Regulatory Update from MHLW/PMDA

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1 December, 2017

Today's Agenda

1. Organizational Updates

2. Update of Recent Topics

3. Future Challenge

4. International Activities

   PMDA Asia Training Center

1. Organizational Updates

Regulatory Authorities in JAPAN

MHLW

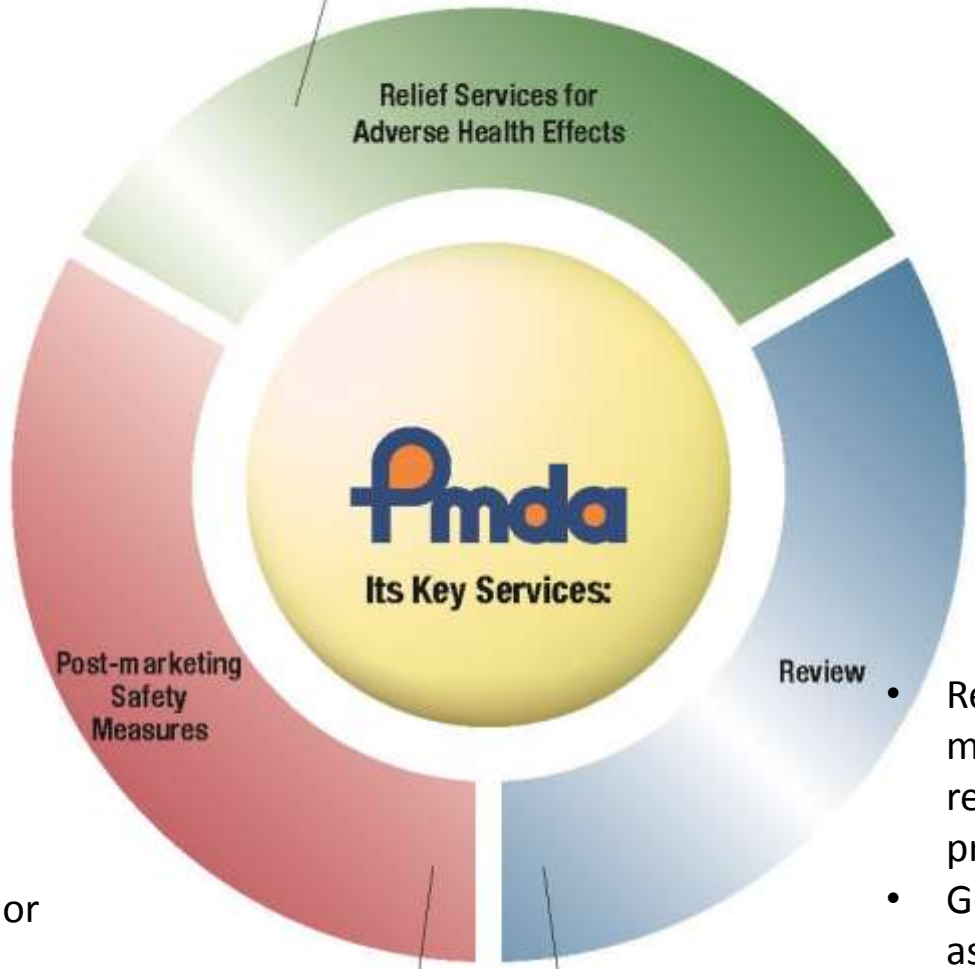
- Final Authorization of applications
- Publishing Guidelines
- Advisory committee
- Supervising PMDA Activities

PMDA

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

Major Services of PMDA

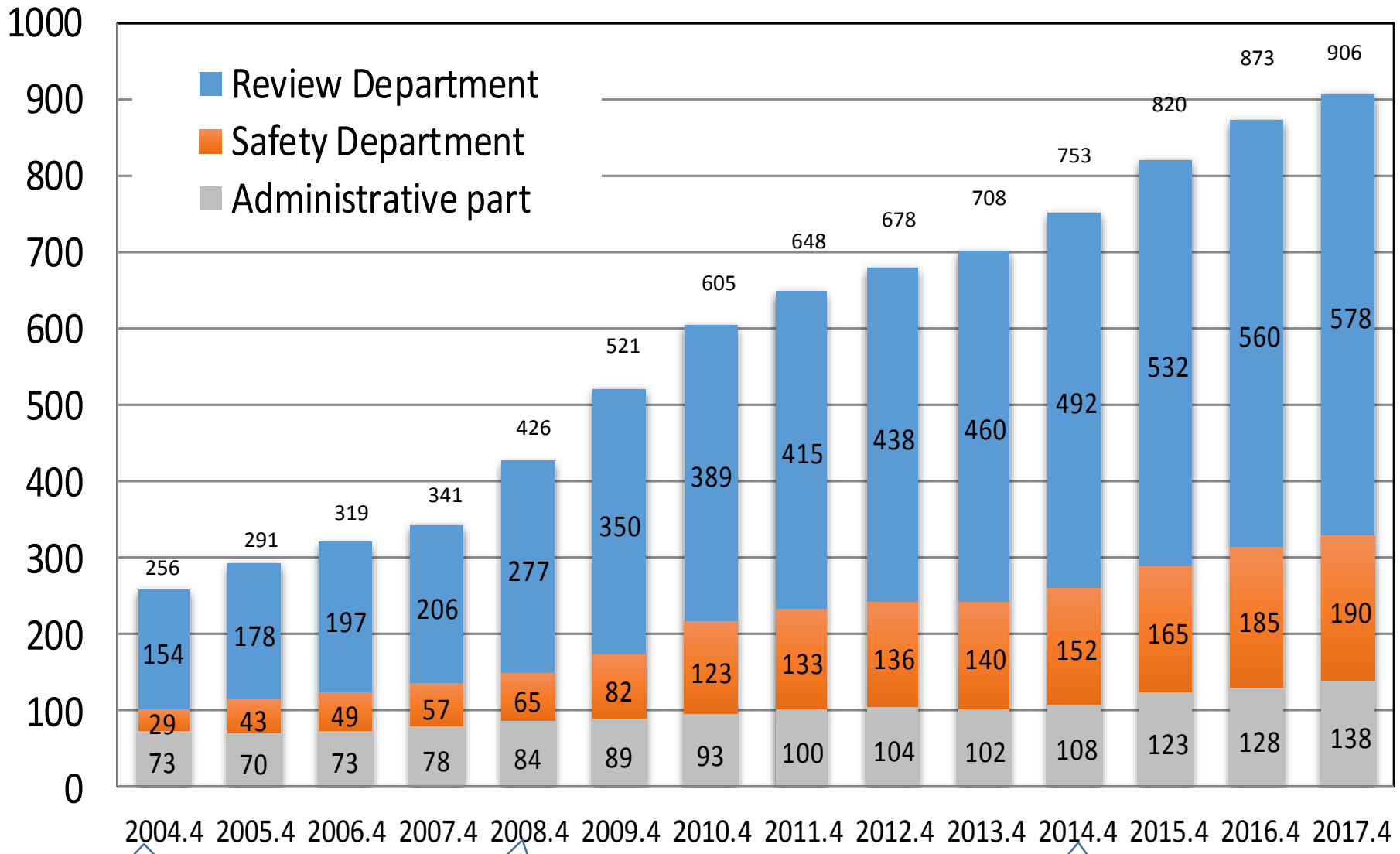
- Relief services for adverse drug reactions and for infections acquired through biological products



- Acceptance and web-based publication of submitted labeling information (package inserts)
- Collection and organization of safety information from authorization holders or medical institutions

- Regulatory review of drugs, medical devices and regenerative medical products
- GLP/GCP/GPSP compliance assessments
- GMP/QMS/GCTP inspections

PMDA's Staff Size



Established PMDA from 4 organization

Dr Kondo became Chief Executive

PMDA become the earliest review regulator (by CIRS)

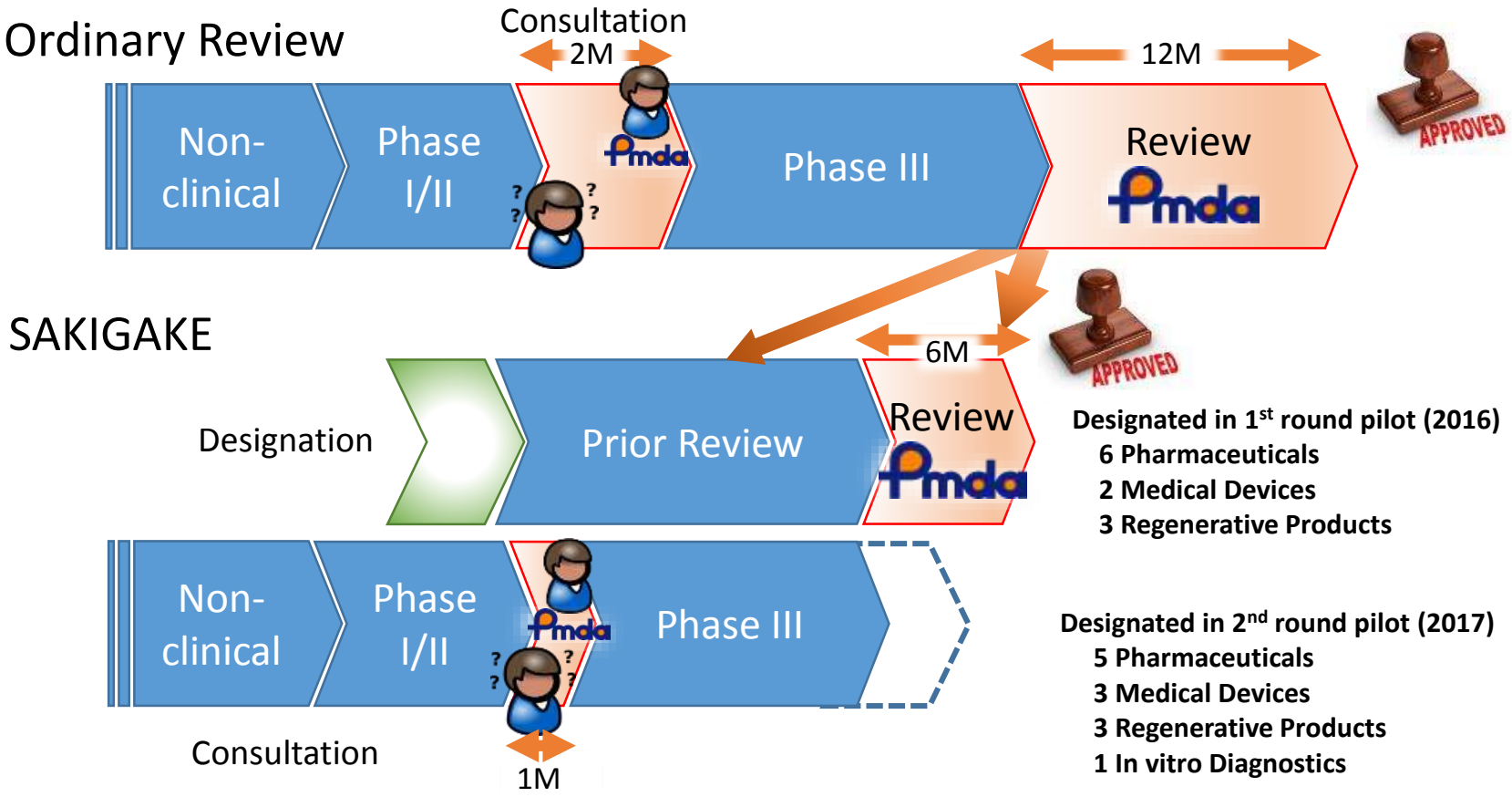
2. Update of Recent Topics

Accelerated review systems

Summary of the Accelerated review system

Type	Area	Designation requirement
Expedited review	Any product categories	Designation is not needed Needed to expedite the review
Priority review		Designation is needed 1. Orphan 2. Apparent improvement of medical care and for severe diseases
SAKIGAKE (Forerunner designation)		Designation is needed • Innovative medical products • For serious diseases • Development & NDA in Japan ・being world's first or simultaneous with other countries • Prominent effectiveness expected on non-clinical and early phase clinical studies
Conditional Early Approval	Drugs	Designation is not needed Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.
	Medical Devices	Designation is not needed - MDs in high clinical needs - Balancing the pre- and post-market requirements
Conditional and Time-limited Authorization	Regenerative Medical Products	Designation is not needed

SAKIGAKE - General Timeframe



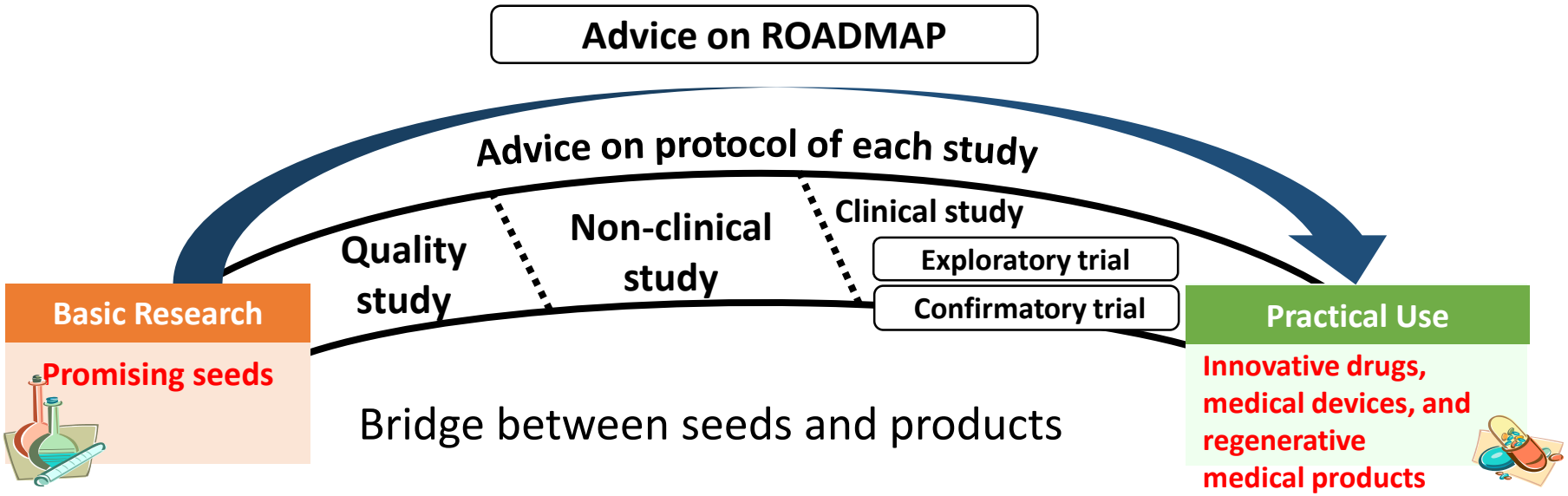
Designated in 1st round pilot (2016)
- **6 Pharmaceuticals**
- **2 Medical Devices**
- **3 Regenerative Products**

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

3rd round pilot : Oct. 5 ~ Nov. 22, 2017

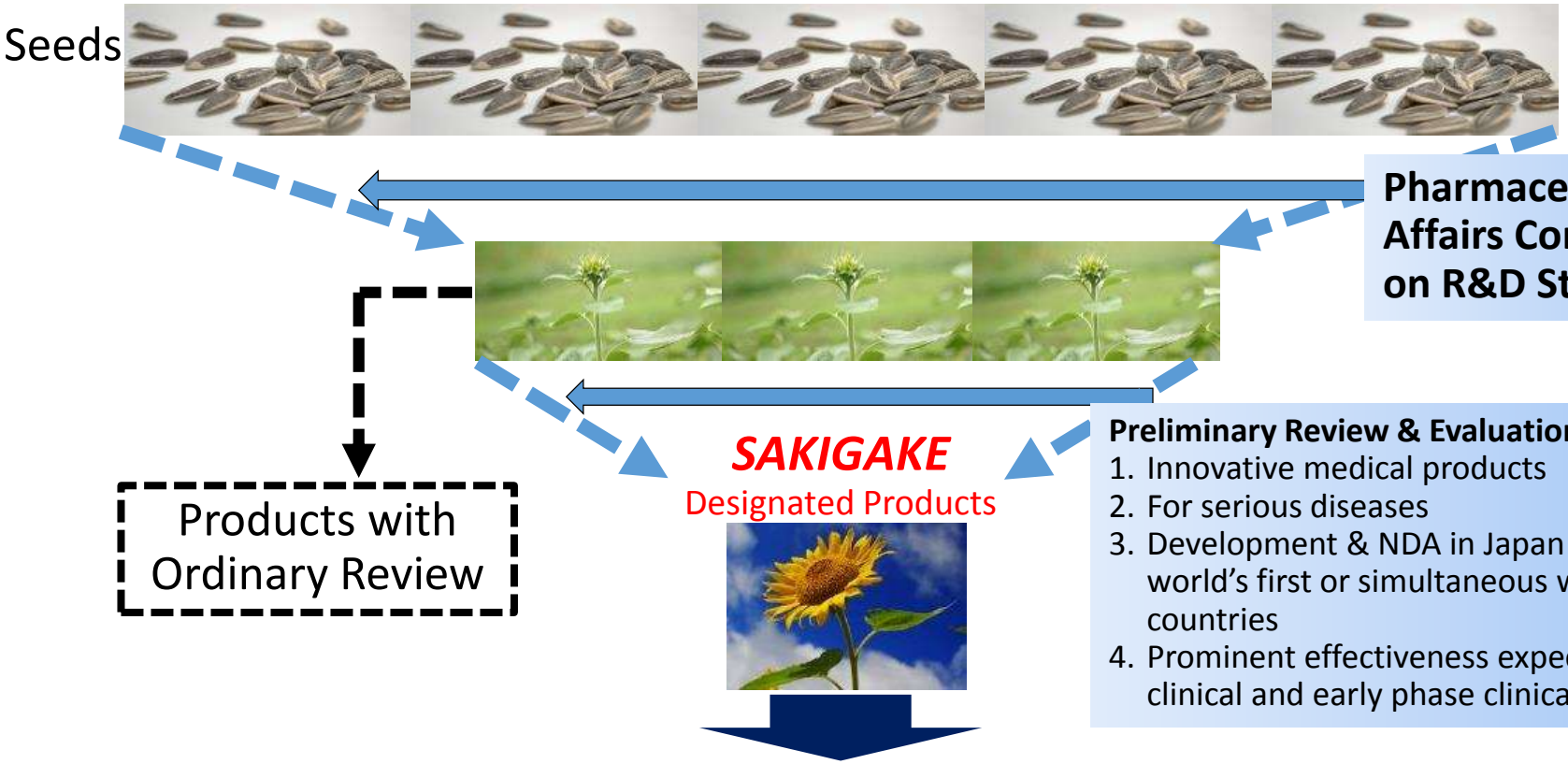
Enhancement of Pharmaceutical Affairs Consultation on R&D Strategy

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



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

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



***SAKIGAKE* process with priorities**

SAKIGAKE vs Breakthrough therapy (US) vs PRIority MEdicines (EU)

	SAKIGAKE	Breakthrough therapy	PRIority MEdicines (PRIME)
Establishment	April 2015 (trial)	July 2012	March 2016
Designation Criteria	• New mode of action • Life threatening or no radical treatment • Prominent efficacy • First NDA in the world	• Serious condition • Substantial improvement on clinically significant endpoint(s)	• Unmet medical need • Potential to address to unmet medical need
Project Manager	• Review partner (Concierge)	• Senior manager • Cross-disciplinary project lead	• Dedicated contact point • Appointment of rapporteur
Consultation	• Priority consultation	• Intensive guidance on an efficient drug development program	• kick-off meeting about the overall development plan and regulatory strategy • Scientific advice at key development milestones
Rolling review	• Eligible (SAKIGAKE comprehensive assessment Consultation)	• Eligible	—
Priority review	• Review within 6 months (shorter than 9 months in ordinal priority review)	• Not automatically designated	• Eligible (Accelerated assessment)
Other	• Relation with drug pricing		

Conditional Early Approval System for Drugs

<Implemented on 20 Oct. 2017>

"Conditional Early Approval System" is a system to put highly useful and effective drugs for treating serious diseases into practical use as early as possible.

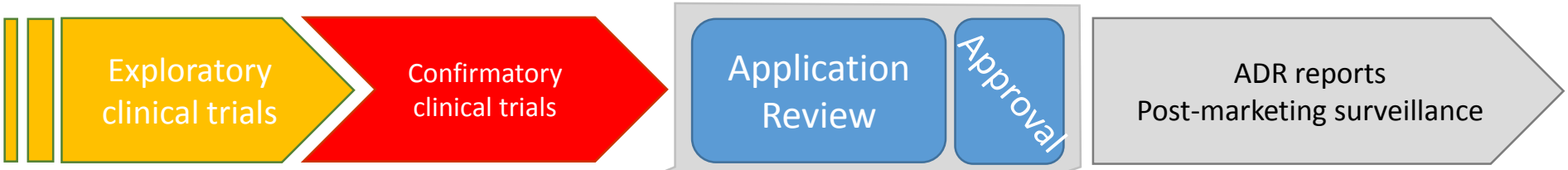
[Candidate product] -Drugs that treat serious diseases for which there are limited treatment options and,

-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



Conditional Early Approval System

- 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

<u>Setting conditions for approval</u>
(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

Conditional Early Approval System for Drugs

Drugs eligible for the system should 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) or
   - 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 or,
   - 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)

Conditional Early Approval System for Innovative MDs

<Implemented on 31 July 2017>

Accelerate approval of MDs in high clinical needs by balancing the pre- and post-market requirements, based on the lifecycle management of the MDs.

■ Present

Long period

Collection of clinical data → Review → Ap pro val → Market - Use

■ Conditional Early Approval for Innovative MDs

Collection of clinical data → Review → App rov al → Market - Use → Partial change application (e.g. expanded indication, etc.)

Cooperation with academia

Cooperation with academia

Planning **Post-market Risk Management**

Post-market Risk Management Plan (draft)

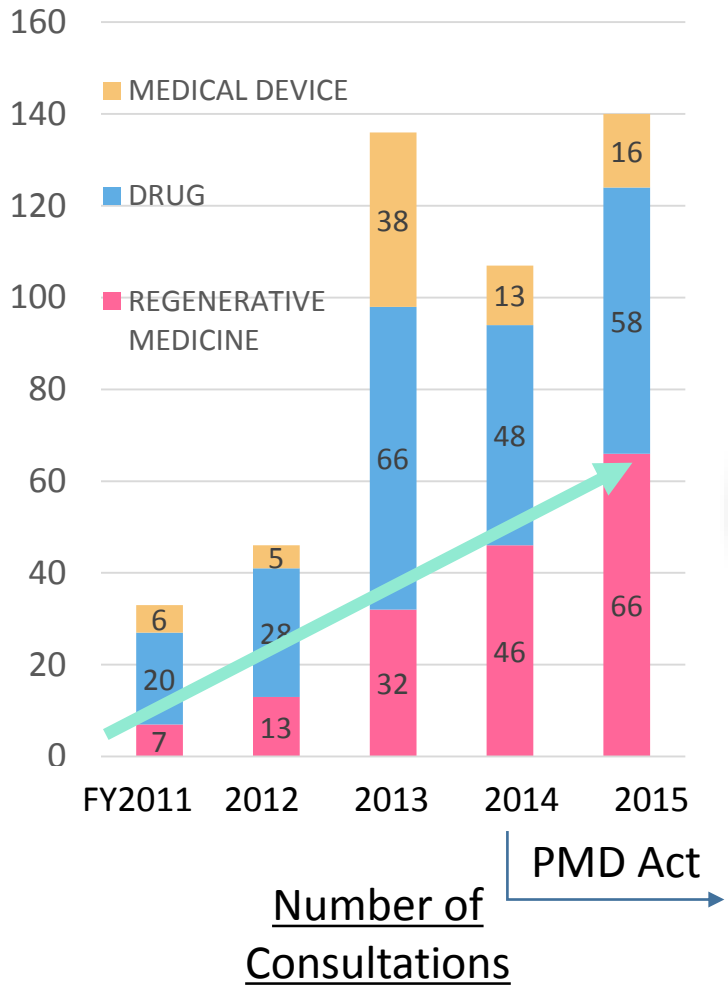
- Implementation of **Post-market Risk Management Measures**
- Data collection to confirm use results, long-term performance

Conditional and Time-limited Authorization of Regenerative Medical Products

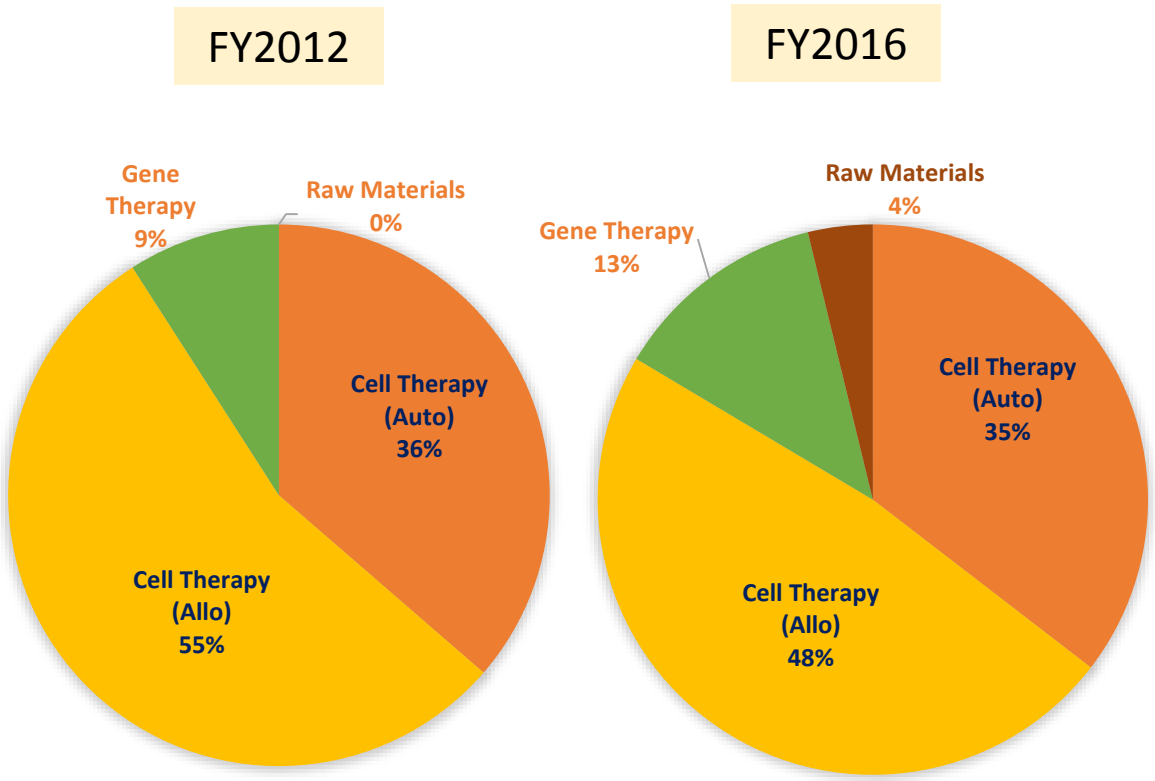
Conventional Regulatory Approval Process

Regulatory System that Facilitate Early Patient Access

Pharmaceutical Affairs Consultation on R&D Strategy on Regenerative Medical Products



Number of Consultations



Breakdown of Consultations on Regenerative Medical Products

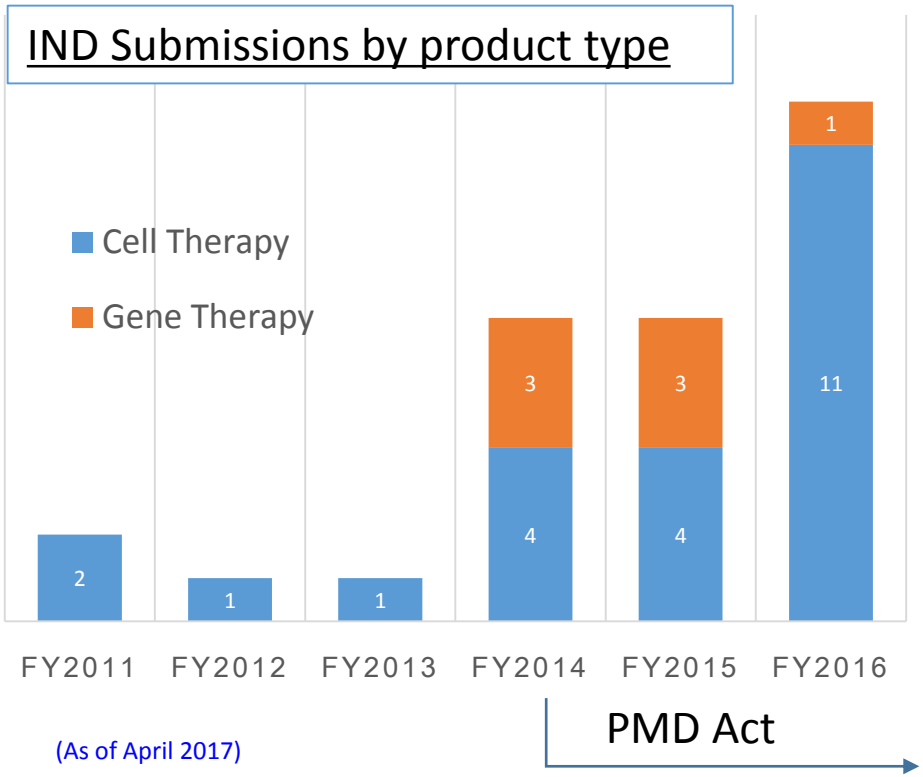
-IND Submission of Regenerative Medical Products- (Clinical Trial Notification)

- Timing

  The first notifications; 31 days before (others; 2 weeks before)

IND Submissions by study type

Study type	Cell therapy	Gene therapy
Sponsor	27	9
Investigator	19	6
Total IND	46	15



(As of April 2017)

Points to Considers for the Evaluation of Regenerative Medical Products

- Cultured human autologous epidermal cell sheet for epidermolysis bullosa (draft)
- Cultured cartilage and products derived from somatic stem cells for articular cartilage repair (2016)
- Products derived from allogeneic iPS cells for articular cartilage repair (2016)
- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic iPS cells-derived retinal pigment epithelial cells (2014)
- Autologous iPS cells-derived retinal pigment epithelial cells (2013)
- Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010)
- Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

2. Update of Recent Topics

Update on Medical Device

Single-use Medical Device (SUD) Reprocessing

■ Japan has introduced SUD Reprocessing from July 2017

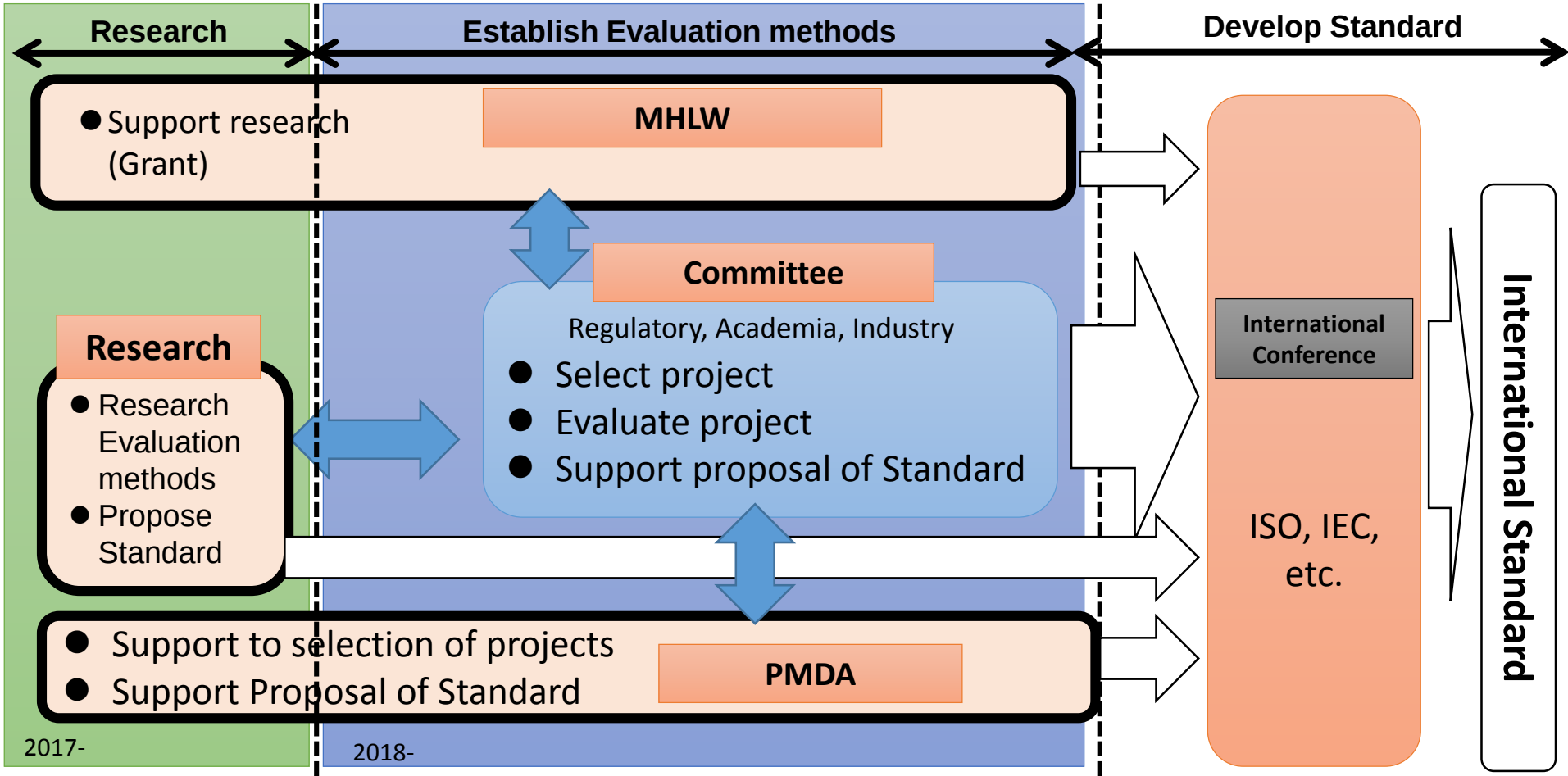
■ Reprocessors needs MAH
■ Reprocessed SUD needs Approval as R-SUD
■ Reprocessors take responsibility for R-SUD's safety issue

Facilitate Development of International Standard for Evaluation method for Innovative MDs

To Enable early introduction of innovative MDs all over the world

I. Facilitate development of evaluation method (Practical, non-clinical, properly predict effectiveness and safety)

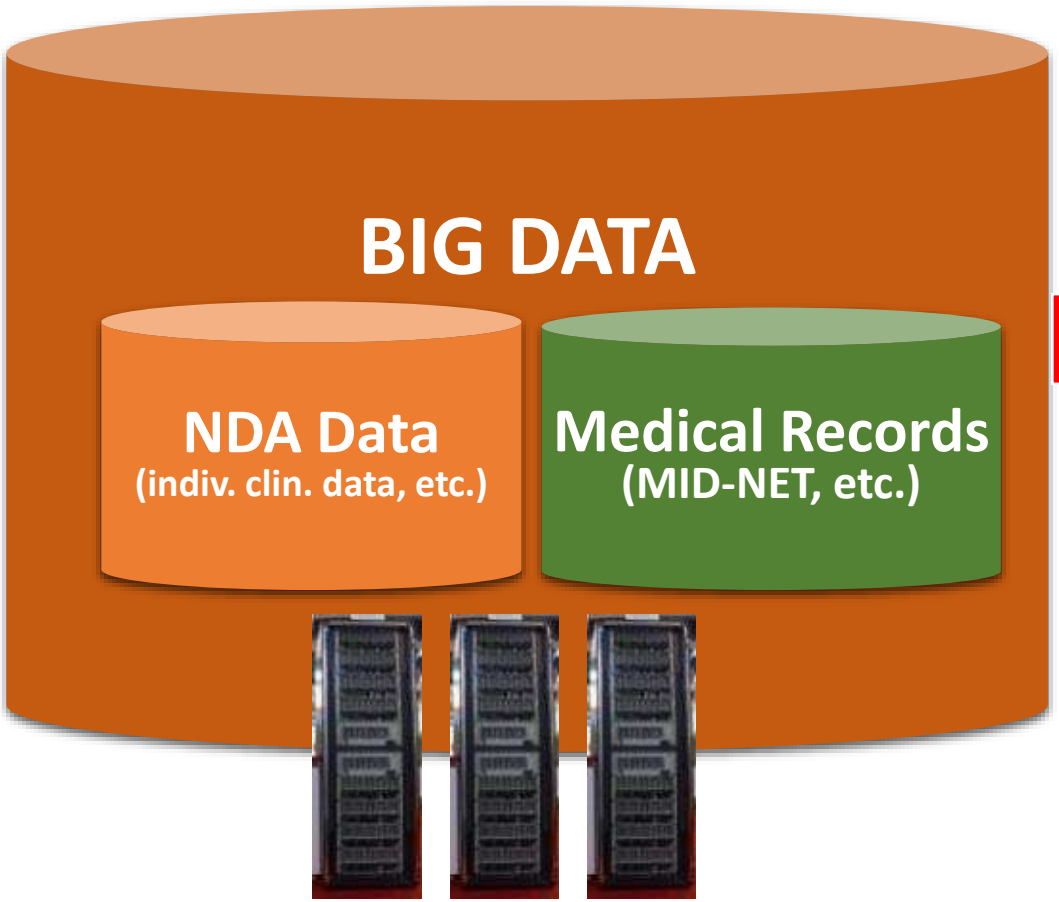
II. Facilitate development of such evaluation method into International Standard



3. Future Challenge

Towards “Regulatory Science Center”

Review/Consultation/Safety for the Next-Level Science

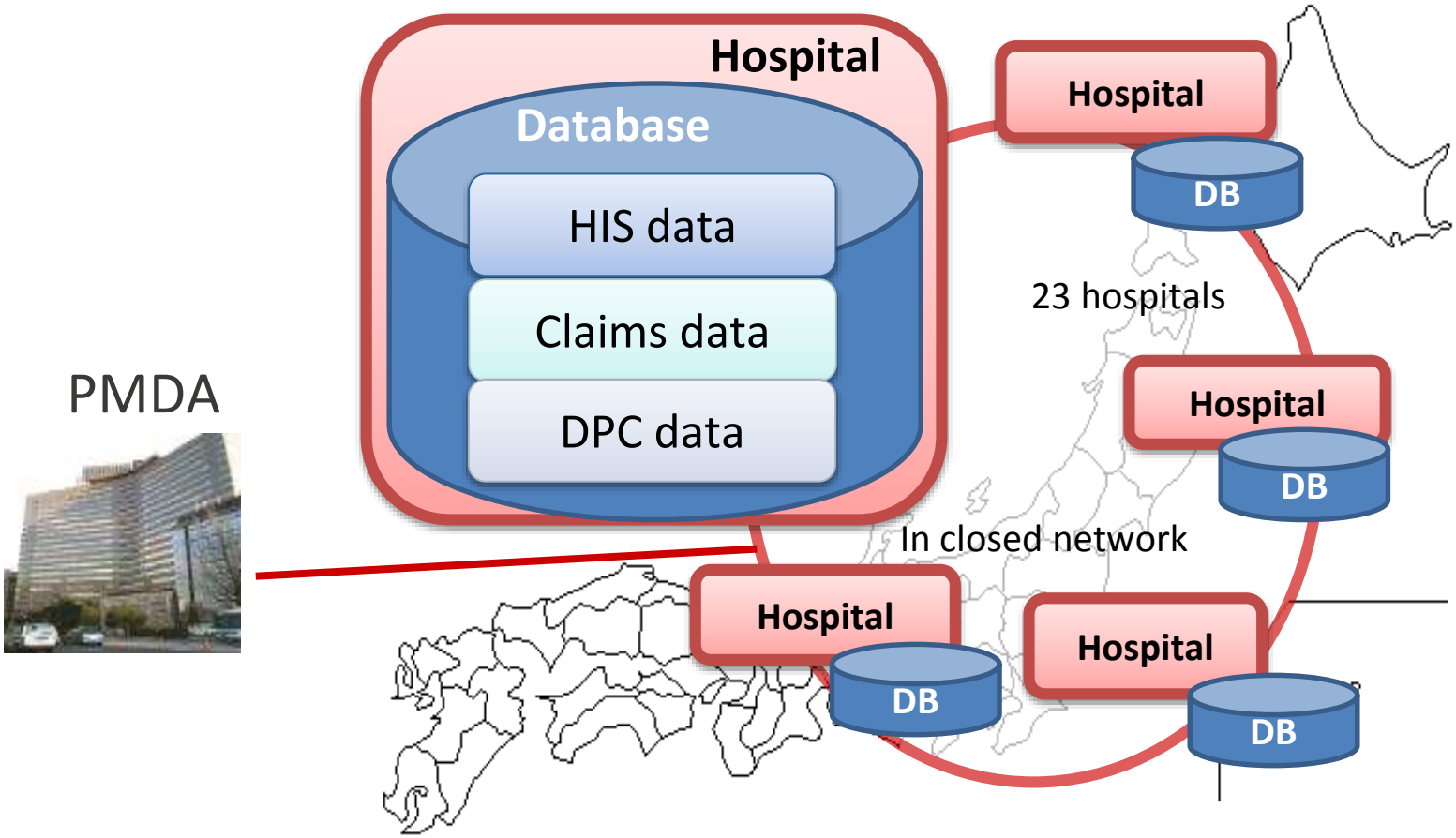


- **Sophisticated NDA review and Consultation**
- **Cross-Products Analysis**
- **Risk Evaluation with Pharmaco-epidemiological data**
- **Utilization of Real World Data to pre/post market evaluation**

Expected establishment:
From April, 2018

MID-NET® Project

- The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients).



An integrated real-time EMRs database with high quality

Clinical Innovation Network (CIN)

National Institute of Biomedical Innovation, Health and Nutrition

Network Hospitals in Japan

Hospitals in Asia

- Acceleration of global clinical trials
- Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs
- Development of registries for patients with intractable diseases
- Rare diseases drug development Gateway

National Center
Clinical Research Core Hospital

- Development of disease registries
- Foundation of a clinical trial consortium and acceleration of clinical research and clinical trials
- Advancement of clinical studies and clinical trials of regenerative medicine
- Establishment of Clinical Trial Cooperation Office

Participation in the consortium

Data provision (with consideration to protect personal information)

Industry

- Utilize data in clinical studies
- Perform speedy and cost-effective clinical trials

Activation of clinical development in Japan
Attracting foreign manufacturers

- **Personnel exchanges**
- **Post-marketing safety measures**

- **Methodological research to utilize disease registry in clinical trial (Regulatory Science)**

- **Support for R&D**
- **Human resource cultivation in the field of clinical research and clinical trial**

PMDA — Jurisdiction: MHLW

AMED — Jurisdiction: CAO, MEXT, MHLW, METI

CIN Promotion Conference

Promotes CIN project by stakeholders composed by National Centers, Industries and Japanese Government

Promotion of Regulatory Science

Science Board

Universities
Research Institutes
Medical institutions

Collaboration with academia

pmda

Science Board

Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies.

Outcome of the Science Board

1st term (FY2012 - 2013)

- Summary of discussion on the assessment of the current status of personalized medicine related to development and regulatory review (2014)
- Summary of discussion on non-clinical pharmacological studies on anticancer drugs (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)

- Discussion on Evaluation of Medical Devices in Pediatric Use (2015)
- Proposal on Basic Principle to Quality Assurance of Cell Therapy (CT) Products (2015)
- Report on the use of non-clinical studies in the regulatory evaluation of oncology drugs (2016)
- Current Status and Perspectives of Placebo-Controlled Studies(2016)
- Report on the Use of Numerical Analysis for Evaluating the Strength of Orthopedic Implants (2016)

The 3rd Term (2016 April-)

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

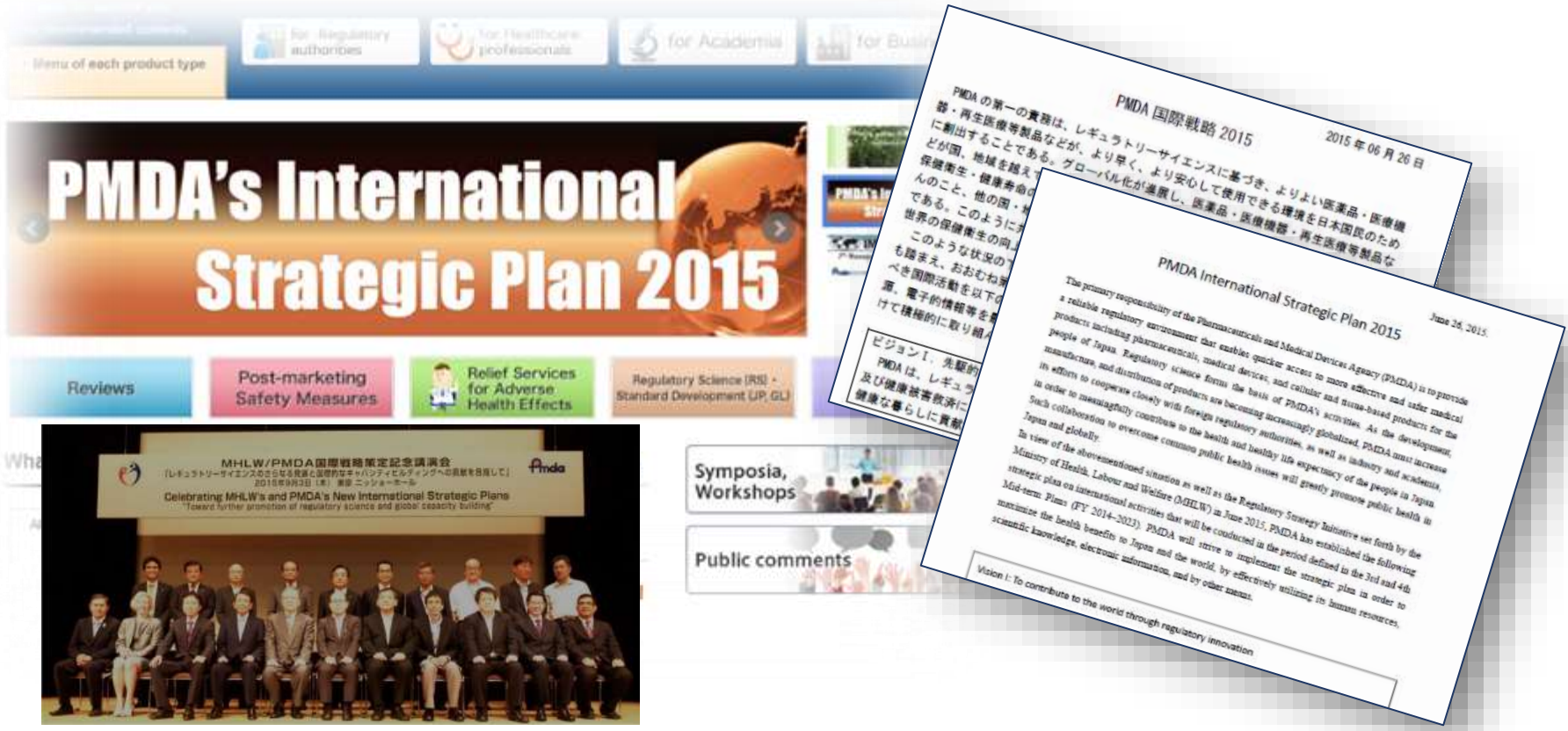
- Discuss “totally new elements of AI” by overviewing new technologies using AI and facilitate them into future medical device review and consultations.

→ Outcome documents will be **published by March, 2018**

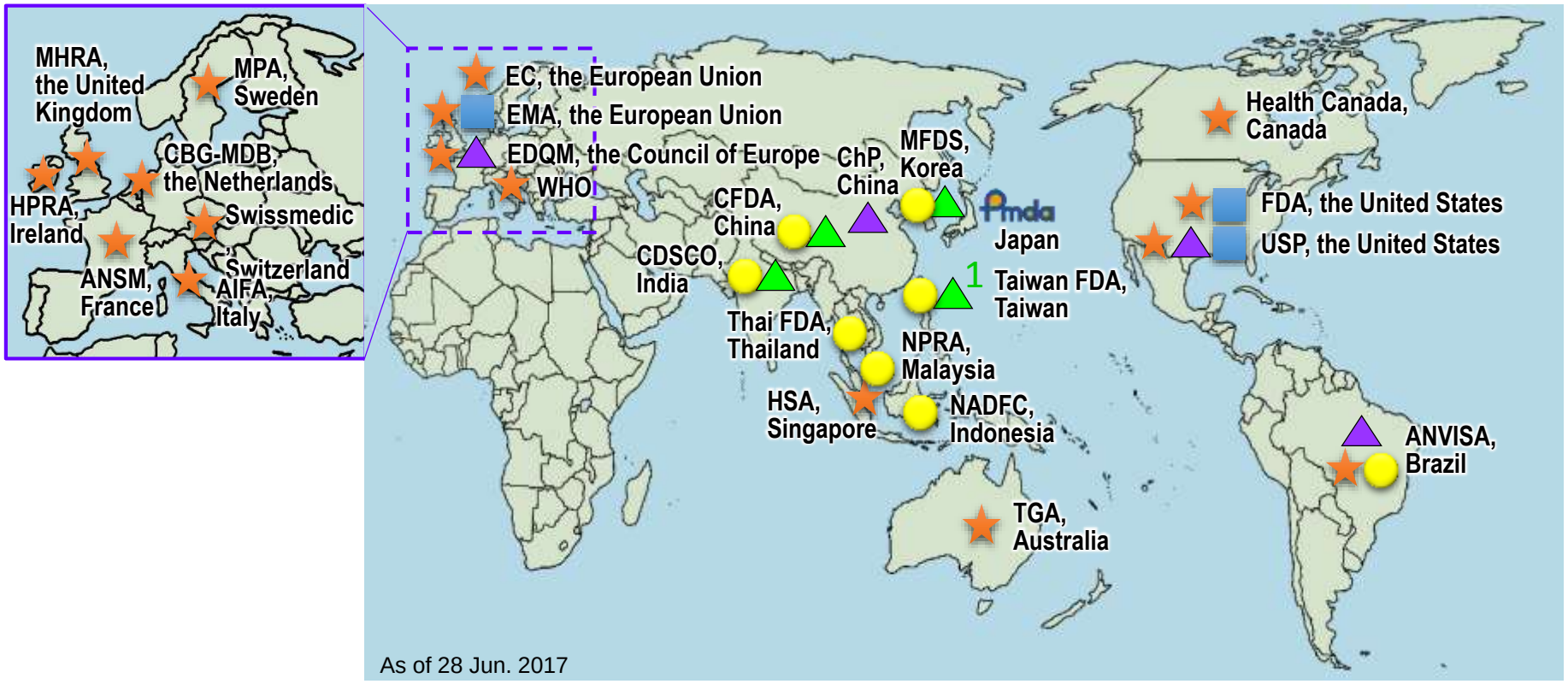
PMDA Website (English)
http://www.pmda.go.jp/english/rs-sb-std/sb/outcome-docs/0001.html

4. International Activities

PMDA International Strategic Plan 2015



Bilateral collaboration



Confidentiality Arrangement signed

Joint symposium held

PMDA staff stationed at the agency

Cooperative Arrangement signed

Cooperative Arrangement on cooperation of pharmacopoeia signed

1 :Cooperative Arrangement has been signed between the Interchange Association of Japan and East Asia Relations of Taiwan

MRA: Japan-EC MRA (GLP, GMP)

Scope of GMP is under consideration to expansion .

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 and the world.
- In FY2016, 161 regulators from 27 countries/regions participated.

Training seminar seminars to Regulatory Authority members by PMDA

PMDA Office

Outside Japan

APEC regions

Lectures, case studies, and on-site training

Establishing a centralized training center for multi-regional clinical trials

PMDA - ATC Planned Trainings: FY2017

No.	Contents	Date	Location	Note
1	Risk Management Plan (RMP)	May 18-19, 2017	Jakarta	30 participants from Indonesia
2	Pharmaceuticals Review	June 26-30, 2017	Tokyo (PMDA)	28 participants from 11 countries
3	Good Manufacturing Practice (GMP)	July 31- Aug. 4, 2017	Yamaguchi City	13 participants from 13 countries
4	Anti-infective Drugs	Oct. 3-4, 2017	Hanoi	30 participants from Vietnam
5	Medical Devices	Nov. 6 - 10, 2017	Tokyo (PMDA)	
6	Good Registration Management (GRM)	Oct. 31- Nov. 2, 2017	Taipei	
7	Pharmaceuticals Review	Dec. 12-15, 2017	Bangkok	
8	Multi-Regional Cinical Trial (MRCT)	Jan. 15-18, 2018	Tokyo (PMDA)	
9	Pharmacovigilance	Feb. 5-8, 2018	Tokyo (PMDA)	

Thank you!

多謝