Latest Trend of Pharmaceutical and Medical Device Regulation in Japan

3rd Japan-Korea Joint Symposium on Medical Products
3rd July 2018

Regulatory Authority in JAPAN

MHLW – PSEH Bureau

Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health Labour and Welfare

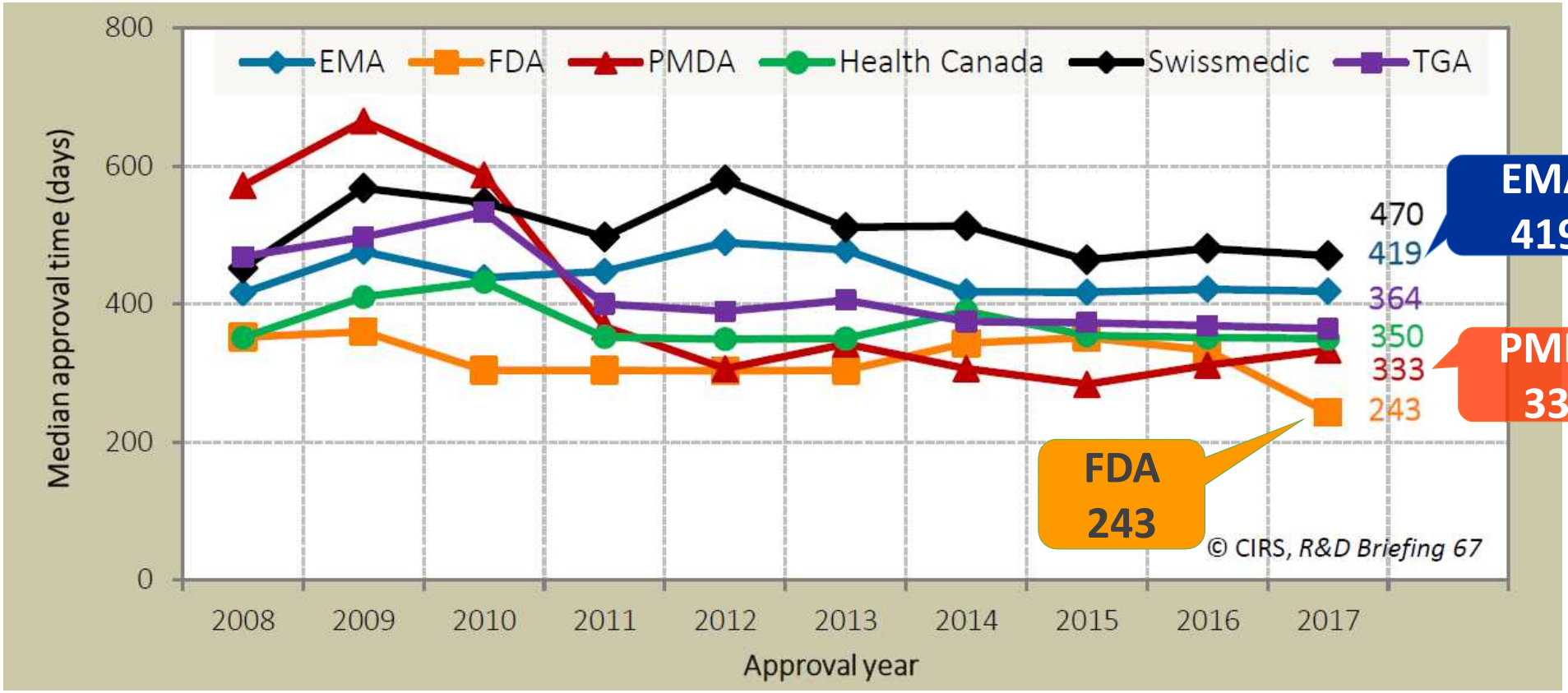
- **Final Authorisation of applications**
- **Administering laws, publishing legislations**
- **Publishing Guidelines**
- **Advisory committee**
- **Supervising PMDA Activities**

PMDA

Pharmaceuticals and Medical Devices Agency

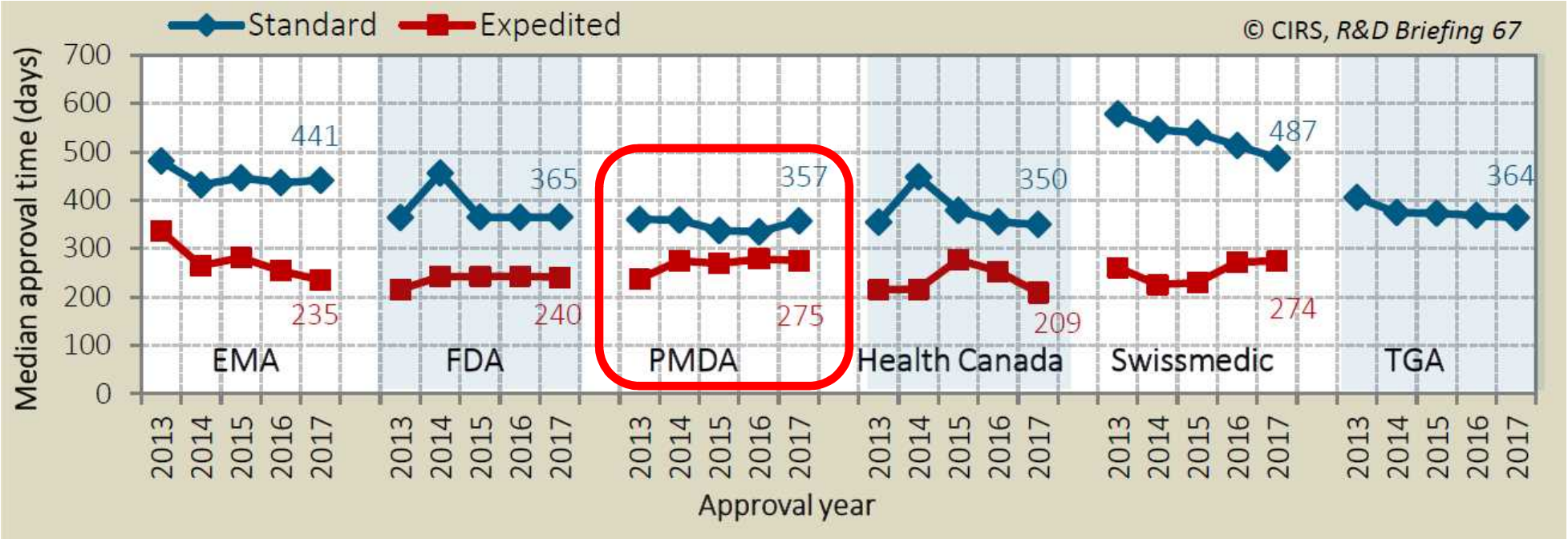
- **Scientific Review for Drugs & Medical Devices**
- **GCP, GMP Inspection**
- **Consultation on Clinical Trials etc.**

New active substance (NAS) median approval time
for six regulatory authorities in 2008-2017 (Pharmaceuticals)



Centre for Innovation in Regulatory Science (CIRS) , 2018, R&D Briefing 67

NAS median approval time by review type
for six regulatory authorities in 2013-1017



PMDA was the agency with the smallest difference
between expedited review median approval time and standard review median approval time in 2017.

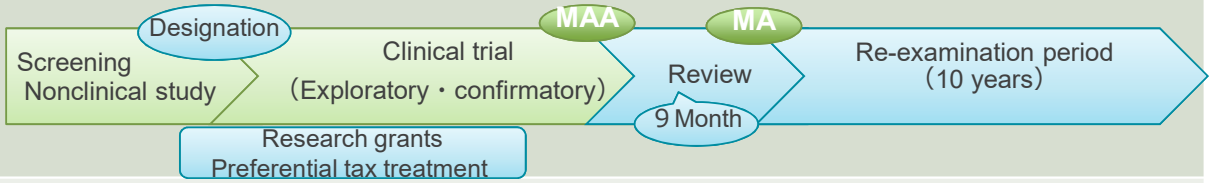
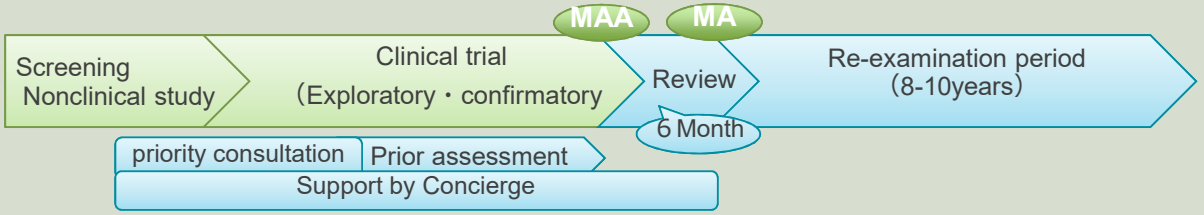
Centre for Innovation in Regulatory Science (CIRS) , 2018, R&D Briefing 67

Lead the World in Regulatory Innovation

Reform to rational and efficient structure based on Regulatory Science

Stage	Agendas for MHLW/PMDA	Activity
Development	○ Support for promising seeds to forward the development	→ Regulatory Sceince Consultation (from July 2011) **Regulatory Sceince Center** (from July 2018)
Review	○ Approaches to cutting-edge technologies (including iPS Cells by collaboration with Academia) ○ Encourage Japan-first development and approvals ○ Improve efficiency of development and review process by utilizing electric data	→ Science Board (from June 2012) → **SAKIGAKE Designation System** (from 2015) → **Conditional Early Approval System for Pharmaceuticals** (from October 2017)
Post -marketing	○ Utilize medical information database to develop more sophisticated safety measures ○ Predictability & Transparency in post-marketing change control	→MIHARI project (from 2009) **MID-NET project** (from April 2018) →**PACMP pilot** (from April 2018)

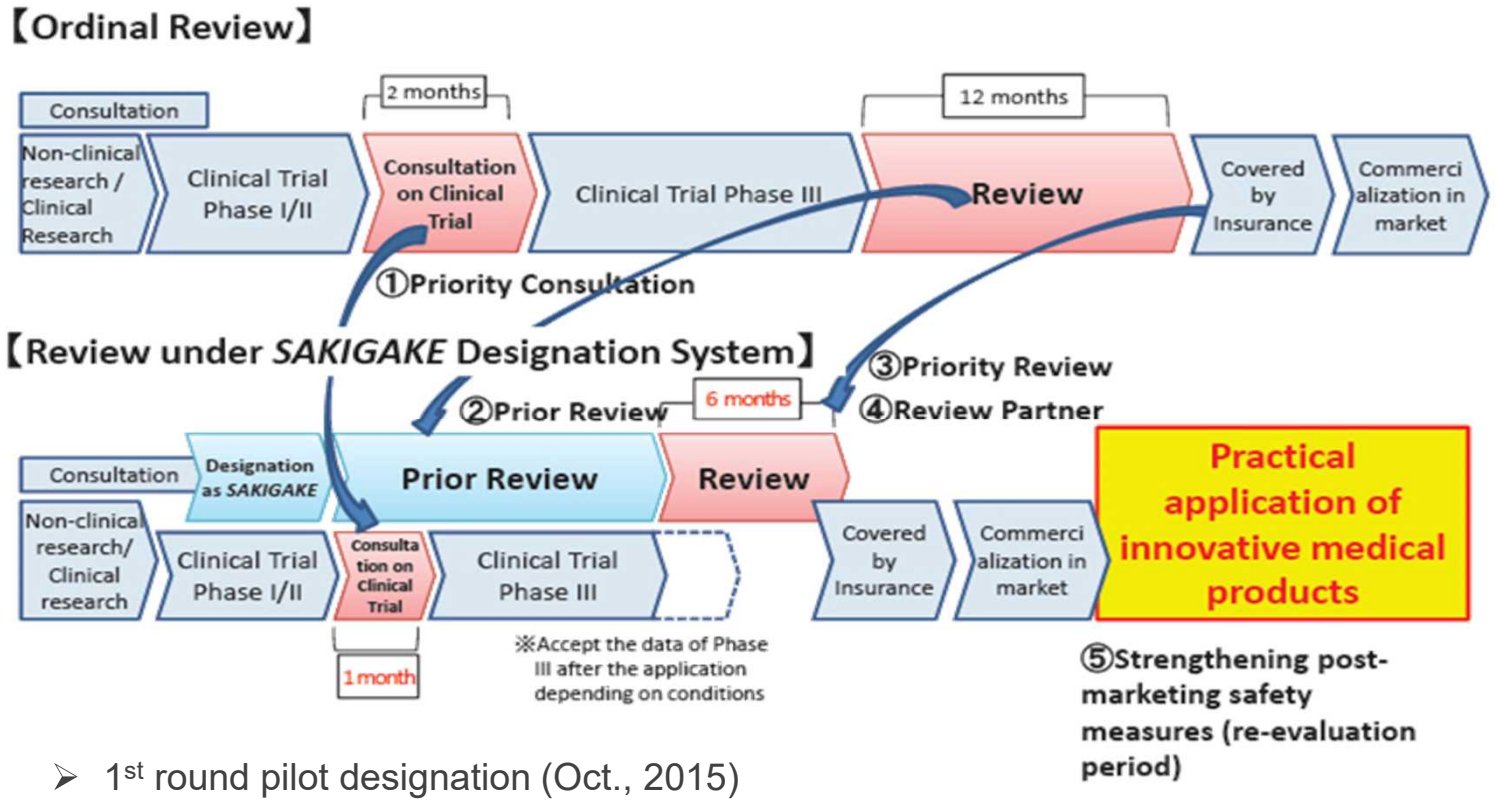
Summary of the Accelerated review system in Japan

Type/Designation requirement	Outline
Basic	
Priority review 1. For severe diseases 2. Apparent improvement of medical care	
Orphan Disease product * In addition to priority review 1. No. of patients is less than 50,000 or intractable diseases designated based on a law 2. Possibility of development	
Conditional Early Approval Pharmaceuticals Medical devices * In addition to priority review 1. Confirmatory clinical trials don't have sufficient feasibility. 2. Confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.	
SAKIGAKE (Forerunner designation) 1. Innovative medical products 2. For serious diseases 3. Development & NDA in Japan: being world's first or simultaneous with other countries 4. Prominent effectiveness expected on non-clinical and early phase clinical studies	

For Regenerative Medical Products, the "Conditional and Time-limited Authorization" is established based on PMD Act.

MAA: Marketing Authorisation Application MA: Marketing Authorisation

SAKIGAKE Designation System (3rd round pilot designation)



- 1st round pilot designation (Oct., 2015)
  6 Pharmaceuticals, 2 Medical Devices, 3 Regenerative Products
- 2nd round pilot designation (Feb. & Apr., 2017)
  5 Pharmaceuticals, 3 Medical Devices, 1 In-Vitro Diagnostic, 3 Regenerative Products
- **3rd round pilot: application (Mar., 2018)**
  6 Pharmaceuticals, 2 Medical Devices, 3 Regenerative Products

3rd Round of SAKIGAKE Designated Products

(newly designated on Mar. 27, 2018)

- Pharmaceuticals -

No.	Name of product	Applicant	Planned indication
1	RTA402	Kyowa Hakko Kirin Co., Ltd.	Diabetic kidney disease
2	JR-141	JCR Pharmaceuticals Co., Ltd.	Mucopolysaccharidosis type II (Hunter syndrome)
3	Tafamidis meglumine	Pfizer Japan Inc.	Transthyretin ardiomyopathy (TTR-CM)
4	MSC2156119J	Merck Serono Co., Ltd.	Advanced non-small-cell lung cancers (stage IIIB/IV) with MET exon 14 skipping mutations
5	Trastuzumab deruxtecan	DAIICHI SANKYO COMPANY, LIMITED	Unresectable advanced and/or recurrent gastric cancers - Exacerbated following cancer chemotherapy - Confirmed HER2 overexpression
6	Entrectinib	Ignyta, Inc.	Solid tumors exhibiting local progression or distant metastasis in adults/children - Tumor progression observed after prior therapy(ies) or where there is no tolerable standard therapy - NTRK fusion gene-positive

3rd Round of SAKIGAKE Designated Products

- Medical Devices - (newly designated on Mar. 27, 2018)

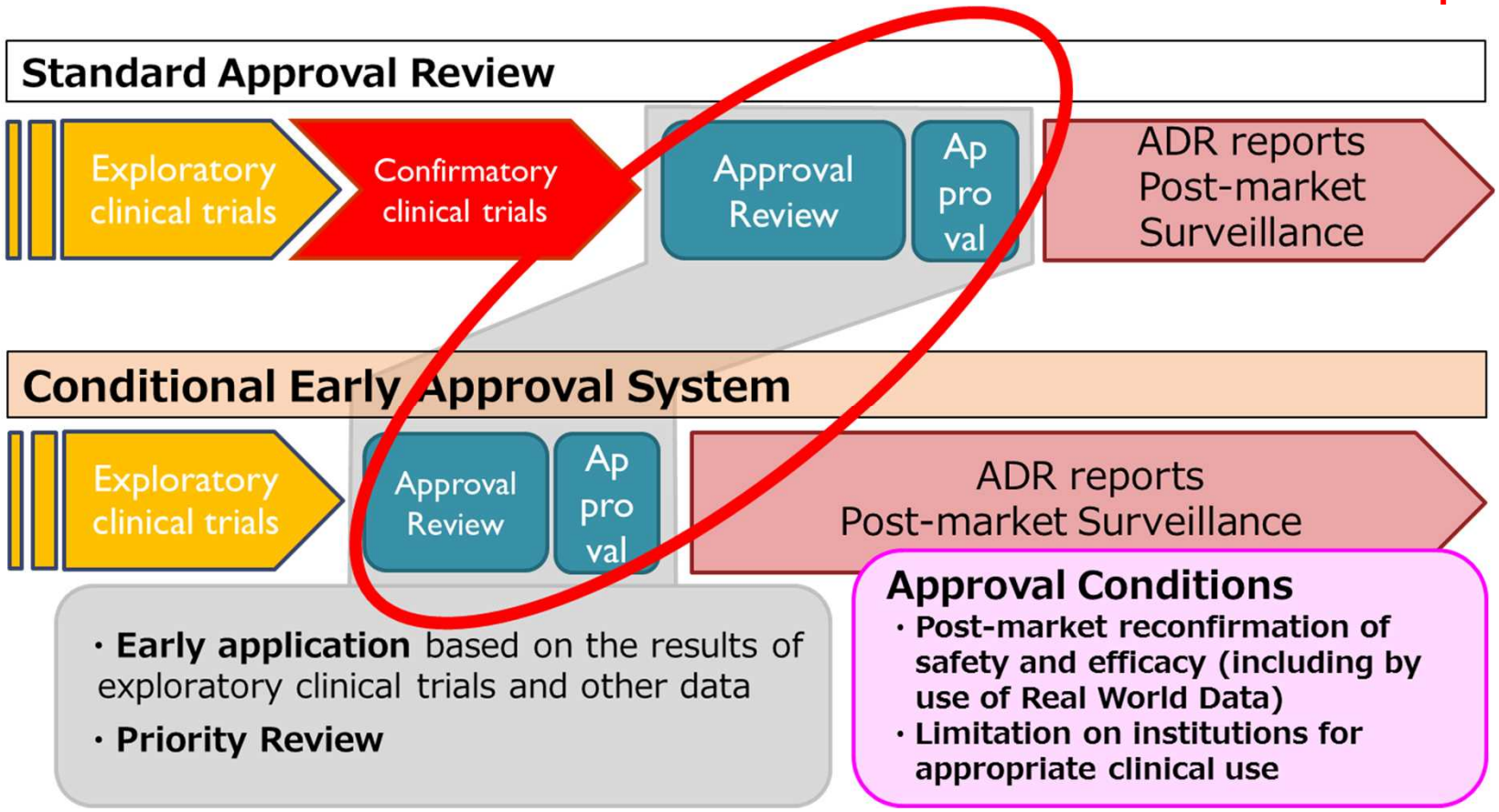
No.	Name of product	Applicant	Planned indication
1	OFT-G1 Cardiac-repair patch (tentative name)	TEIJIN LIMITED.	A Cardiac-repair patch used during cardiovascular intervention - Comprised of bioabsorbable and non-bioabsorbable synthetic polymeric threads and a bridging gelatin membrane - Applied to correct blood flow, maintain hemoperfusion, and to construct/reconstruct surrounding tissues
2	CliniMACS CD34 System	Miltenyi Biotec K.K.	Product capable of facilitating synostosis - CD34-positive cells obtained by selective isolation - Administered to the site of non-union bone fracture with collagen-containing soft-tissue injection materials as a scaffold

- Cellular and Tissue-based Products (Regenerative Medical Products) -

No.	Name of product	Applicant	Planned indication
1	TBI-1301	Takara Bio Inc.	Product used to treat synovial sarcoma using autologous lymphocytes - Reintroduced to the patient after transferring receptor genes *in vitro* (these receptors specifically bind to cancer antigens)
2	CLBS12	Caladrius Biosciences, Inc.	CD34 cell therapy used to facilitate angiogenesis to address critical limb ischemia - CD34 positive cells isolated from patient's own peripheral blood
3	AVXS-101	AveXis, Inc.	Product used to treat spinal muscular atrophy - SMN genes transferred to the patient - Facilitates SMN protein expression and normalizes neuromuscular junction function

Conditional Early Approval System for Pharmaceuticals

<Implemented on 20 Oct, 2017>



To realize early access to innovative treatments that are:

- For severe diseases with limited choice of treatments
- Difficult to conduct confirmatory clinical trials due to small number of patients or prolonged follow-up period

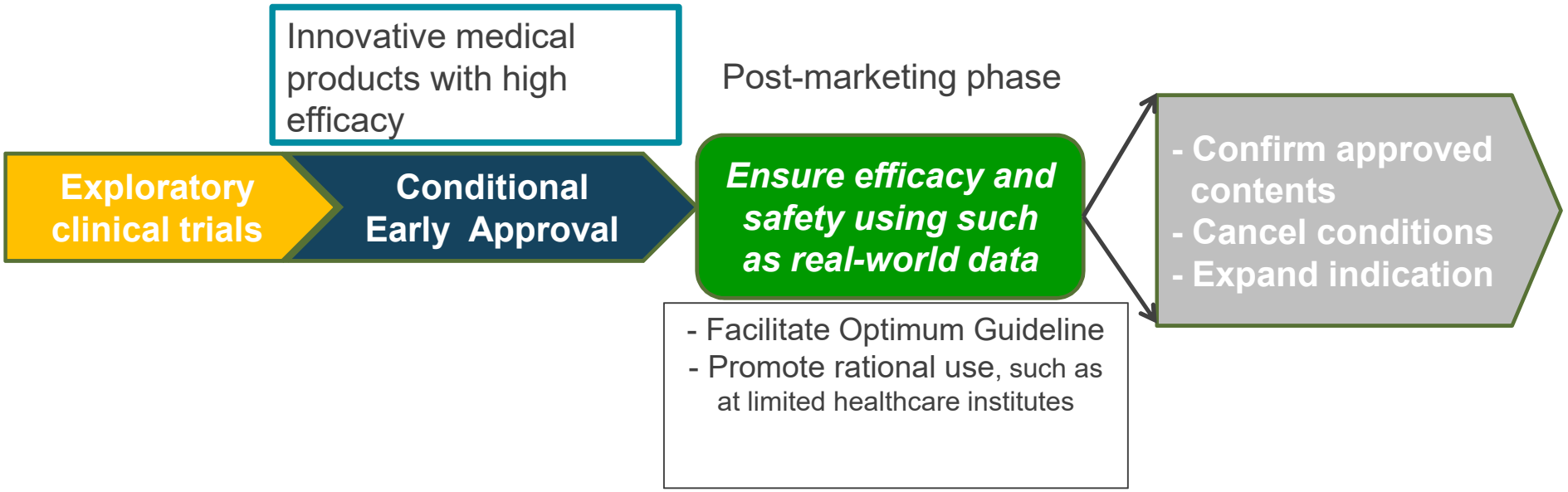
Conditional Early Approval System (for pharmaceuticals)

--- Image of "Condition" ---

- Efficacy and safety will be ensured by using the rational and scientific post-marketing data (including the Real-World Data※). Regulations will be modified to confirm the approved content and expand indications.

※ **Real-world data includes MID-NET and registry data of Clinical Innovation Network.**

- Promote "Optimal use Guideline" based on regulatory science as well.
- Details of "Conditional Early Approval" will be finalised by summer of 2017.

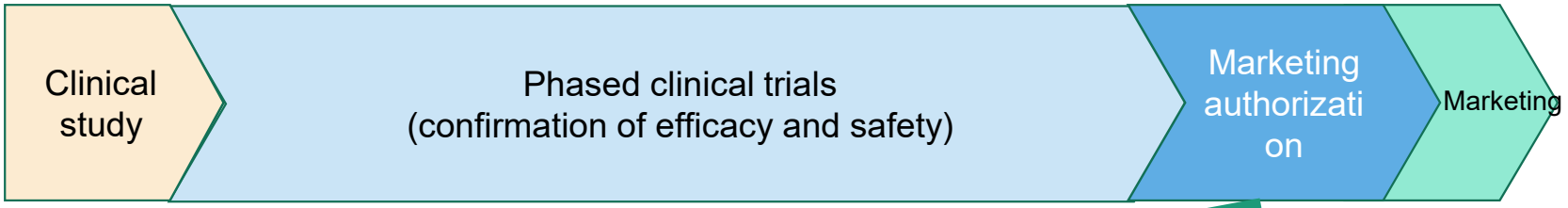


Expedited approval system under PMD Act*

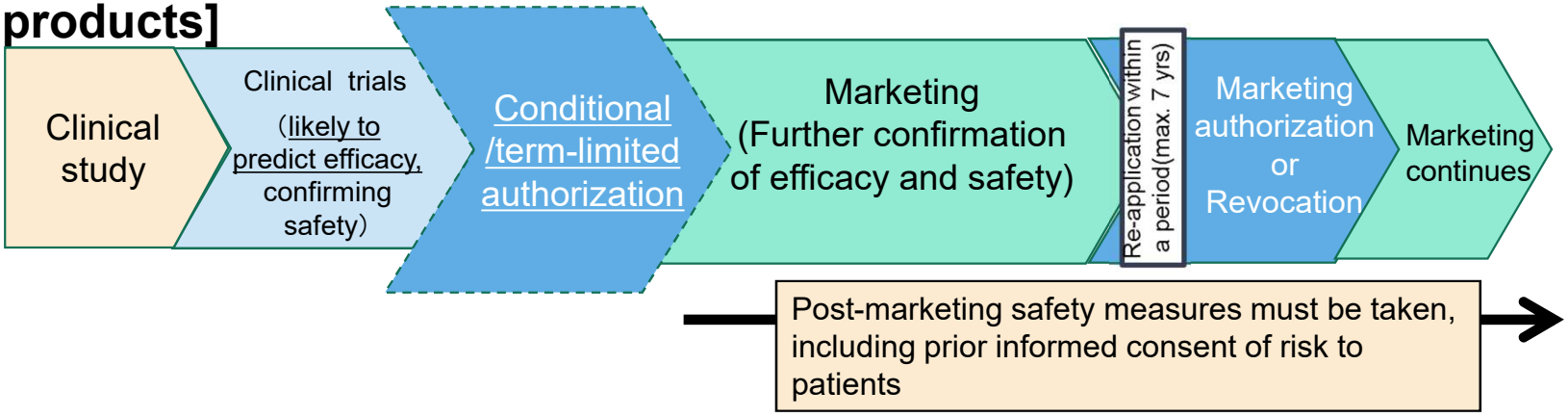
< Drawback of traditional PAL approval system >**

Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]



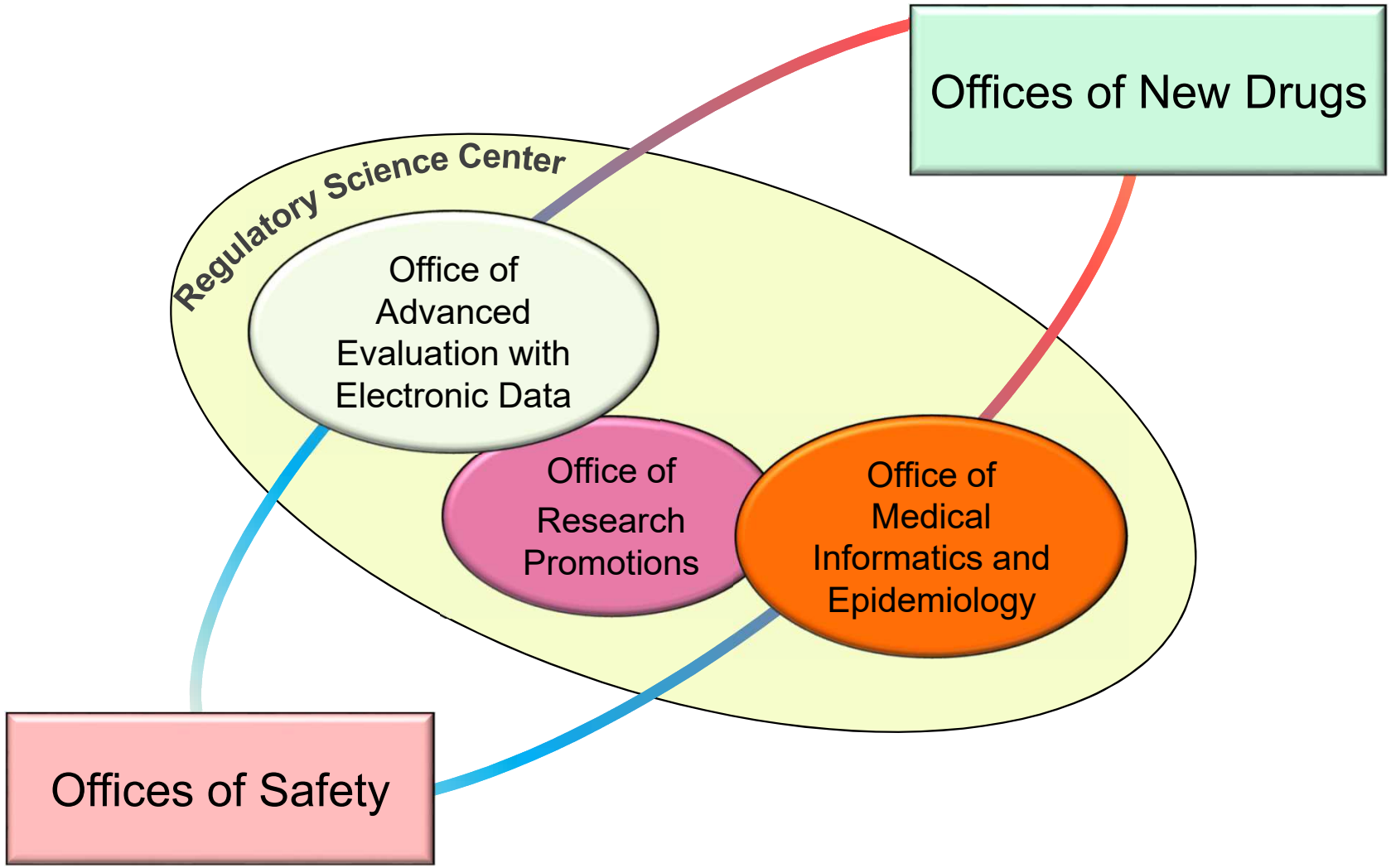
[New scheme for regenerative medical products]



* PMD Act: the Act on Pharmaceuticals and medical devices (enacted in November 2014)

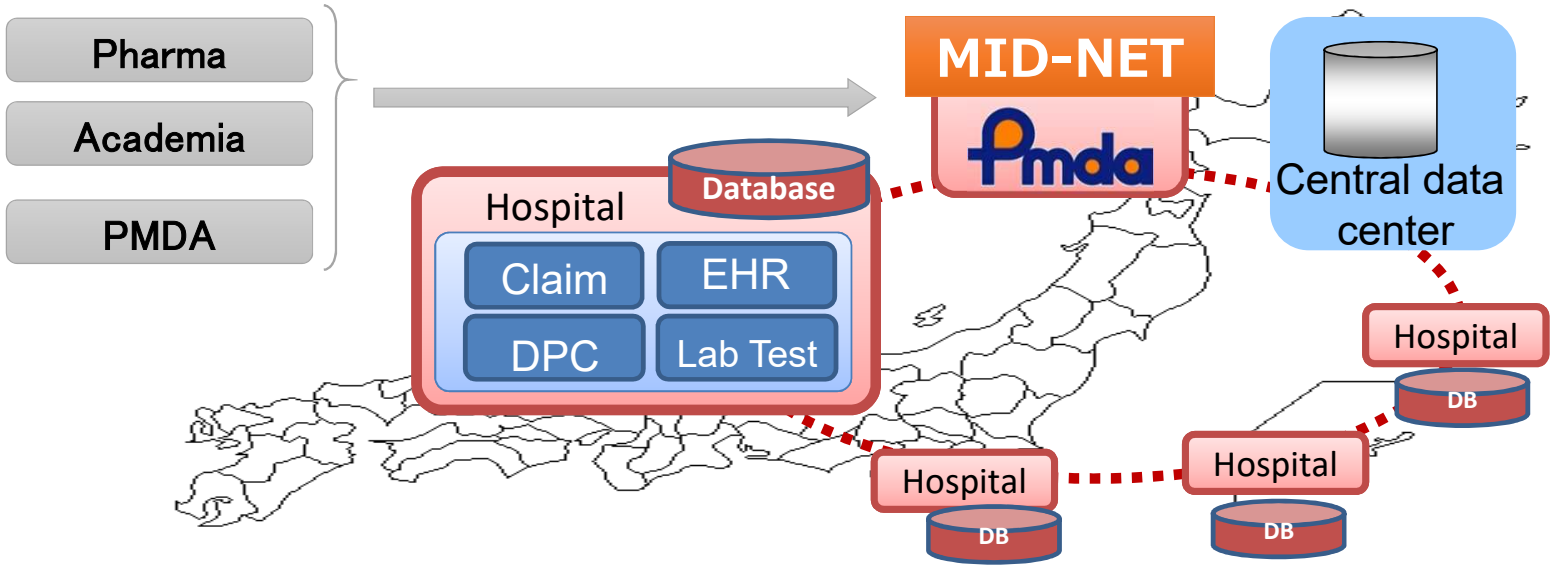
** PAL: the Pharmaceutical Affairs Law (replaced by PMD Act)

Regulatory Science Center
- Collaboration with other PMDA Offices -



MID-NET® (Medical Information Database Network) Project

- Analyze electronic health records, insurance claim data, diagnosis procedure combination (DPC, counterpart of US's DRG) data, lab test results, etc.
- Enables advanced pharamacoepidemiological analysis
- Covers 23 major hospitals and 4 million patients (as of Feb. 2018).
- Full operation since April 2018, MID-NET charges $430,000/Drug.



12th Summit of Heads of Medicines Regulatory Agencies

On 24 - 25 October 2017, the 12th Summit convened in Kyoto, Japan. 86 participants from 29 countries and regions joined.

The following meeting were also held.

- **International Coalition of Medicines Regulatory Authorities (ICMRA) meeting**
- Bilateral meeting (Japan and 9 countries and regions)
- Asian network meeting (9 Asian countries and regions participated, the first meeting)
- Summit of Heads of Medicines Regulatory Agencies Symposium (gathered about 1500 audiences)

12th Summit & ICMRA 2017 Outcomes

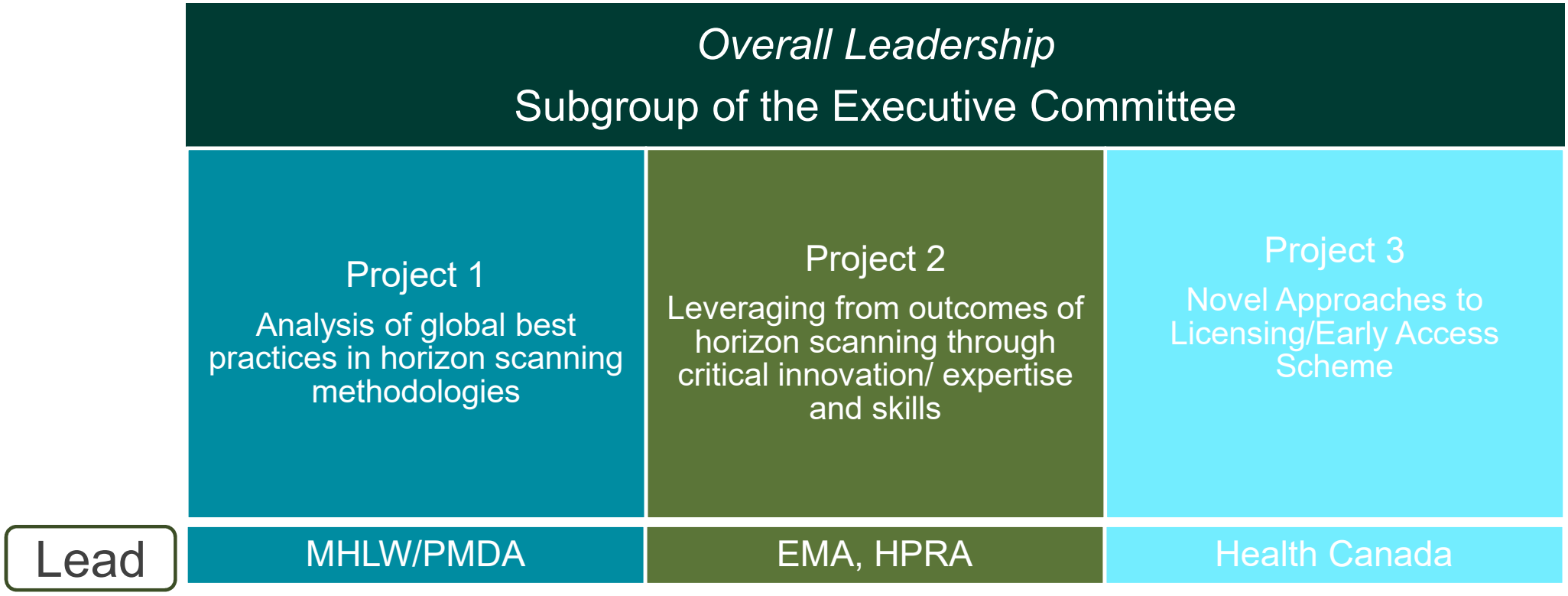
- **Merger of Summit and ICMRA: "ICMRA Summit" in 2018, US**

- **12th Summit**
  - **Regenerative Medicine Products**: Promote discussion for international regulatory convergence
  - **Real World Data**: Promote information exchange on the use of RWD such as through international symposium
  - **AMR**: Regulators' roles including clinical evaluation guideline
  - **Counterfeit drugs**: More collaborated network by Regulators and WHO

- **ICMRA**
  - **Innovation**: Project launched, e.g., Horizon Scanning
  - **Supply Chain Integrity**: Report on Track & Trace Systems
  - **Pharmacovigilance**: Report on the use of Big Data
  - **Crisis Management**: Network by Regulators and WHO

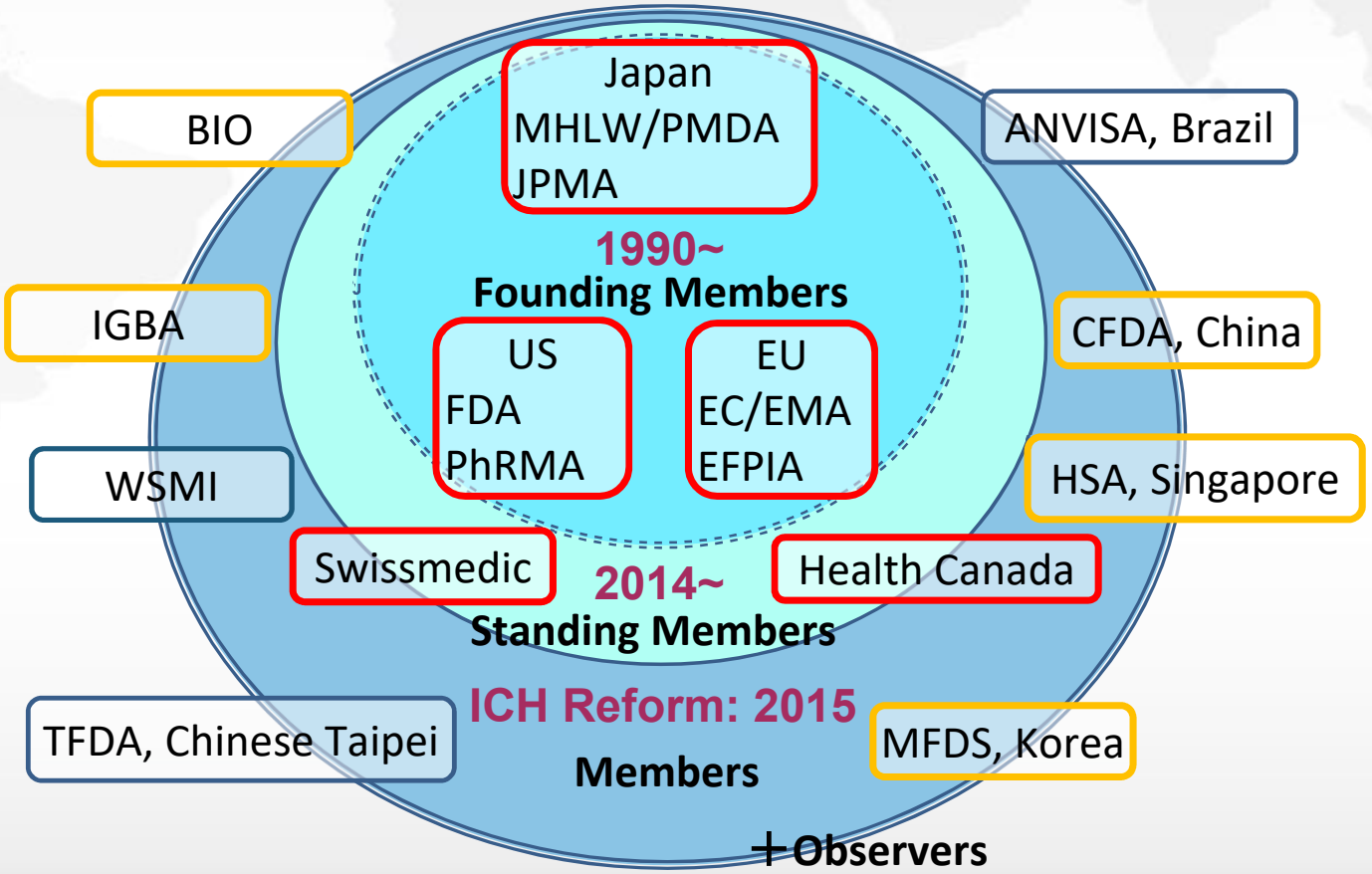
ICMRA Innovation Project

Major focus on "Horizon Scanning"
Interim report will be made at DIA Japan, November 2018 in Tokyo



ICH: Expanding Memberships

International Council for Harmonisation of
Technical Requirements for Pharmaceuticals for Human Use



ICH Meeting, June 2018 in Kobe, Japan --- Selection of New Topics ---

Five new topics are selected:

- Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation: Q2(R2)/Q14 (MHLW/PMDA, FDA)
- Continuous Manufacturing: Q13 (FDA)
- Clinical electronic Structured Harmonized Protocol (CeSHarP): M11 (PhRMA)
- Drug Interaction Studies (FDA)
- Adaptive Clinical Trials (PhRMA)

First three EWGs are planned to start at ICH Charlotte meeting in Nov., 2018.

Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

- Plan, design and coordinate training for Regulatory Authority staffs (established in 2016)
- Provide **training opportunities** including **on-site training**

- Help raise the level of Regulations in Asia and the world.
- **In FY2017, 235 regulators from 27 countries/regions participated.** (50% increase from 2016)

Training seminar seminars to Regulatory Authority members by PMDA

Lectures, case studies, and on-site training

Establishing a centralised training center for multi-regional clinical trials

International Reputation of Asia Training Center

- From Attendees (FY 2017)

✓ Nine training seminars and 235 attendees from 27countries/regions

✓ More than 70% of attendees rated as “Very good” according to the questionnaire

- Official approval of APEC LSIF RHSC Training “Centers of Excellence” for Regulatory Science from APEC

✓ Area: Global clinical trials/GCP inspection, Pharmacovigilance

- Stipulate utilization of ATC in the Joint Statement of ASEAN-JAPAN Health Ministers (July 15th in 2017)

PMDA contributes to mutual understanding and cooperation in Asia

Asia Training Center planned seminars in FY2018

	Contents	Date	Location
1	Pediatric Review	June 11-14, 2018	Tokyo (PMDA)
2	Pharmaceuticals Review	June 18-22, 2018	Tokyo (PMDA) and Toyama Prefecture
3	Good Registration Management (GRM)*	September 26-28, 2018	Taipei
4	Pharmaceuticals Review	October 15-16, 2018	Naypyidaw, Myanmar
5	Medical Devices Review	November 12-16, 2018	Tokyo (PMDA)
6	Good Manufacturing Practice (GMP) **	November 26-30, 2018	Utsunomiya, Tochigi Prefecture
7	Pharmaceuticals Review	December 10-13, 2018	Jakarta, Indonesia
8	Multi-Regional Clinical Trial (MRCT)*	January 21-24, 2019	Tokyo (PMDA)
9	Pharmacovigilance*	February 4-7, 2019	Tokyo (PMDA)

*APEC-LSIF-RHSC CoE Workshop **With the support of PIC/S