（局）長　殿

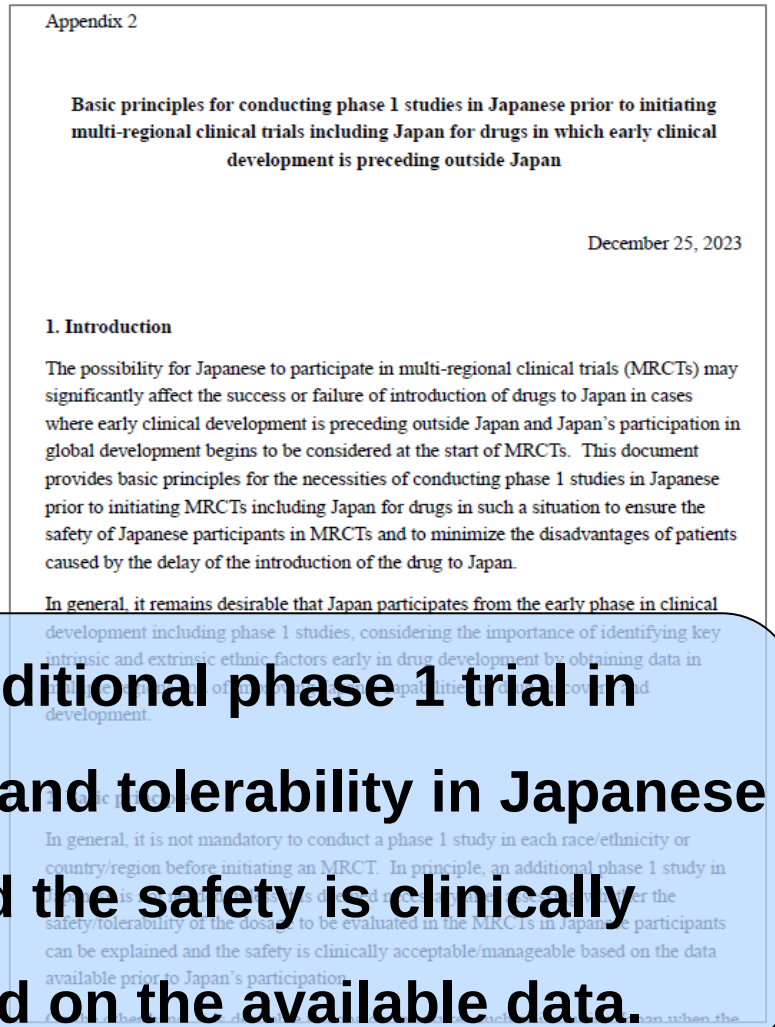
別添２

海外で臨床開発が先行した医薬品の国際共同治験開始前の
日本人での第Ⅰ相試験の実施に関する基本的考え方について

令和５年 12 月 25 日

１．はじめに

海外で先行して早期の臨床開発が進められ、その後の国際共同治験が実施される段階において日本の参加の検討が始まった医薬品の場合においては、国際共同治験への日本人の参加の可否がその後の日本での当該医薬品の導入の成否に大きく影響する可能性がある。本文書は、そのような状況において適用されることを想定して、国際共同治験に参加する日本人の安全性を確保するとともに、当該医薬品の導入が日本で遅れることによる患者の不利益を



Appendix 2

Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan

December 25, 2023

1. Introduction

The possibility for Japanese to participate in multi-regional clinical trials (MRCTs) may significantly affect the success or failure of introduction of drugs to Japan in cases where early clinical development is preceding outside Japan and Japan's participation in global development begins to be considered at the start of MRCTs. This document provides basic principles for the necessities of conducting phase 1 studies in Japanese prior to initiating MRCTs including Japan for drugs in such a situation to ensure the safety of Japanese participants in MRCTs and to minimize the disadvantages of patients caused by the delay of the introduction of the drug to Japan.

In general, it remains desirable that Japan participates from the early phase in clinical development including phase 1 studies, considering the importance of identifying key intrinsic and extrinsic ethnic factors early in drug development by obtaining data in

development.

In general, it is not mandatory to conduct a phase 1 study in each race/ethnicity or country/region before initiating an MRCT. In principle, an additional phase 1 study in

safety/tolerability of the dose to be evaluated in the MRCTs in Japanese participants can be explained and the safety is clinically acceptable/manageable based on the data available prior to Japan's participation.

It is stated that in principle, an additional phase 1 trial in Japanese is not needed, if the safety and tolerability in Japanese participants can be explained and the safety is clinically acceptable and manageable based on the available data.

https://www.pmda.go.jp/english/rs-sb-std/rs/0011.html

Approaches to oversea start-ups/ventures

<BIO International Convention 2024> June 2024

- Promote attractiveness of obtaining Marketing Authorisation in Japan to venture companies by introducing Japan's efforts to harmonize pharmaceutical regulations and PMDA's efforts to make Japan a reference country in the Asian region.
- Conducted in cooperation with the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of Economy, Trade and Industry (METI).

<DIA Euro, DIA Global > March and June 2024

- PMDA Townhall to provide Information on the Japanese Pharmaceutical Regulation and Market Situation
  - Japan's approval system (SAKIGAKE, priority review, conditional approval, etc.)
  - Pre-trial consultation system and contact information
  - Introduction of the NHI drug price system, etc.
- Conduct a brief consultation with companies seeking to develop medical products in Japan.

<Future expected Plan>

- To communicate in PMDA's own language (in English).
- Establish Washington D.C. office at an early stage, and collaborate with JETRO and others, based in the US to encourage venture companies to bring their products to Japan’s market.

Information Dissemination at the PMDA Website

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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Safety Alert & Recalls/ Review Reports/ Package Inserts etc. | Formats DL

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Reviews and Related Services

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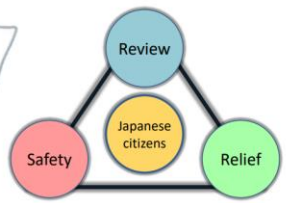
PMDA's support to Venture companies

Pharmaceuticals and Medical Devices Agency



SAKIGAKE (Forerunner) drugs - Designation System

<Objective>

To put innovative products into medical practice in Japan

<Criteria for designation>

1. Innovativeness - new mode of action
2. Severity of the target disease - life-th
3. Prominent efficacy - no existing thera
   improvement in efficacy or safety con
4. Plan/System - to submit the NDA in J

Examples of the world-first approval granted in Japan

These were designated as SAKIGAKE and/or Orphan Drugs.

First approval in Japan!

Establishment of PMDA's Overseas Offices

Objective: Contribute to innovative medicines access in close collaboration with PMDA Tokyo Headquarters through enhanced on-site communication

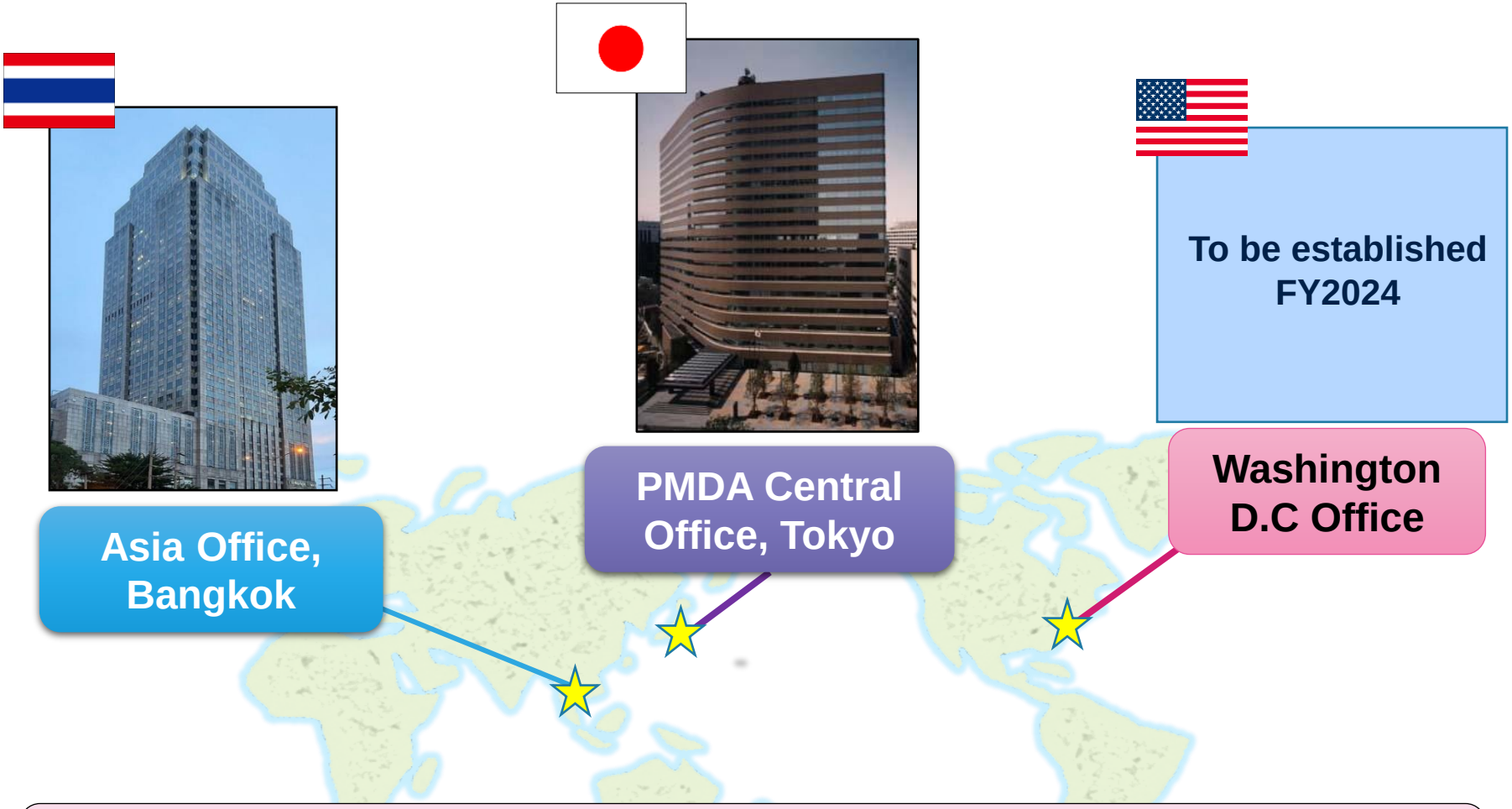
Asia Office, Bangkok , Thailand

- Strengthening cooperation with ASEAN regulators
- Supporting promotion of regulatory harmonisation among Asian countries
- Supporting the development of clinical research network to facilitate smooth clinical development

Washington D.C. Office, USA

- Close collaboration with FDA
- Facilitate PMDA consultation which Industry in US wants to develop innovative products in Japan and disseminate regulatory information

PMDA's International Hubs



Establishment of PMDA's international hubs
to enhance international contribution/capability for regulatory proposal

PMDA's 5th mid-term plan

United States-Japan Joint Leaders' Statement

United States-Japan Joint Leaders' Statement

Global Partners for the Future (excerpt)

We are also working to align global health security and innovation, including in such areas as pandemic prevention, preparedness, and response and promoting more resilient, equitable, and sustainable health systems. Today, we announce that the U.S. Food and Drug Administration and the Japan's Pharmaceuticals and Medical Devices Agency (PMDA) intend to collaborate and exchange information on oncology drug products to help cancer patients receive earlier access to medications and to discuss future drug development and ways to prevent drug shortages. We welcome PMDA's future representative office in Washington, D.C., to facilitate this cooperation.

FACT SHEET: Japan Official Visit with State Dinner to the United States (excerpt)

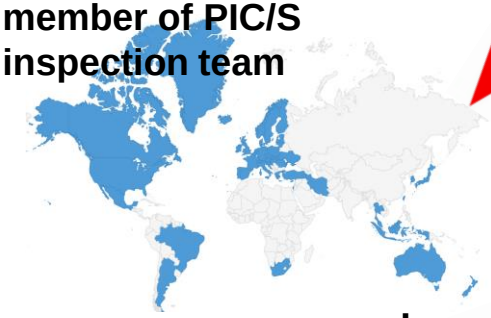
Biotechnology, Biopharmaceutical, and Health-Related Cooperation

Tackling Cancer Together: In alignment with the Biden Cancer Moonshot to end cancer as we know it, the U.S. Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) intend to collaborate and exchange information on oncology drug products. Specifically, under initiatives Project Nozomi and Project Orbis, FDA and PMDA intend to work to enable earlier access to cancer medication for patients and hold discussions on future drug development, including multiregional clinical trials and ways to prevent drug shortages.

Advancing Pharmaceutical Innovation: The United States and Japan welcome the Japan's Pharmaceutical and Medical Devices Agency (PMDA)'s intent to establish an office in the Washington, D.C. metro area. This office provides opportunities to enhance PMDA's cooperation with the U.S. Food and Drug Administration (FDA) and facilitate information sharing with private industry.

Staff Stationed at the PIC/S Office (Geneva)

Participation in the inspection for countries applying for participation as a member of PIC/S inspection team



Engagement in international harmonization activities of GMP

Sharing information and discussion with WHO

Staff stationed

Improvement of inspection ability of PMDA

Improvement of inspection ability of PMDA

Enhancement of cooperation with Asian authorities with cooperation from WHO

Enhancement of reliance with Asian authorities

[Strong Advantage]

- ✓ Obtaining recent international trends for GMP area
- ✓ Ensuring the inspection system to take the initiative in carrying out GMP inspections for manufacturing sites in Asian regions
- ✓ Enhancing cooperative activities with overseas regulators and conducting strategic efforts to establish the reliance system

FY2024 Outline of NHI Drug Pricing System Reform

(Approved by the Central Social Insurance Medical Council on December 20, 2023)

Appropriate Evaluation of Innovative New Drugs to Eliminate Drug Lag/Drug Loss

(1)Evaluation of early introduction in Japan

- Corrective Premium for early introduction （5% ≦ A ≦ 10%） [II. 1. (1) (i)]
- Adjustment to average overseas price after listing [II. 1. (1) (ii)]
  - imported formulations, whose foreign price wasn't available at the time of listing
  - the maximum price increase shall be 1.20 times the NHI price before

(2)Review of the Price Maintenance Premium (PMP) [II. 1. (2) (i)]

- To abolish adjustment of the premium (premium x 1.0 ~ 0.8 → all 1.0)
- The following items will be added as item requirements for the PMP.
  - May be eligible for evaluation under the Pediatric Premium
  - Eligible for the Corrective Premium for early introduction in Japan

(3)Evaluation of new drugs at the time of NHI price listing

- Review of approach for granting the Corrective Premium rate [II. 1. (3) (ii)]
  - the premium rate will be determined flexibly within the scope of the current rules

(4)Pediatric drug evaluation

- Evaluation for simultaneous development in adults and children [II. 1. (5) (ii)]
  - the premium rate of the Pediatric Premium will be evaluated higher at the time of NHI price listing, NHI drug price revision, and re-pricing following market expansion.

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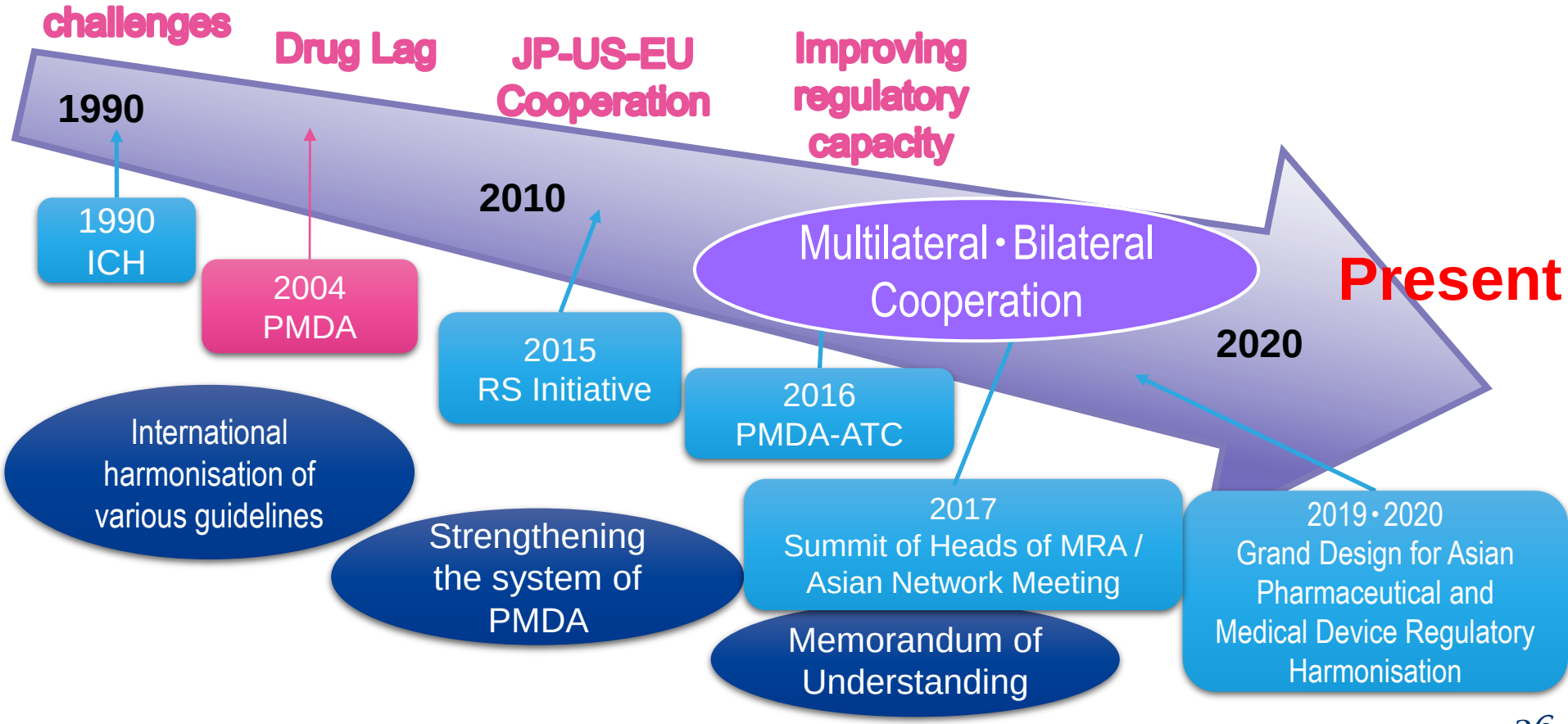
The History of Japan's Regulatory Harmonisation

- Japan has been leading regulatory harmonisation as a founding member of ICH since 1990, together with the U.S. and Europe.
- After the establishment of PMDA (2004), **PMDA has promoted regulatory harmonisation and regulatory science for 10 years.**
- Based on this experience, PMDA promotes strengthening cooperation with Asian countries.



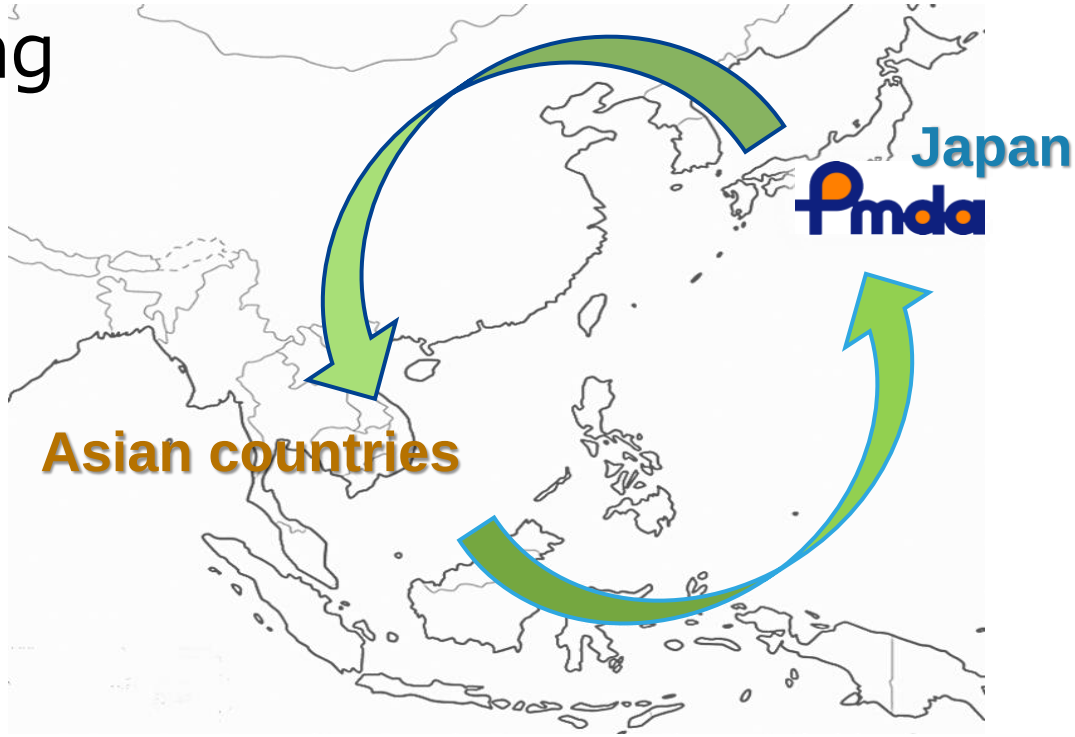
International Collaboration and Reliance in Pharmaceutical Regulations

To ensure fast and stable access to products that are quality-assured, effective and safe

- ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use)
- ICMRA (International Coalition of Medicines Regulatory Authorities)
- PIC/S (Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme)
- PDG (Pharmacopoeia Discussion Group)

Cooperation with Asian regulators

- Asian Network Meeting (ANM)
- Symposium
- Bilateral Meeting
- Seminar



The 6th Asian Network Meeting

- Date and venue: 24 April 2024 in Tokyo (Hybrid meeting)

- Co-hosts: NMPA China, CDSCO India,
  MHLW/PMDA Japan and HSA Singapore
- Topics:
  1. Digitalization and fast patient access -How can we prepare for it?-
  2. R&D for innovative pharmaceuticals in Asia from regulatory perspective -How to promote and collaborate

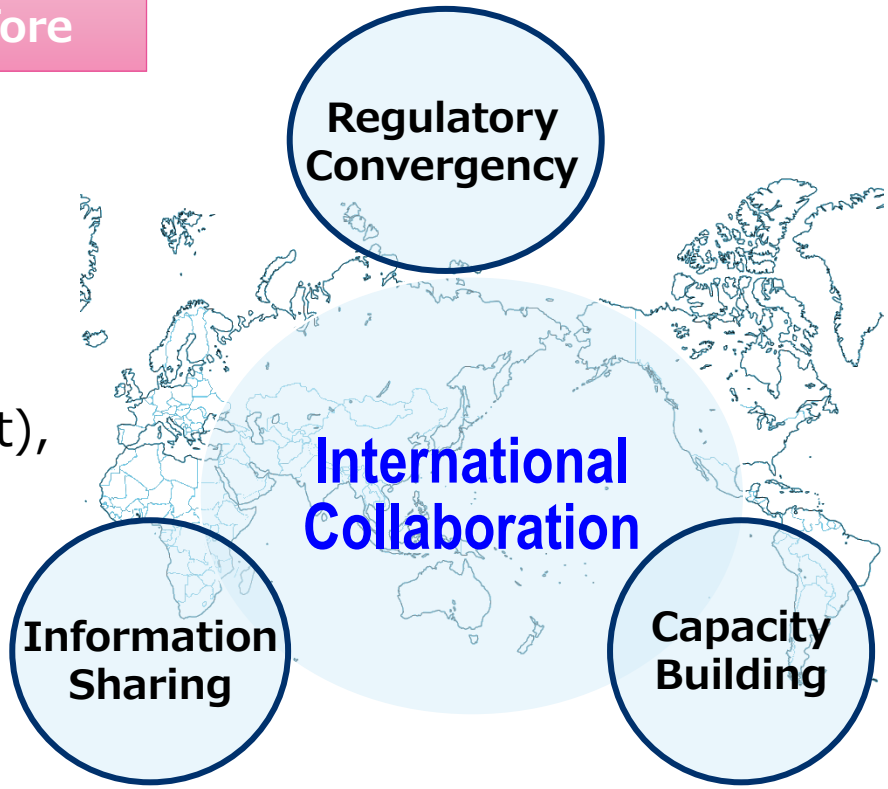
Importance of international collaboration

International Collaboration and Reliance

Significantly important than ever before

- ✓ Globalisation of supply chain
- ✓ Emergence of new technologies
- ✓ Limited human resources
- ✓ Response and Preparedness for pandemic (COVID-19 and the Next), etc...

→ Fast and Stable access to Innovative medical products



Major countries/regions where Japan is covered by reference country systems

(As of April 2024)

1. Drugs

- The number in brackets is the year in which Japan was covered

Country	System
EU	• Acceptance of GMP・GLP inspection results（2002）
Switzerland	• Acceleration of review of drugs（2010）
Thailand	• Acceleration of review of drugs（2015） • Referencing of Japanese pharmacopoeias（2019）
Taiwan	• Acceptance of review results of non-clinical studies（2016） • Acceleration of review of drugs（2016）
India	• Exemption from execution of Ph3 trial in India（2019）
Indonesia	• Acceleration of review of drugs（2000）
Malaysia	• Acceleration of review of indication expansion（2004） • Acceleration of review of drugs（2024）
Vietnam	• Referencing of Japanese pharmacopoeias （2018）
Australia	• Acceleration of review of drugs（2019）
Ukraine	• Acceleration of review of drugs（2016）
UAE	• Acceleration of review of drugs（2018）
Philippines	• Acceleration of review of drugs（2022）
El Salvador	• Acceleration of review of drugs（2023）
Peru	• Acceleration of review of drugs（2023）
UK	• Acceleration of review of drugs（2024）

(Other) MHLW and PMDA are positioned as SRA（Stringent Regulatory Authority）defined by WHO.

2. Medical devices and in vitro diagnostics（IVD）

Country	System
Singapore	• Acceleration of review of medical devices and IVD（2010）
Mexico	• Acceleration of review of medical devices（2012）
Malaysia	• Acceleration of review of medical devices and IVD（2014）
India	• Acceptance of Japanese QMS inspection results of medical device and IVD （2015） • Exemption from execution of clinical trials in India（2017）
Taiwan	• Reduction of materials for quality management system of medical device and IVD（2018）
Australia	• Acceleration of review of medical devices and IVD（2018）
Vietnam	• Acceleration of review of medical devices and IVD（2018）
Thailand	• Acceleration of review of medical devices and IVD（2019）
El Salvador	• Acceleration of review of medical devices and IVD（2023）
Peru	• Acceleration of review of medical devices and IVD（2023）
Brazil	• Acceleration of review of medical devices and IVD（2024） *Enforcement in June

(Other) Japanese mechanism on approval/certification system of medical devices is recommended as “Global model framework” of WHO.

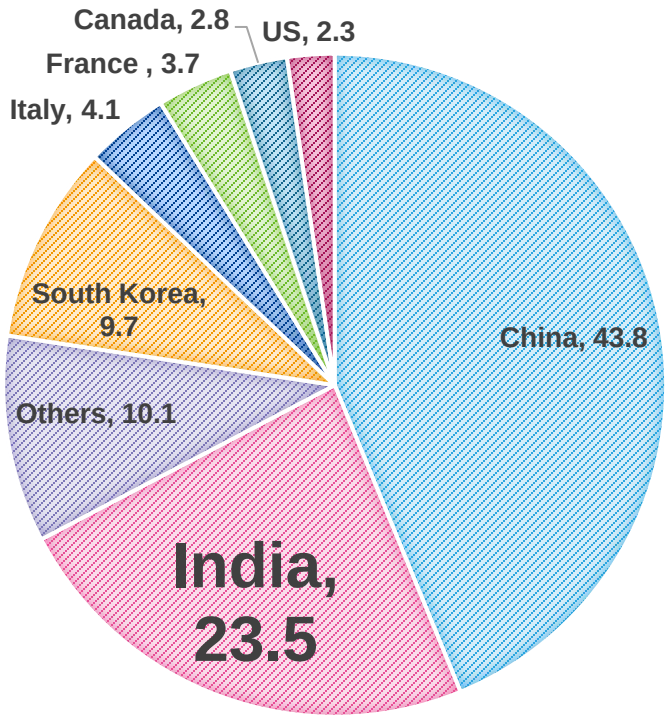
3. Status of utilization of the abbreviated review system for drugs（ASEAN）

Country	Items approved through abbreviated review system
Thailand	3
Indonesia	1
Philippines	3

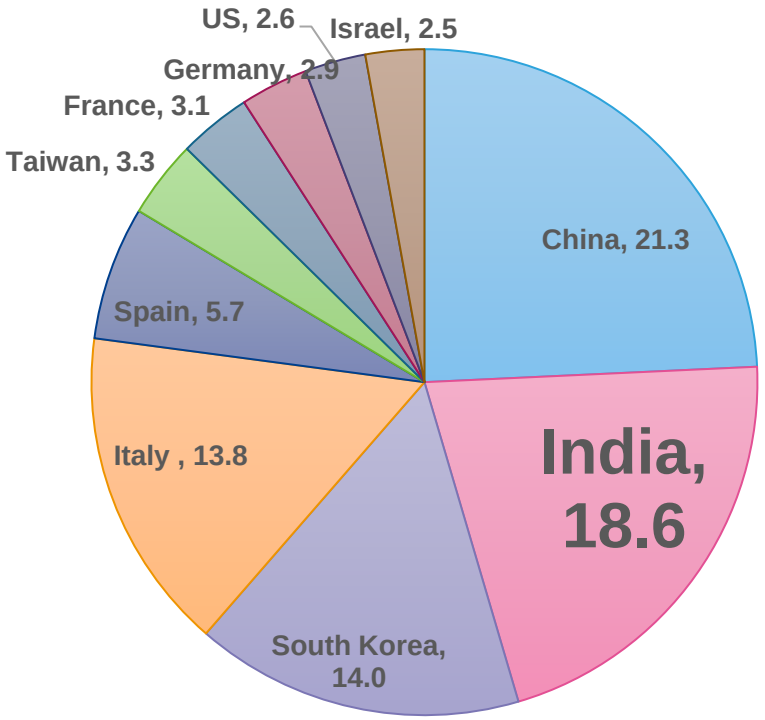
India - important country for pharma in Japan

Origin of imported APIs to Japan

Origin of APIs imported as crude/finished products and refined/processed domestically (% company)

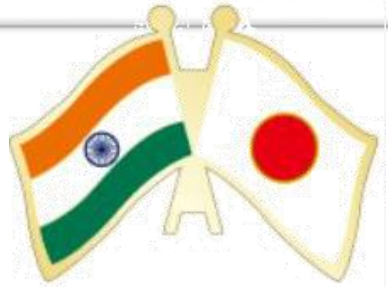


Origin of APIs imported as crude/finished products and use as-is (% company)



Source: Report on the Study and Revision of the Roadmap for the Promotion of Generic Drug Use
(March 2024. Study commissioned by the Ministry of Health, Labour and Welfare)

India - important country for me, too



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Regulatory updates in Japan

Thank you !

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7th India-Japan Medical Products Regulatory Symposium
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