Regulatory Science and Work together for global patients

– “Rational Medicine Initiative”–

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Pharmaceuticals and Medical Devices Agency (PMDA)

10 Apr 2018

APAC 7th Symposium

Regulatory agency should consider holistic approach to medicine

1. Philosophy
2. Regulatory Science
3. International Partnerships

Regulatory Authorities in JAPAN

MHLW

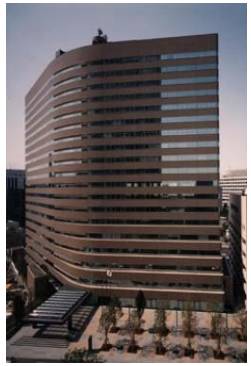
Pharmaceutical Safety and Environmental Health Bureau, MHLW

- **Final Authorization of applications**
- **Publishing Guidelines**
- **Advisory committee**
- **Supervising PMDA Activities**

PMDA

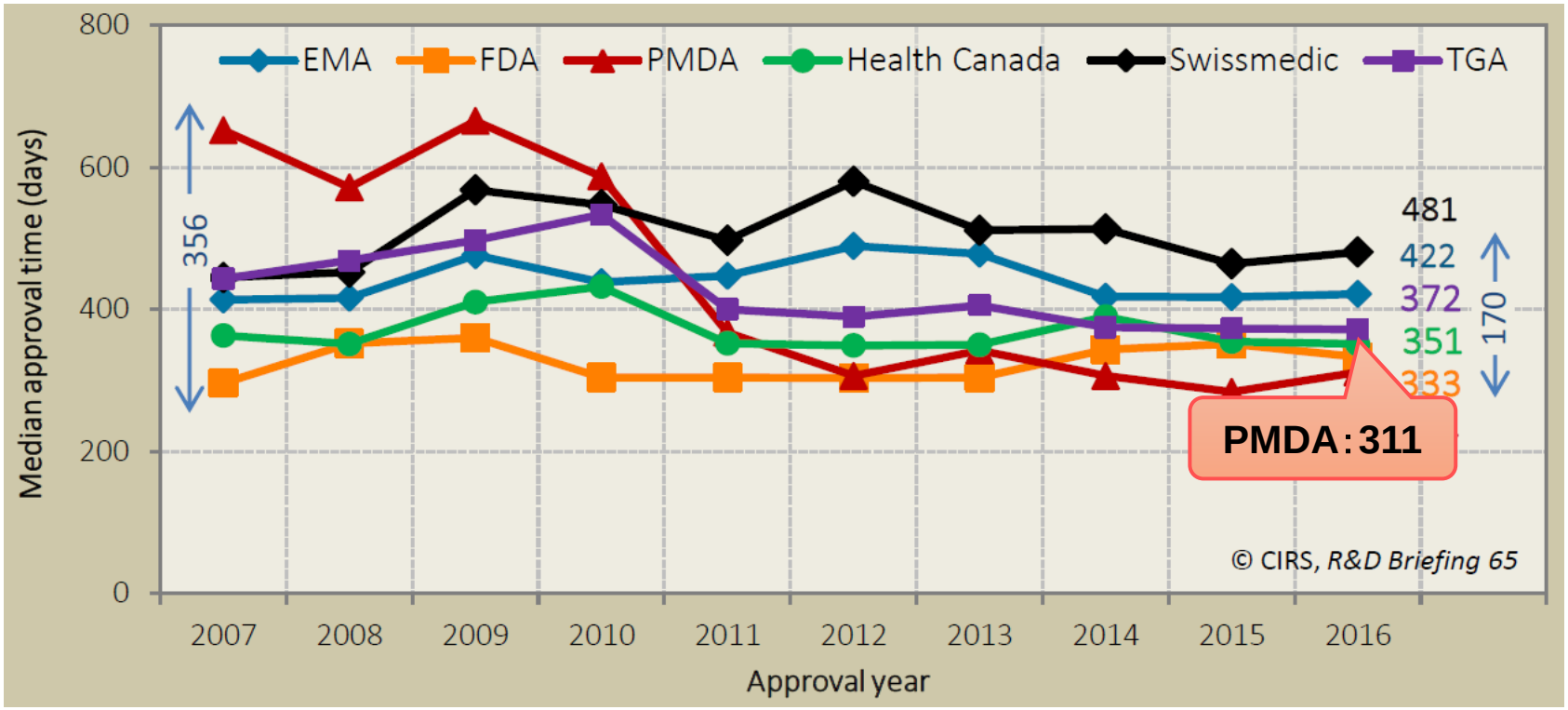
Pharmaceuticals and Medical Devices Agency

- **Scientific Review for Drugs & Medical Devices**
- **GCP, GMP Inspection**
- **Consultation on Clinical Trials etc.**



Comparison of median review periods for new APIs between 2007 and 2016

New active substance (NAS) median approval time for six regulatory authorities in 2007-2016



In 2016, PMDA approved the highest number of new APIs (48), followed by Swissmedic (40), Health Canada (33), TGA (32), EMA (28), and FDA (23).

PMDA has achieved the world's fastest median review periods for new APIs for the past 3 consecutive years.

Centre for Innovation in Regulatory Science (CIRS), 2017, R&D Briefing 65

1. Philosophy

- Certification of the concept
  - our activity goes for the nation
  - Mission to protect life and the health of the own nation
- Setting standard of conduct
  - Gain a trust as the organization
  - Let the concept sink in the organization

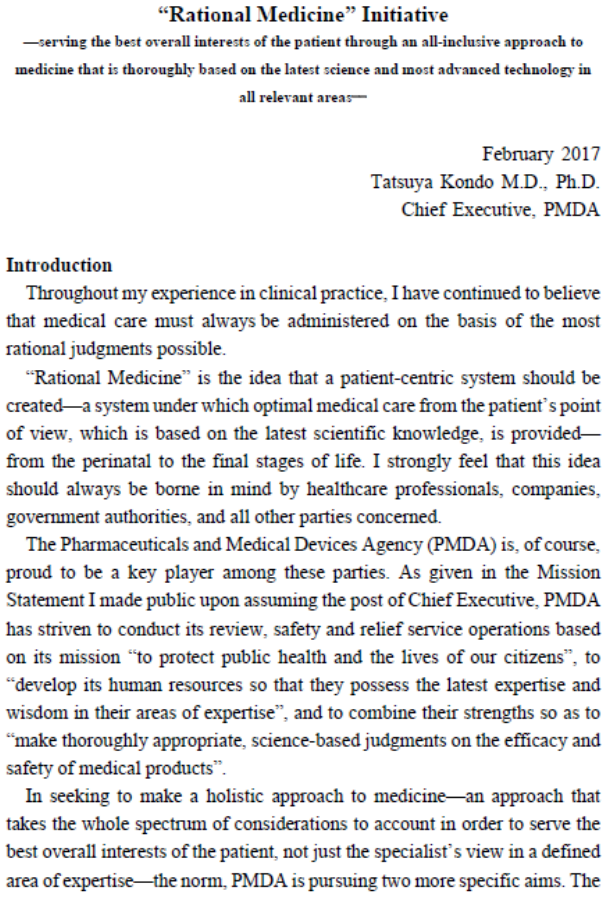
PMDA Philosophy (September, 2008)

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.

The “Rational Medicine” Initiative



“Rational Medicine” Initiative

—serving the best overall interests of the patient through an all-inclusive approach to medicine that is thoroughly based on the latest science and most advanced technology in all relevant areas—

February 2017
Tatsuya Kondo M.D., Ph.D.
Chief Executive, PMDA

Introduction

Throughout my experience in clinical practice, I have continued to believe that medical care must always be administered on the basis of the most rational judgments possible.

“Rational Medicine” is the idea that a patient-centric system should be created—a system under which optimal medical care from the patient’s point of view, which is based on the latest scientific knowledge, is provided—from the perinatal to the final stages of life. I strongly feel that this idea should always be borne in mind by healthcare professionals, companies, government authorities, and all other parties concerned.

The Pharmaceuticals and Medical Devices Agency (PMDA) is, of course, proud to be a key player among these parties. As given in the Mission Statement I made public upon assuming the post of Chief Executive, PMDA has striven to conduct its review, safety and relief service operations based on its mission “to protect public health and the lives of our citizens”, to “develop its human resources so that they possess the latest expertise and wisdom in their areas of expertise”, and to combine their strengths so as to “make thoroughly appropriate, science-based judgments on the efficacy and safety of medical products”.

In seeking to make a holistic approach to medicine—an approach that takes the whole spectrum of considerations to account in order to serve the best overall interests of the patient, not just the specialist’s view in a defined area of expertise—the norm, PMDA is pursuing two more specific aims. The

Published on Feb. 2017

“Rational Medicine“ Initiative
http://www.pmda.go.jp/english/about-pmda/0012.html

What is “Rational Medicine”?

A Patient-centric System

- From the perinatal to the final stages of life
- Based on the latest scientific knowledge
- Providing a holistic approach to medicine

All concerned parties, including healthcare professionals, medical companies, and government authorities must work hard to realize this idea.

Concept of the “Rational Medicine” Initiative

Develop new evidence of evaluation methods to evaluate quality, efficacy, and safety of medical products, based on discussions at the PMDA’s Science Board

- Provide our citizens with earlier access to medical products using innovative new technologies which have only just become available
- Provide optimal medical treatment as benefits of Rational Medicine

2. Regulatory science

- Establishment of the Regulatory Science Center in 2018

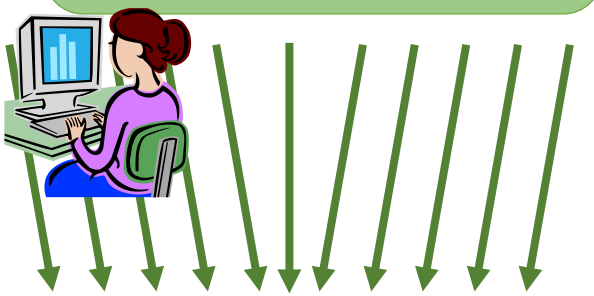
The advocator of Regulatory Science
Dr. Mitsuru Uchiyama
(Deputy Director General, National Institute of Health Sciences in Japan, at the time)

- Formulation of guidelines to encourage the optimal use of novel medical products
- Discussions by PMDA's Science Board to contribute to the introduction of innovative medical technologies

Ethical Science and Technology for the People and Society

Science → Technology

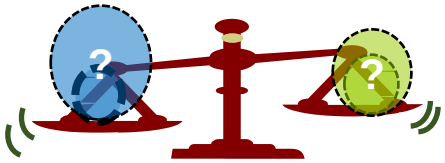
RS Microscopia
Science for Evaluation Method
(Quality, Efficacy, Safety)



DB

Knowledge Accumulation

RS Macroscopia
Science for Evaluation Method
(Comprehensive Judgment)



DB

Knowledge Accumulation

Deduction

RS Macroscopia

Technology for regulatory adaptation

Achievements from RS Engineering（e.g.）

- **Establish evaluation method for cutting-edge technology**
- **Respond to translational research**
- **Modelling & Simulation**
- **Develop guidelines**
- **Establish review standards**
- **Draft legislation etc.**

Evaluation Criteria for Countries with Advanced R&D Capabilities (Kondo, March 2017)

R&D/Innovation Capabilities - Basic Science

- Inventions (patents), discoveries, and overall creativity (Absolute Value > Relative Value)
- Number of Nobel Prizes, etc.
- Ethics – measures to prevent dishonest, improper, or negligent activities (Scientific Integrity)
- Research environment/culture – champions rationality and diverse viewpoints and actively motivates researchers to excel
- Tolerance – Preventing excessive and counter-productive pressure for results
- Adequate budget and effective fiscal management

Capacity to Assess R&D/Innovation - Regulatory Science

- Fairly evaluating novel ideas (all ideas considered and judged equally)
- Well-established Regulatory Science-based policies: "the science of evaluation methods" and "the science of rational regulations"

Ability to Advance New Products to Market – Translation and Commercialization

- Ensuring the reliability, morality, diligence, compliance competency, and business incentives of industry

Market Value

- Market size
- Perception of market trends
- Sense of certainty regarding future outlook

Science Board

Basic Research

Seeds of new drug / medical devices

Quality Tests → Non-clinical tests → Clinical Trial → Review → Approve → Post Marketing

Pharmaceutical Affairs Consultation on R&D Strategy	Clinical Trial Consultation	Review	Post Marketing Safety Measure

Offices of Review (Drugs & Medical Devices), Office of Safety

Office of Regulatory Science

Practical use

Innovative medical products

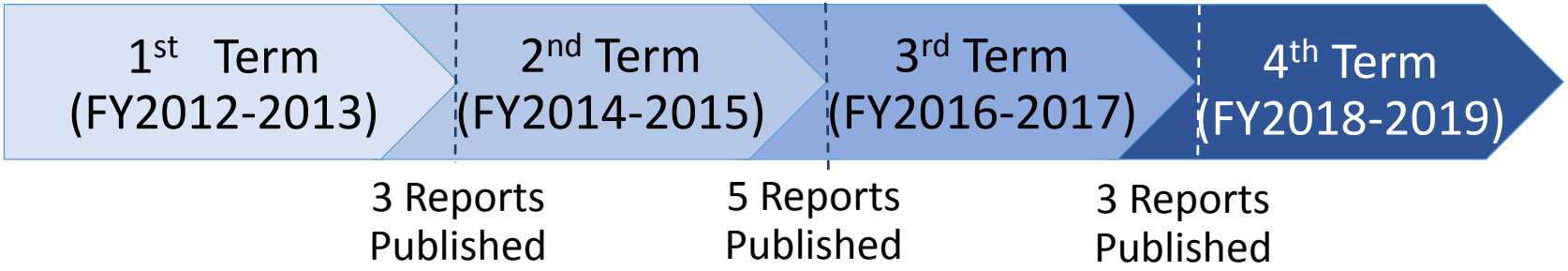
Science Board

Established in May 2012; to discuss how PMDA can better cope with products with advanced science & technology in each developmental stage (basic research, development support, product review, and PMS).

Board members — **Communication**

Academia (Knowledge of the Latest Innovative Technologies)

Science Board (Outcome Documents)



Major Outcome Reports

1st term (FY2012 - 2013)

- Current perspective on evaluation of tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells (iPSCs) and iPSCs as their starting materials (2013)

2nd term (FY2014 - 2015)

- Report on the use of non-clinical studies in the regulatory evaluation of oncology drugs (2016)

3rd term (FY2016 - 2017)

1. Clinical evaluation of rare cancer

- Discuss current situation of clinical evaluation and possible evaluation methods of disease areas in which efficacy of drug by comparative studies is difficult, such as in rare cancers, due to the number of patients is specifically limited among rare diseases (no more than 50,000 patients).

2. Facilitating R&D of Academia-originated Pharmaceuticals

- Sort out problems of bottleneck of drug discovery in academia, and discuss their solutions

3. Artificial Intelligence and its application in medical field

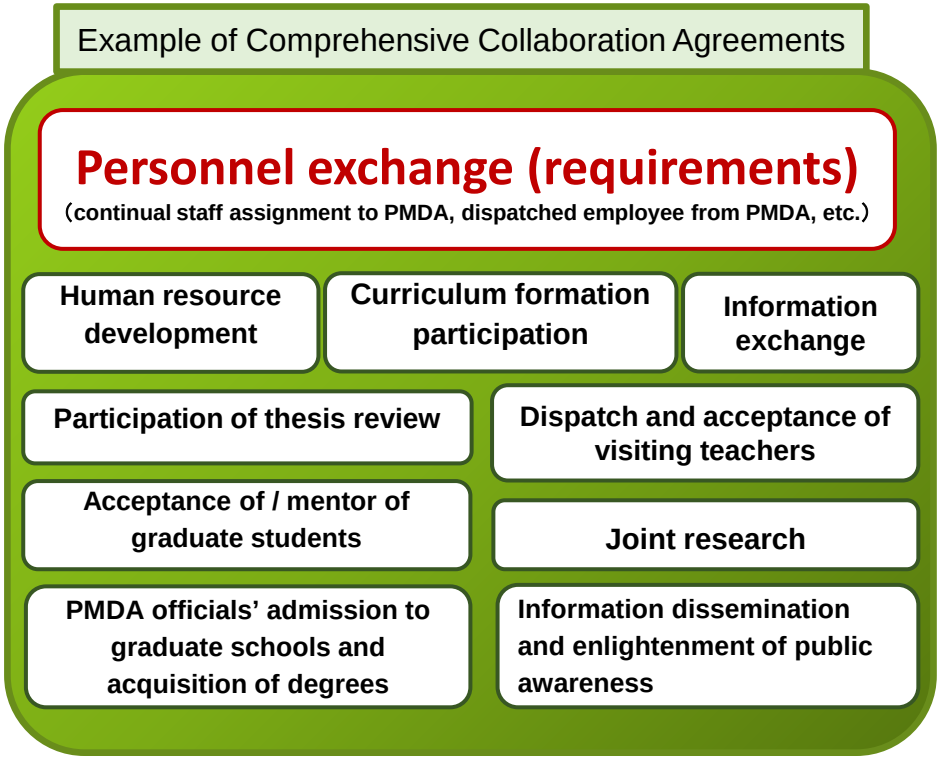
- Discuss “totally new elements of AI” by overviewing new technologies using AI and facilitate them into future medical device review and consultations.

→ Outcome documents English version will be published

PMDA Website (English)
http://www.pmda.go.jp/english/rs-sb-std/sb/outcome-docs/0001.html

Comprehensive Partnership Agreements

We collaborate with academia etc. and establish a system of promoting cooperation and collaboration with specialized agencies in a wide range of fields in order to promote regulatory science and contribute to improvement of medical standards in efficacy, safety, quality assurance and assurance of reliability.



- **Target Partner for Collaboration**
- **Personnel Exchange**
- **Theme of Collaboration**

Collaboration partners:

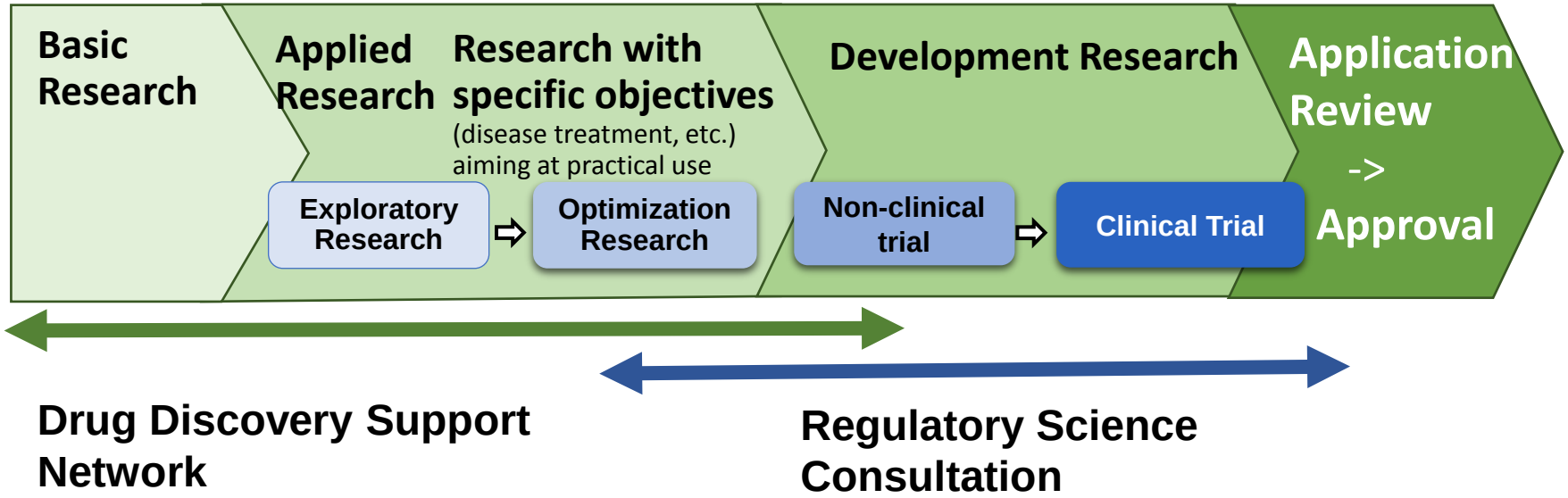
- National Cancer Center (February, 2016)
- Hiroshima University (March, 2016)
- Keio University (March, 2016)
- Tsukuba University (March, 2016)
- National Center for Neurological and Medical Research (July, 2016)
- Tohoku University (October, 2016)
- National Center for Global Health and Medicine (March,2017)
- National Cerebral and Cardiovascular Center (July, 2017)
- National Center for Chile Health and Development (January, 2018)

Partnership Agreement with Japan Agency for Medical Research and Development (AMED)

(August 19, 2015)

1. Utilizing Pharmaceutical Affairs Consultations on R&D Strategy
2. Support AMED to evaluate projects
3. Mutual cooperation to improve clinical research infrastructures
4. Sharing information

Seamless Activity from Research to Approval
- Collaboration PMDA & AMED -



Innovations

Innovation of Medical Products

Academia
Research institutions
Industry

Innovation of Regulatory Science

Regulatory Authorities

Regulatory Innovation

Stage	Agendas for PMDA	Activity
Development	○Assist promising new treatments to transition through the stages of product development ○Provide support system for innovation to be incorporated into practical use	→ Pharmaceutical Affairs Consultation on R&D Strategy (from July 2011) →Amended the RS General Consultation and RS Strategy Consultation (from April 2017)
Review	○Approaches to cutting-edge technologies (including iPS cells through collaborations with academia) ○Support early practical use of regenerative medical products ○Encourage the development innovative drugs, medical devices, and regenerative products in Japan first ○Improve efficiency of development through review process utilizing electric data and consultation based on accumulated data ○Promote early approval of medical devices in high-medical needs ○Promote early practical application of drugs with usefulness for serious diseases	→ Science Board (from May 2012) → Conditional Time-limited Authorization (from November 2014) → SAKIGAKE Designation System (from FY 2015) → Advanced review system (from October 2016) →Conditional Early Approval System for innovative medical devices (from July 2017) →Conditional Early Approval System for pharmaceuticals (from October 2017)
Post -marketing	○Utilize medical information database in practical use to develop more sophisticated safety measures such as comparison of side effect frequency, identification of side effects, and efficacy measurement for safety measures	→ MIHARI project (from FY 2009) MID-NET project (scheduled to be operated in FY 2018)

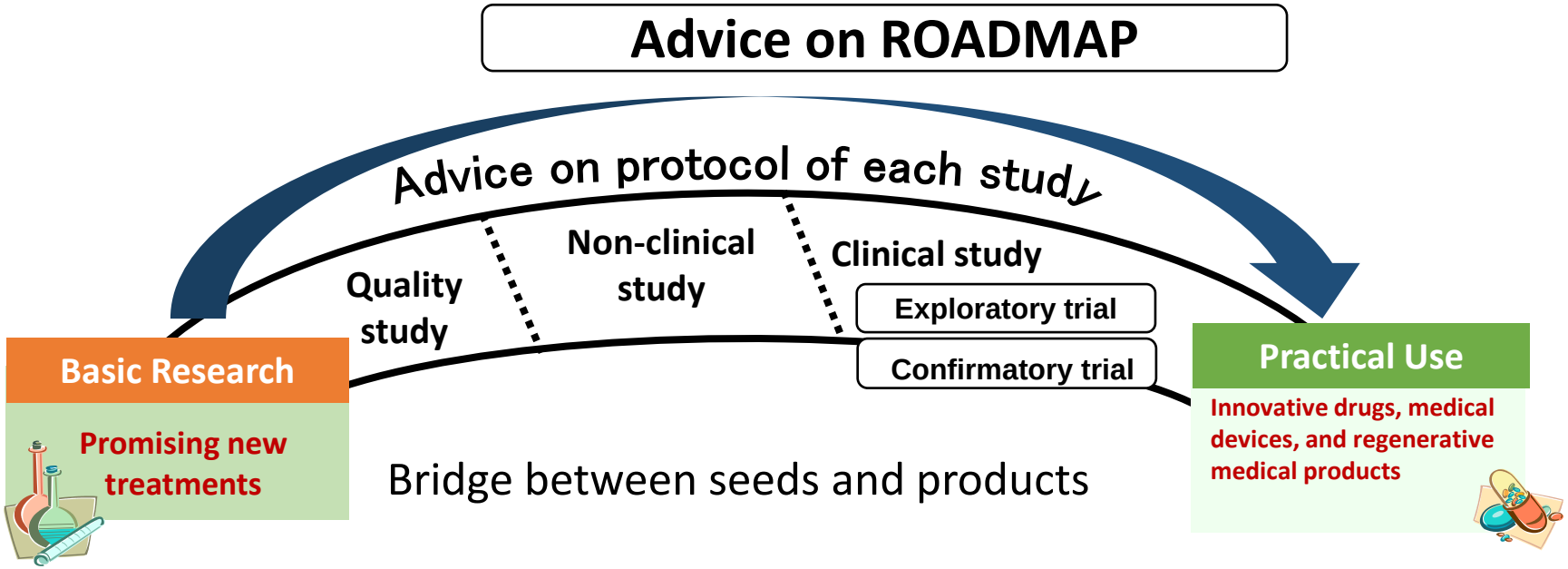
Reform PMDA to rational and efficient structure based on Regulatory Science
- to deliver more effective and safer drugs, medical devices, and regenerative medical products to clinical settings.

PMDA's activities toward innovation

- Support through Regulatory Science Consultation
- *SAKIGAKE* designation System
- Conditional Ealey Approval System for Pharmaceutical Products
- MID-NET® project

RS General and Strategy Consultations Offered by PMDA

- Facilitate development of medical products by academia by developing a more reliable ROADMAP.
- Contribute to the promotion of clinical trials led by academia.



*** In collaboration with AMED (Japan Agency for Medical Research and Development), PMDA will actively support the establishment of an exit strategy through Pharmaceutical Affairs Consultations on R&D Strategy.**

SAKIGAKE and Pharmaceutical Affairs Consultation on R&D Strategy (Concept)

Seeds

Pharmaceutical Affairs Consultation on R&D Strategy

Preliminary Review & Evaluation

1. Innovative medical products
2. For serious diseases
3. Development & NDA in Japan being world's first or simultaneous with other countries
4. Superior efficacy expected in non-clinical and early phase clinical studies

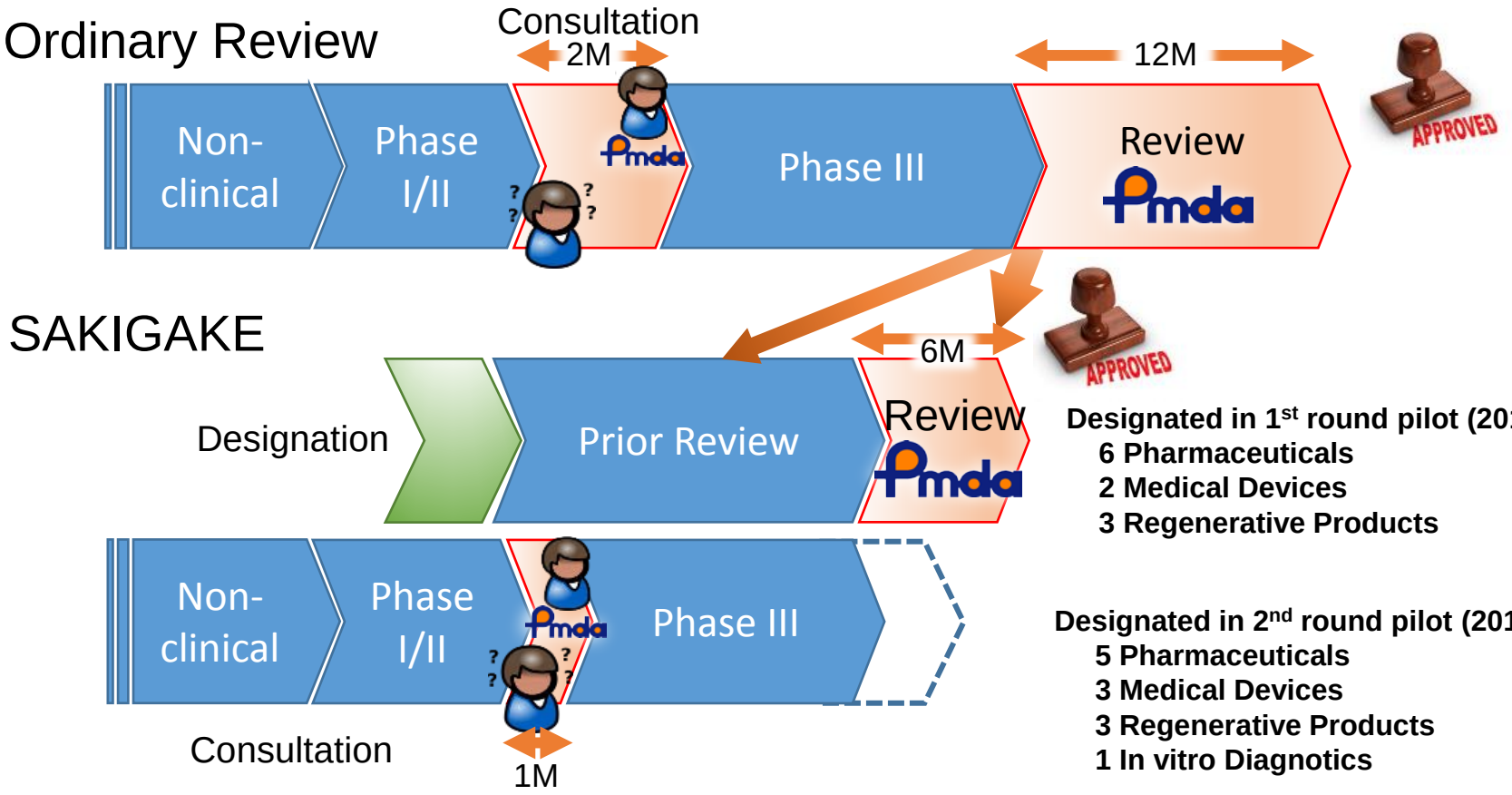
Ordinary Review Products

SAKIGAKE

Designated Products

***SAKIGAKE* process with priorities**

SAKIGAKE - General Timeframe



Designated in 1st round pilot (2016)
- **6 Pharmaceuticals**
- **2 Medical Devices**
- **3 Regenerative Products**

Designated in 2nd round pilot (2017)
- **5 Pharmaceuticals**
- **3 Medical Devices**
- **3 Regenerative Products**
- **1 In vitro Diagnotics**

3rd round pilot :
Currently open to application (Oct. 5 ~ Nov. 22, 2017)

Conditional Ealey Approval System for Pharmaceutical Products

To put drugs with high usefulness that are effective in treating serious diseases into practical use as early as possible

[Candidate product] -Drugs that treat serious diseases for which there are limited treatment options

-Drugs that it is difficult to conduct clinical trials or it takes long period because the number of patients is small

[Requirement] MHLW/PMDA needs to

- Confirm a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials at the time of submission
- Clarify management of conditions for approval such as imposing to conduct research which is necessary for reconfirmation of post-marketing efficacy and safety

Standard regulatory review process

Exploratory clinical trials → Confirmatory clinical trials → Application Review → Approval → ADR reports Post-marketing surveillance

Conditional Early Approval System

Exploratory clinical trials → Application Review → Approval → ADR reports Post-marketing surveillance

- Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.
- Shorten overall review times for priority review products

Setting conditions for approval (e.g.)

- **Reconfirmation of post-marketing efficacy and safety** (including using real-world data)
- **Setting requirements such as facility requirements if needed for proper use**

Drugs eligible for the system

Meet the all requirements from 1 to 4 listed below

Requirements for the present priority review*

1. Seriousness of indications
   - Diseases which have significant impact on lives (life-threatening diseases)
   - Progress of disease is irreversible and the disease has a significant impact on daily lives
   - Others

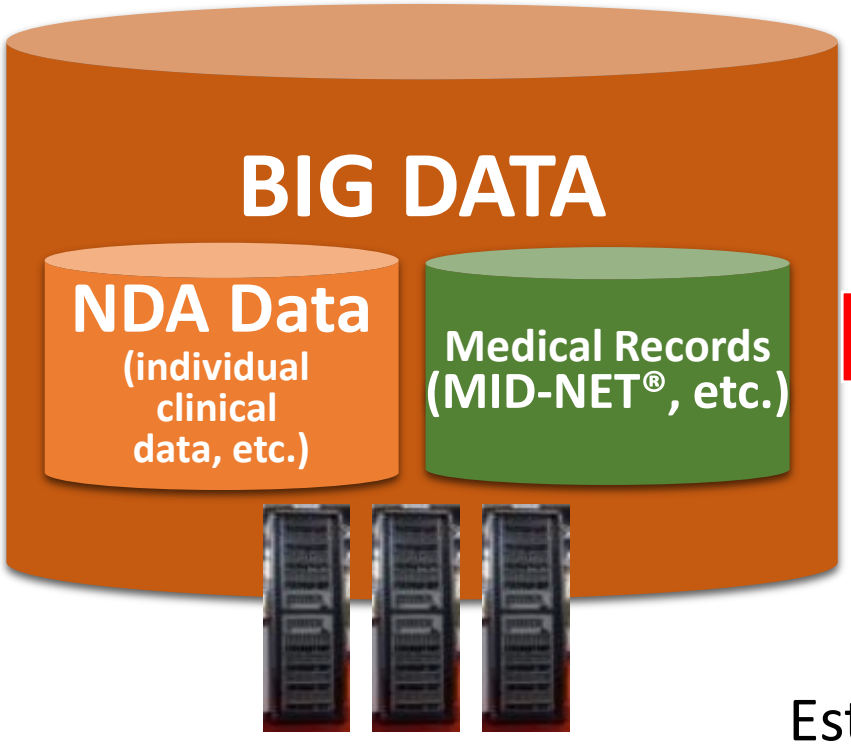
2. Medical usefulness
   - No existing remedies, preventive therapies or diagnostics
   - Medical usefulness is better than that of existing remedies, preventive therapies or diagnostics in terms of efficacy, safety, and patient's physical and mental burden

3. Being difficult to conduct confirmatory clinical trials or considered to take considerable time to complete trials because of a limited number of patients

4. Considered to have of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials

* "Handling of priority review and others" (Notification 0122 No.12 issued by the Director of Pharmaceutical Safety and Environmental Health Bureau, Notification 0122 No.2 issued by the Director of Medical Device Evaluation Division, January 22, 2016)

Towards “Regulatory Science Center”
～Review/Consultation/Safety for the Next-Level Science～

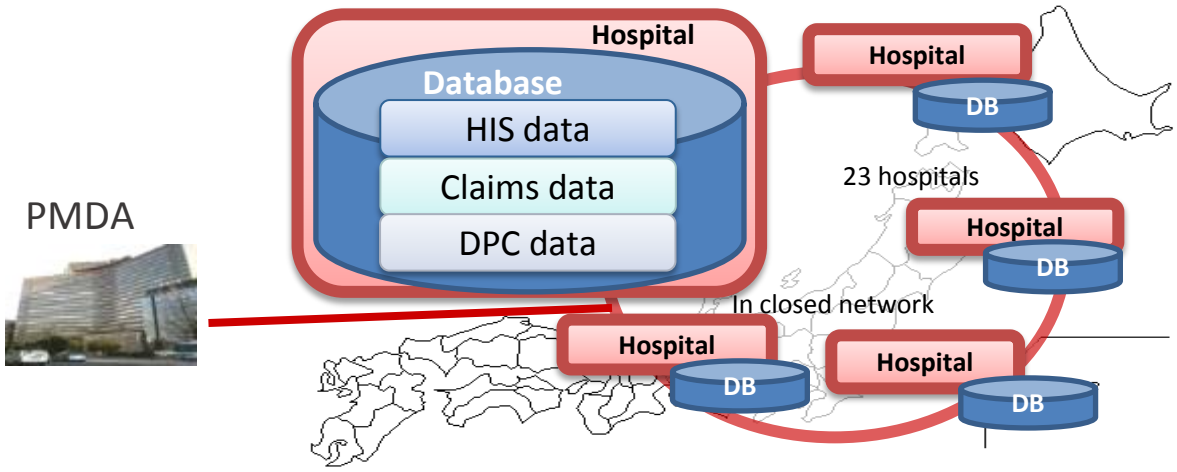


- Sophisticated NDA review and Consultations
- Cross-Product Analysis
- Risk Evaluation using Pharmacoepidemiological data
- Utilization of Real World Data to pre-/post-marketing evaluations

Established April 2018

MID-NET® Project

- The Medical Information Database Network is a Japanese system enabling real-time assessment of drug safety (currently covering 4m patients).



MID-NET is a fully integrated, high-quality, real-time EMR database

3. International Partnerships

- Proactive engagement in activities for international regulatory coordination
- Providing training on global study and regulatory oversight to foreign regulatory authorities
  (*e.g., through the Asia training center, etc.)
- Organized the “International Summit of Heads of Medicines Agencies” and other related symposia in Japan

International Cooperation

Examples of Current Global Activities

Summit | ICH | IMDRF | PIC/S | ICDRA

APEC LSIF RHSC | PDG | IGDRP | ICMRA

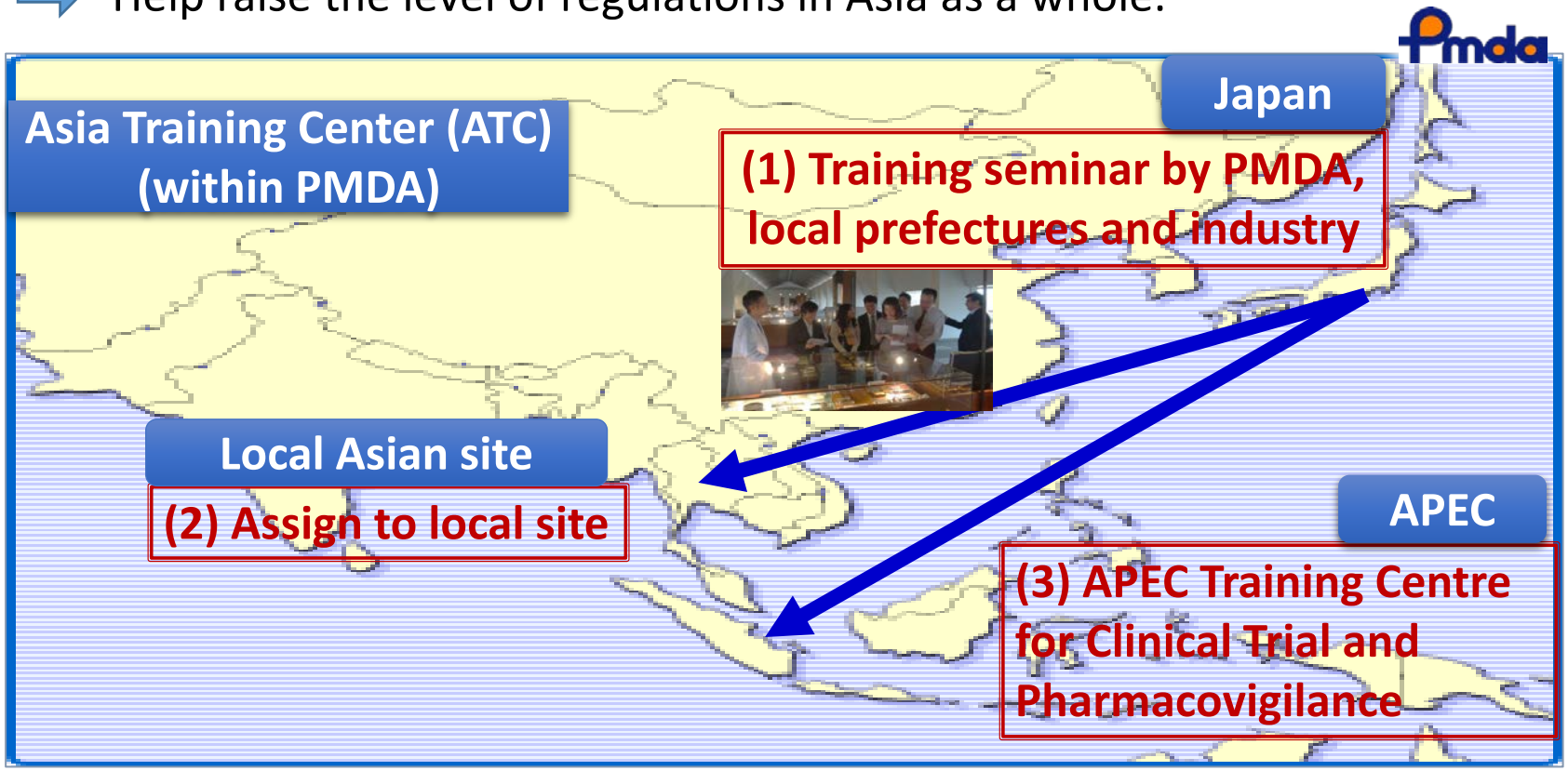
and more…

Abbreviation	Official Name
Summit	International Summit of Heads of Medicines Regulatory Agencies
ICH	International Council on Harmonization
IMDRF	International Medical Device Regulators Forum
PIC/S	Pharmaceutical Inspection Co-operation Scheme
ICDRA	International Conference of Drug Regulatory Authorities
APEC LSIF RHSC	APEC Life Sciences Innovation Forum Regulatory Harmonization Steering Committee
OECD MAD	OECD Mutual Acceptance of Data
PDG	Pharmacopoeial Discussion Group
IGDRP	International Generic Drug Regulators Program
ICMRA	International Coalition of Medicines Regulatory Authorities

Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (Est. April 2016)

- Plan, design and coordinate training for Asian regulatory authority staff
- Provide **training opportunities** including **on-site training**

➡ Help raise the level of regulations in Asia as a whole.



PMDA Asia Training Center's Program

MRCT/GCP Inspection Workshop
APEC Pilot CoE Program, Jan. 23-26, 2017

32 participants from 14 Economies

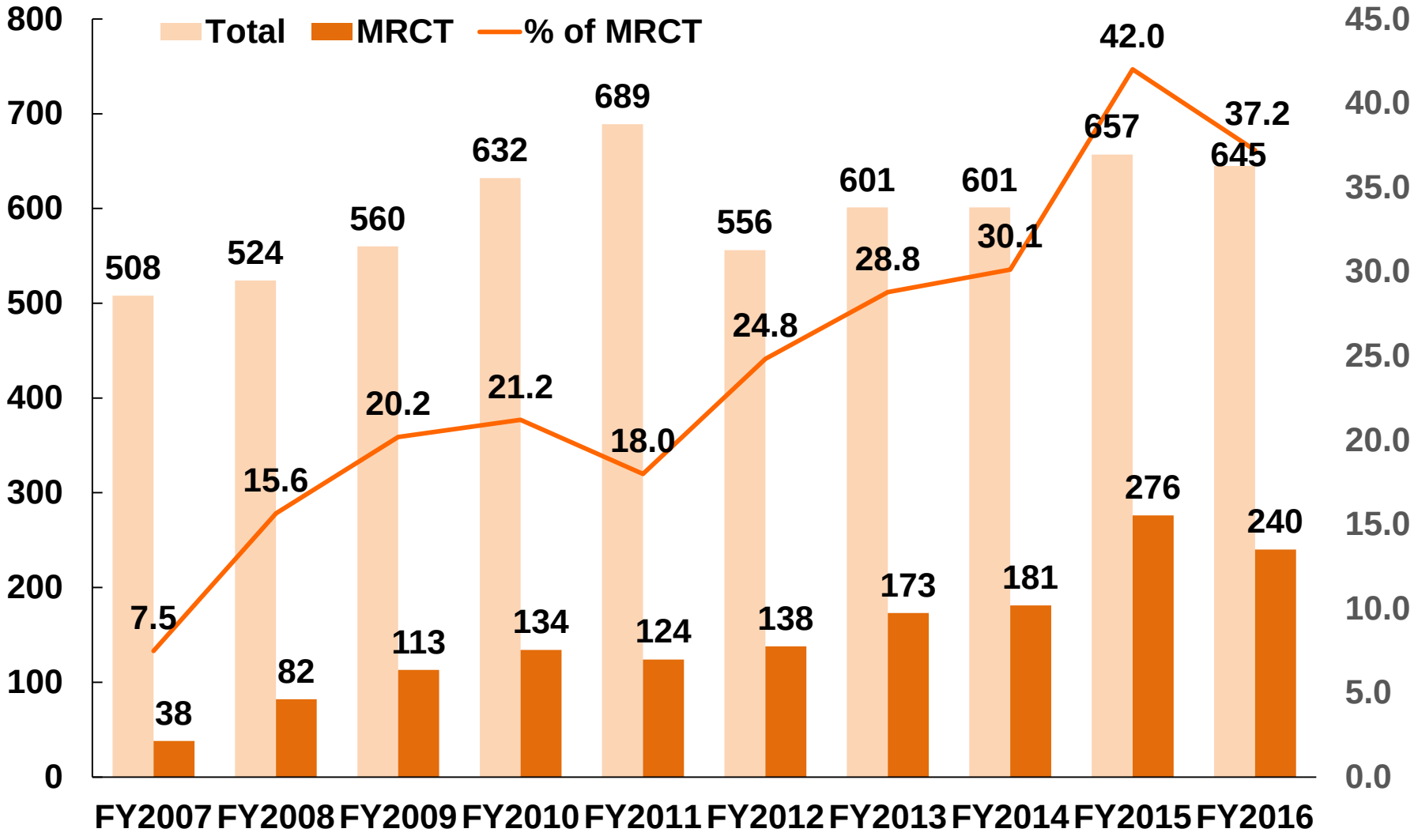
Malaysia, Philippines, Chinese Taipei, Indonesia, Peru, Brazil, Myanmar, Sri Lanka, Tanzania, Thailand, China, Mexico, Nepal, Papua New Guinea

Pharmacovigilance Workshop
APEC Pilot CoE Program, Feb. 6-9, 2017

28 participants from 15 Economies

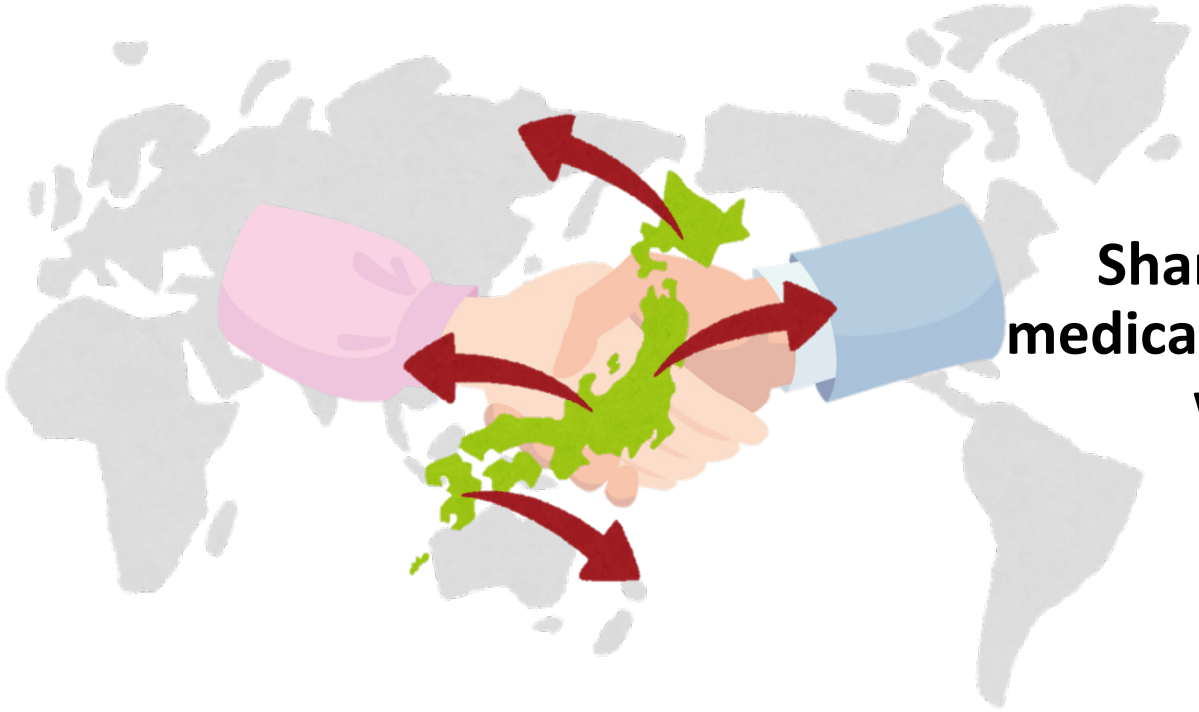
Chile, China, India, Indonesia, Korea, Malaysia, Myanmar, Nepal, Peru, Philippine, Poland, Singapore, Taiwan, Thailand

Trends of MRCT-related Clinical Trial Notifications in Japan



Innovative Product/Regulation from Japan to the World

- Facilitating the practical adoption of innovative products
- Expedite patient access to highly innovative products worldwide



Sharing potential new medical products from Japan with the world

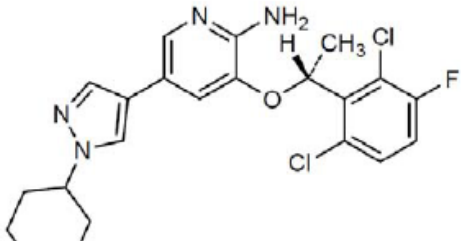
English translation of the review reports are publicly available at PMDA website

Review Report

February 20, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Xalkori Capsules 200 mg and 250 mg
[Non-proprietary name]	Crizotinib
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	March 31, 2011
[Dosage form/Strength]	A capsule containing 200 or 250 mg Crizotinib
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html

12th International Summit of Heads of Medicines Regulatory Agencies and related symposium in Japan (Major Results)

1. Major achievement during 12th International Summit of Heads of Medicines Regulatory Agencies

(1) Promotion of International regulatory harmonization for regenerative products

・Promoting international harmonization for regenerative medical products by utilizing existing global framework at each agency

(2) Use of real-world data (RWD)

・Promoting discussion among agencies (e.g. by holding international symposium) for the purpose of effectively coping with various technical issues, which each agency faces in use of RWD for pharmaceutical regulation, by gathering findings from agencies

(3) Integration of International Summit of Heads of Medicines Regulatory Agencies and ICMRA (from the next meeting) ***Next year's meeting will be held in the US***

2. Major achievements at the ICMRA Summit

Agreed on initiation of "innovation project" (early regulatory activities on innovative technologies) based on the action plan proposed by Japan (Agreed on three activity areas)

・Among these activity areas, Japan leads "methodology analysis of horizon scanning* in each country"

* Horizon scanning・・・an effort to explore upcoming innovative technology comprehensively, access its effect on regulation, and serve with making suitable regulation to innovative technology

International Summit of the Heads of Medicines Regulatory Agencies (open symposium)

- **Held to report the outcome of the Summit/ICMRA meeting the next day**
- **First attempt at an open symposium linked to the summit**

- Date: Oct. 27 2017 (Fri) (10:00-17:45)
- Location: Kyoto International Conference Center – Main hall
- Hosted by: MHLW, PMDA, Kyoto prefecture, DIA Japan
- Sponsor: Japan Pharmaceutical Manufacturers Association (JPMA)
  The Japan Federation of Medical Devices Associations (JFMDA)
- Main contents:

1. Innovative Technologies and their Commercialization

- A lecture by Shinya Yamanaka, MD, PhD (Recipient of the 2012 Nobel Prize in Physiology or Medicine): Development of iPS cells)
- Lectures on actions taken by the pharmaceutical/medical device industry

  Yoshihiko Hatanaka, President, JPMA

  Masaya Watanabe, Chairman, JFMDA

2. Measures Taken and Challenges Faced by Pharmaceutical Regulatory Authorities

-Mainly Based on the Results of the 12th Summit and ICMRA Meeting

- Lecture by core members of the Summit/ICMRA
  Ian Hudson, Chief Executive (MHRA)
  Guido Rasi, MD, Executive Director (EMA)

PMDA will continue to contribute

- To the product development throughout the product lifecycle
- To the health and healthy life expectancy of the people in Japan, and globally
- To the world through close communication with the Science Board, academia, overseas regulatory authorities

PMDA Initiatives to advance Rational Medicine

1. Promoting innovation by improving the quality and rationality of review process
2. Further promoting regulatory science
3. Increasing the sophistication of safety measures through the use of real-world data
4. Further enhancing international partnerships

PMDA is devoting its utmost efforts towards the realization of Rational Medicine