Implementation of International Regulatory Harmonization Strategy

（Regulatory Science Initiative : RSI）

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Ministry of Health, Labour and Welfare (MHLW)

April 7, 2016

Proposal in 2014 to reconstruct the efficiency of clinical development of new drugs

The NEW ENGLAND JOURNAL of MEDICINE

The most expensive step in creating a new drug is conducting clinical trials. Conducting a trial costs $25,000 or more per patient studied, and phase 3 trial programs consume more than 40% of a sponsoring company's expenditures.

Unfortunately, every patient is not equally valuable when it comes to clinical trials, and many clinical development programs are economically inefficient in that they are excessively large relative to the amount of information they yield, especially in light of the information-technology breakthroughs that have lowered the cost of data acquisition and analysis over the past 20 years.

The Calculus of Cures

Robert Kocher, M.D., and Bryan Roberts, Ph.D.

In 2013, the Food and Drug Administration (FDA) approved 27 new drugs for marketing. Eight of these drugs are for orphan diseases, including six rare cancers. In fact, more than half of the 139 drugs

least two of these dimensions. Many drugs designed for orphan diseases and cancers are good investments of scarce capital, since they tend to have relatively low development costs and selling

published on February 26, 2014, at NEJM.org.

From Venrock, Palo Alto (R.K., B.R.), and the Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles (R.K.) — both in California.

① **Efficient development provided by conditional approval of drugs, and post-marketing surveillance**

② **Costs for drugs could be reduced by as much as 90%, and the time required by 50%**

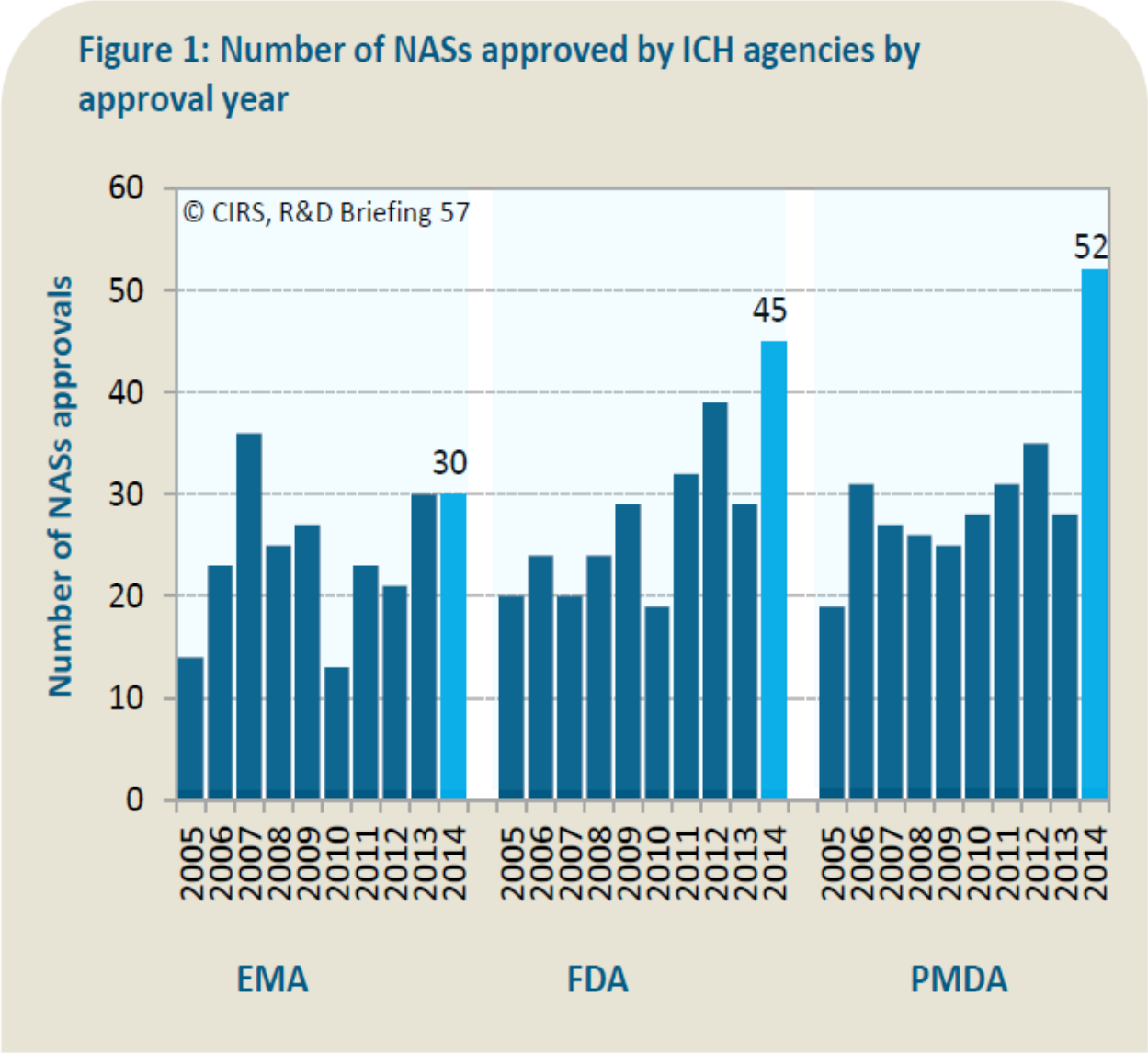
③ **Utilization of high-quality patient registries & electronic health records is prospective**

Redesigning trials to include fewer patients, providing conditional approval of drugs, and requiring post-marketing surveillance could have a profound effect, allowing smaller development programs to achieve greater success. ①

We estimate that development costs for drugs could be reduced by as much as 90%, and the time required by 50%, if the threshold for initial approval were defined in terms of efficacy and fundamental safety. ②

Cutting costs and time, while requiring high-quality and transparent patient registries for independent safety monitoring, would be a more informative and cost-effective approach. With the widespread adoption of electronic health records and the introduction of many low-cost data-analysis tools, it is now feasible to develop mandatory post-marketing surveillance programs that make thousand-patient trials obsolete. ③

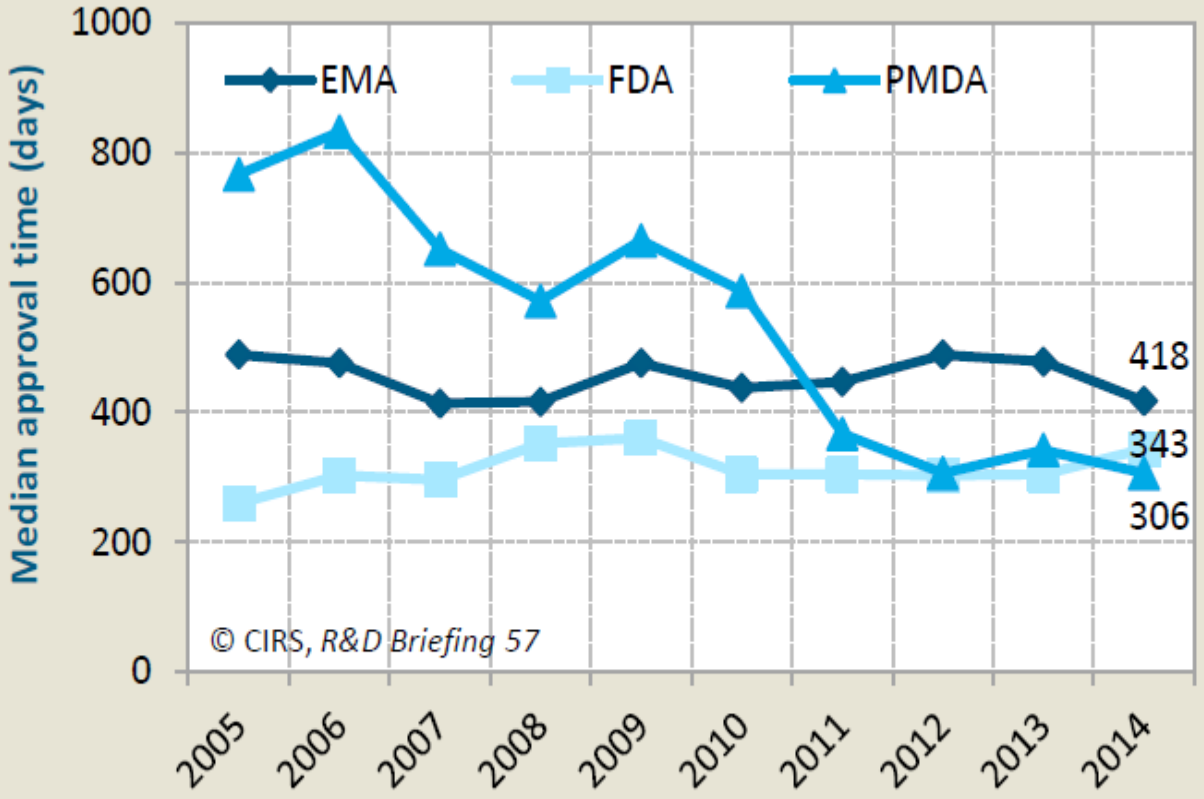
High performance in amount of business



http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

High performance at review speed

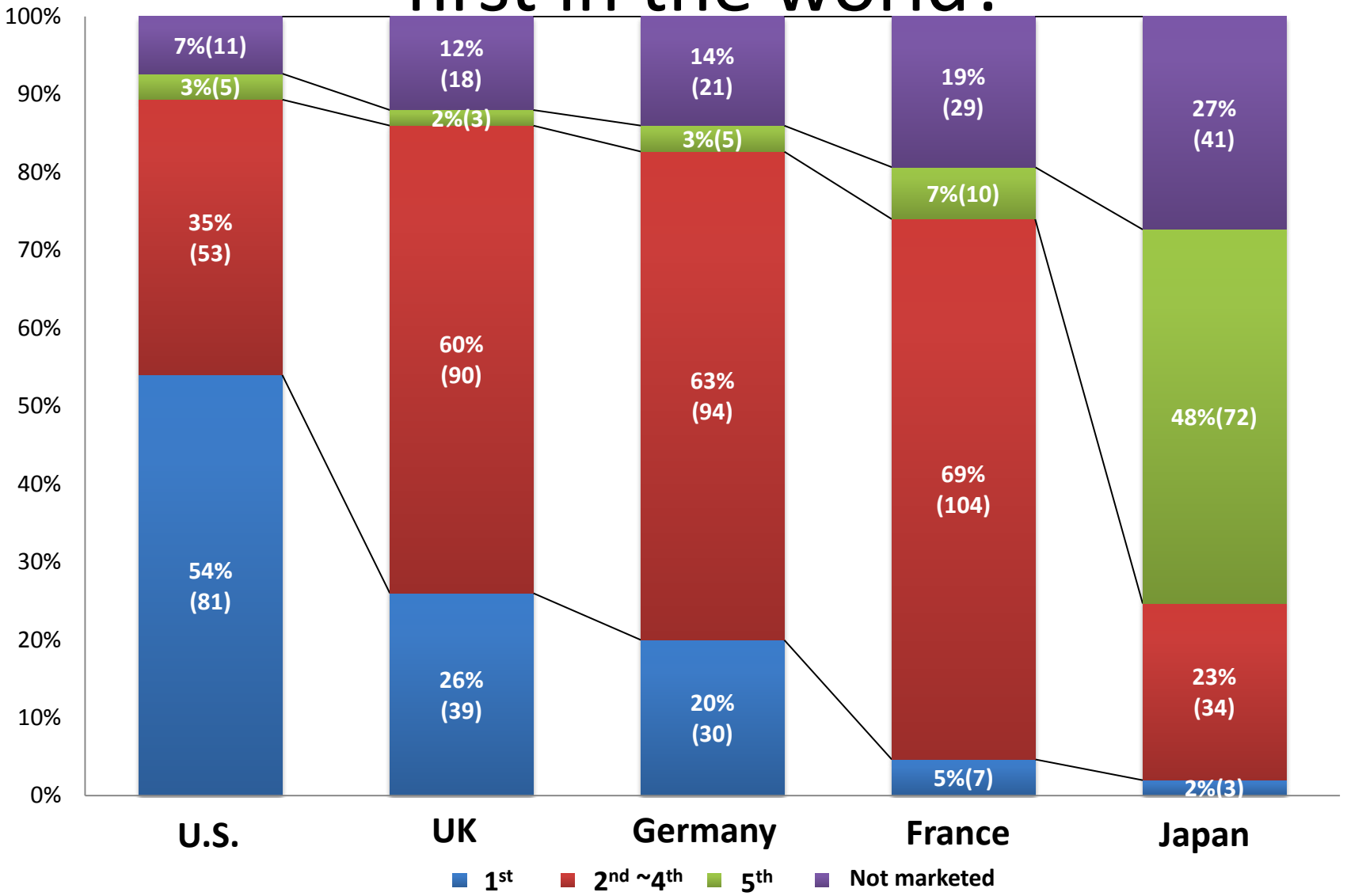
Figure 2: Median approval time for NASs approved by ICH agencies by approval year



***Note**: The EMA approval time includes the EU Commission time*

http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

In which country are new drugs marketed first in the world?



Source: ⓒ2015 IMS Health. World Review, Life Cycle, created by Pharmaprojects, Office of Pharmaceutical Industry Research（no reprint or copy）
Note: Surveyed in February 2015

SAKIGAKE Designation System

– To put innovative products into practice in Japan first in the world –

Designation Criteria

- Medical products for diseases in dire need of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

Designation Advantage

1. Prioritized Consultation [Waiting time: 2 months→1 month]

2. Substantialized Pre-application Consultation [de facto review before application]

3. Prioritized Review [12 months → 6 months]

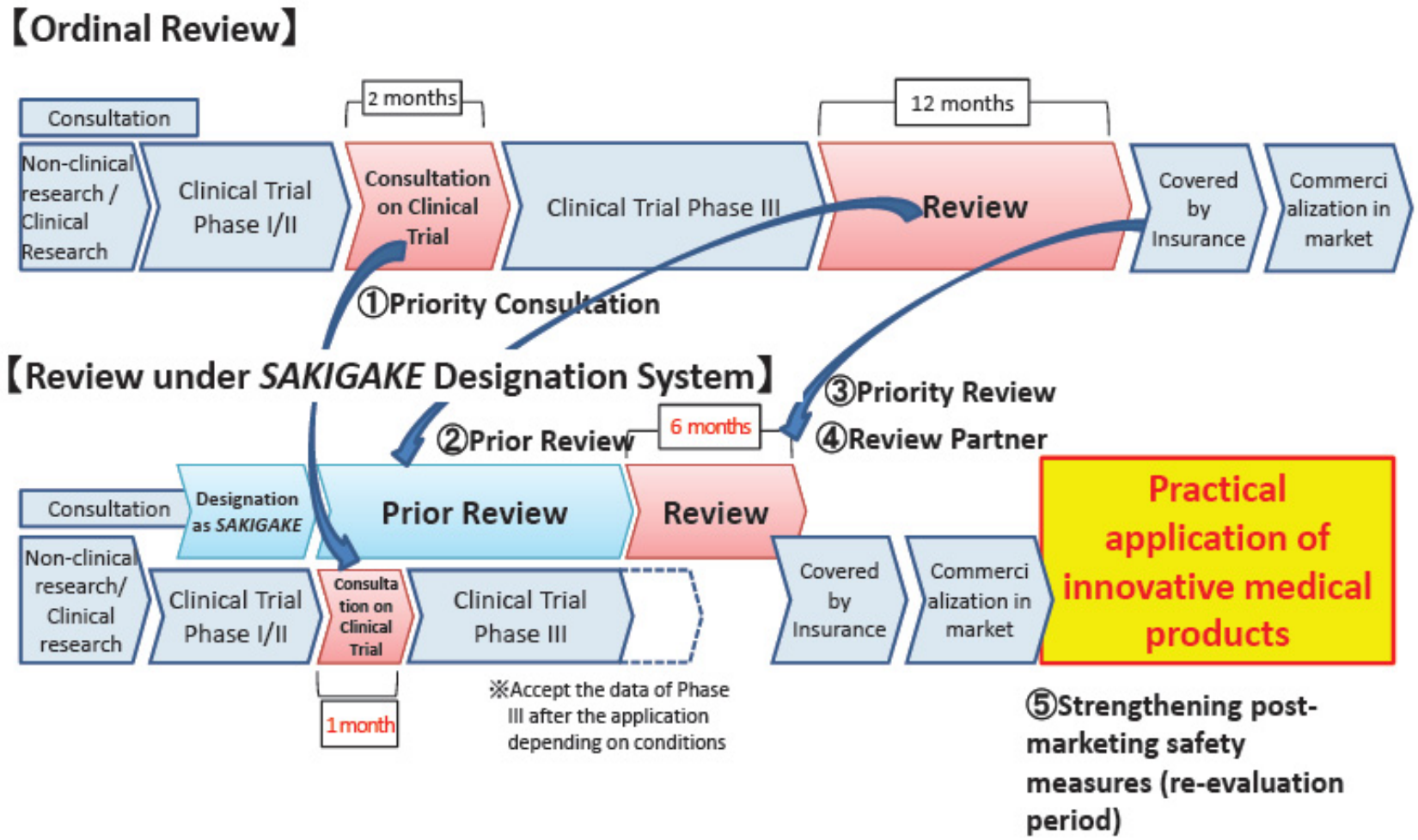
4. Review Partner [PMDA manager as a concierge]

5. Substantial Post-Marketing Safety Measures[Extension of re-examination period]

Designation Procedure

1. Initiation by applicant 2. Initiation by the MHLW

SAKIGAKE General Timeframe



SAKIGAKE Designation (1): Pharmaceuticals
(27 October 2015)

No.	Product name	Expected indication
1	**Sirolimus (NPC-12G)**	Angiofibroma associated with nodular sclerosis
2	**NS-065/NCNP-01**	Duchenne muscular dystrophy (DMD)
3	**S-033188**	Influenza A or B virus infection
4	**BCX7353**	Management of angioedema attacks in patients with hereditary angioedema (HAE)
5	**ASP2215**	First-relapsed or treatment-resistant FLT3 mutation-positive acute myeloid leukaemia
6	**Pembrolizumab (genetical recombination)**	Unresectable, advanced and recurrent gastric cancer

SAKIGAKE Designation (2): Medical Devices and Regenerative Medicine Products (10 February 2016)

No.	Product name	Expected performance/effectiveness
MD1	**Titanium Bridge** (Hinge-type plate with titanium)	Adduction-type spasmodic dysphonia
MD2	**Absorbing barrier for adhesion prevention** (Trehalose solution)	Reduction of postoperative adhesion prevention by Intraperitoneal injection
RP1	**STR01** (Autologous bone marrow-derived stem cells)	Improvement of neurological symptoms and functional impairment due to spinal cord injury
RP2	**G47Δ** (Recombinant herpes virus)	Glioma
RP3	**Autologous intracardiac stem cells**	Improvement of heart function in children with congenital heart disease

FDA's Breakthrough Therapy Designation

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Perspective

Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation

Rachel E. Sherman, M.D., M.P.H., Jun Li, J.D., Ph.D., Stephanie Shapley, M.B.A., Melissa Robb, R.N., and Janet Woodcock, M.D.

N Engl J Med 2013; 369:1877-1880 | November 14, 2013 | DOI: 10.1056/NEJMp1311439

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Article | References

Many people with serious or life-threatening illnesses for which there are no satisfactory treatments are understandably eager to gain access to new therapies and are willing to trade off greater

EMA announced new priority review system

Paving the way for promising medicines for patients

Why PRIME is needed

Many patients with serious diseases have no or only unsatisfactory therapeutic options and should be able to benefit from scientific advancement and cutting edge medicines as early as possible.

PRIME aims to bring promising innovative medicines to patients faster by optimising and supporting medicine development.

International Regulatory Harmonization Strategy

– Regulatory Science Initiative (RSI) – (June 2015)

Objective

Proactively contribute to the international regulatory harmonization and cooperation by sharing Japan's knowledge on regulations (regulatory science) with the world.

⇒ **Aim to resolve the global drug/device lag and contribute to global health**

⇒ **Revitalize the pharmaceutical and medical device industries**

Implementation of the strategy

1. Establishment of the basis for approving innovative products – SAKIGAKE Project–

2. Establishment of office and center for international regulatory cooperation in MHLW and PMDA

3. Engagement in bilateral partnerships and multilateral frameworks to strengthen international cooperation

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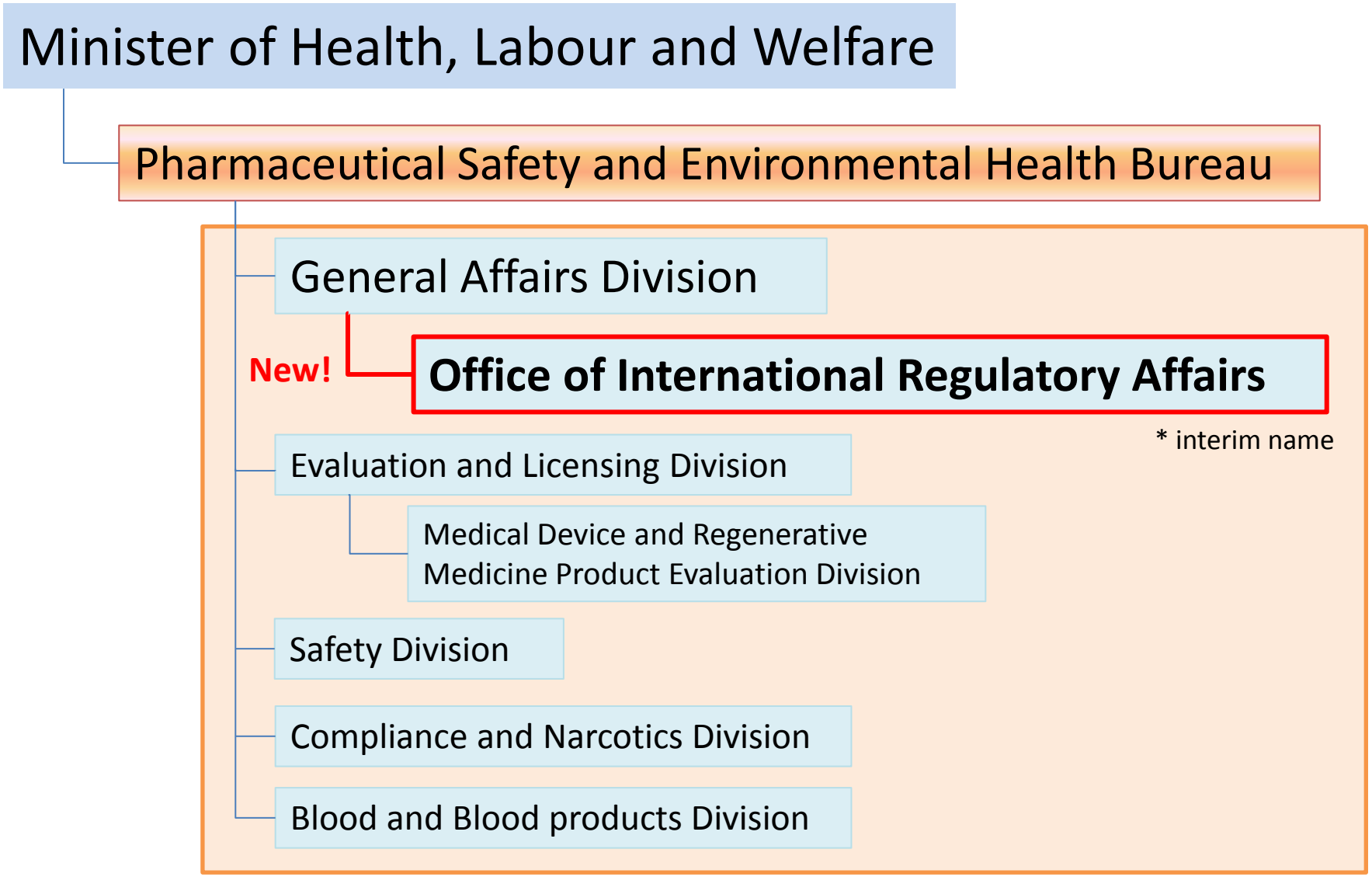
Establishment of "Office of International Regulatory Affairs" in MHLW (As of Apr. 2016)



Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

- 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.

Asia Training Center (within PMDA)

Japan

(1) Training seminar by PMDA, local prefectures and industry

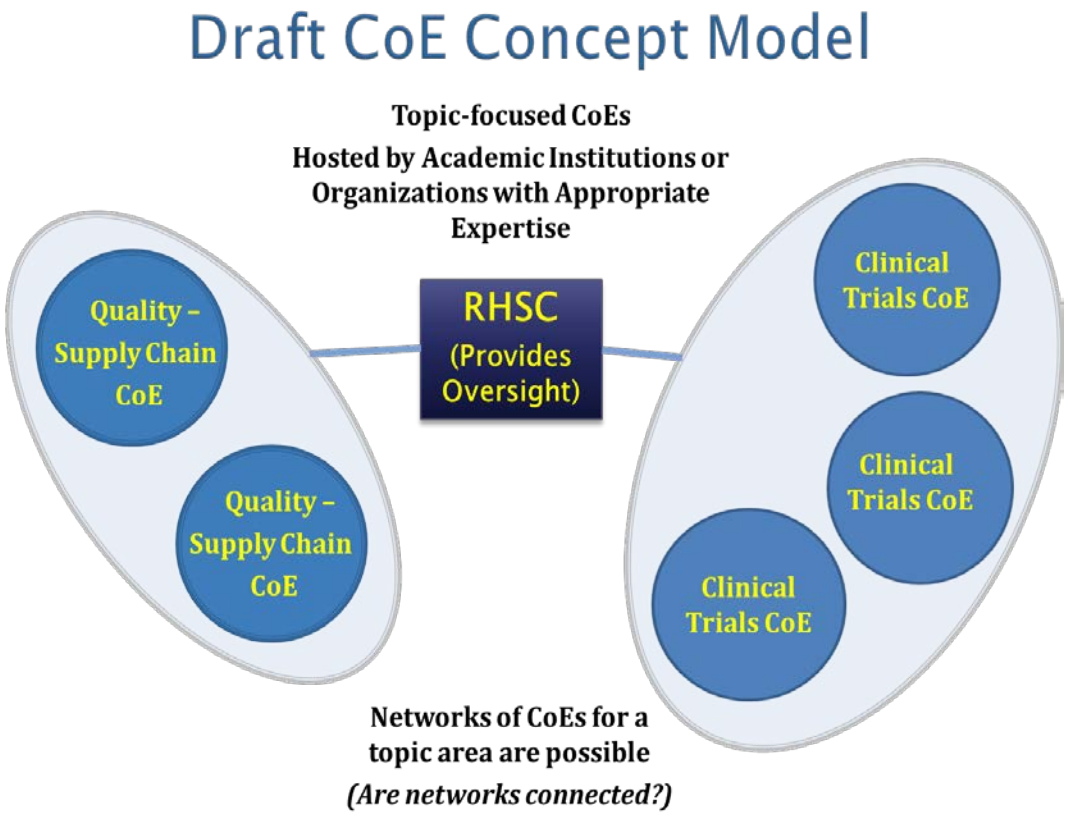
APEC

Local Asian site

(2) Assign to local site

(3) APEC Training Centre for Clinical Trial and Pharmacovigilance

APEC Training Centers of Excellence (CoE)



Project	Champion
Multi-regional Clinical Trials (MRCT)/GCP inspections	Japan/Thailand
Global Supply Chain Integrity	US
Good Registration Management	Chinese Taipei/Japan
Biotechnological Products	Korea
Pharmacovigilance & Medical Device Vigilance	Korea
Cellular Therapies	Singapore

Training centers (academia) will be designated for each project. The centers will provide trainings for regulators in APEC area.

Prioritized work projects and projects where CoE will be established (red colored)

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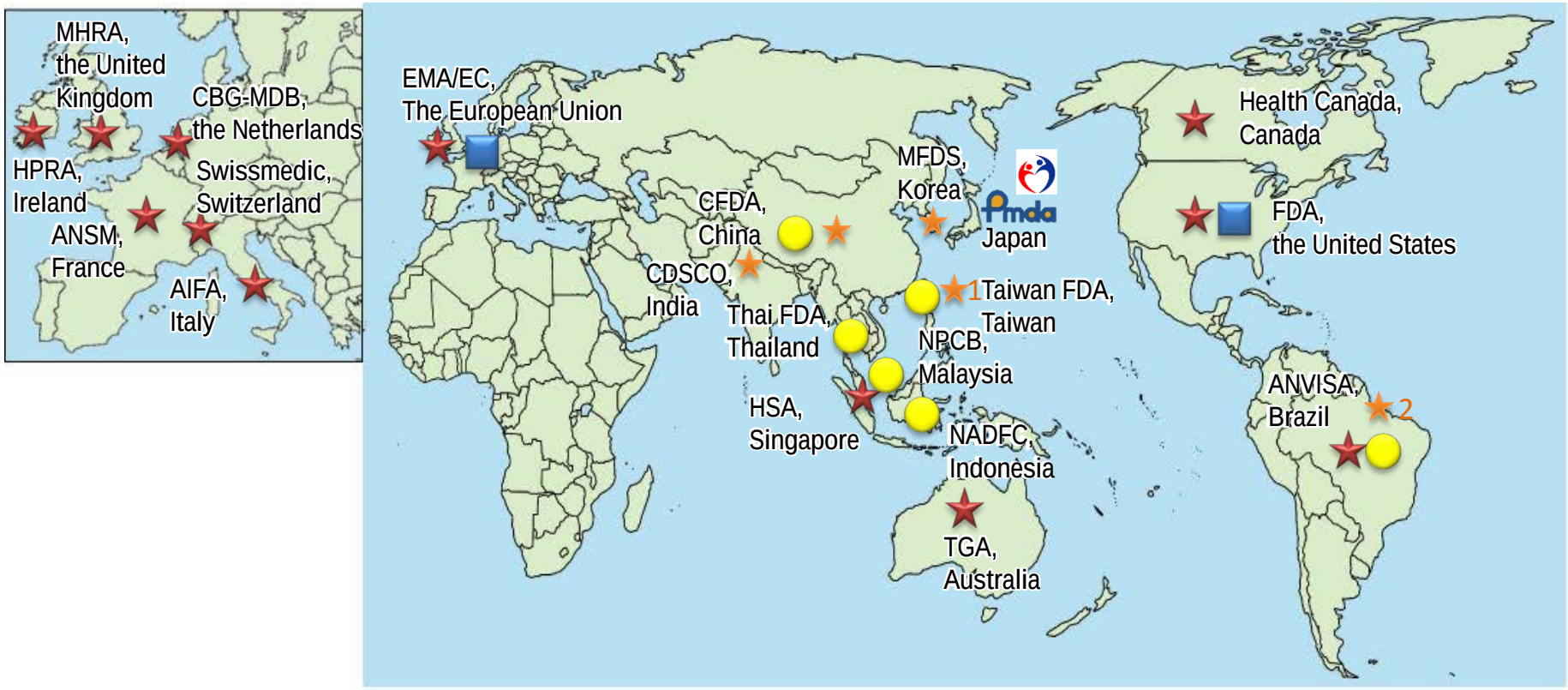
MHLW/PMDA Bilateral Partnerships



Confidentiality Arrangement signed

PMDA staff stationed at the agency

Joint symposium held

Cooperative Arrangement signed

1 Taiwan: Memorandum of Understanding (MOU) for the "Establishment of the Framework of the Cooperation on Medical Products Regulation" has been signed between the Interchange Association of Japan and the East Asia Relations of Taiwan.

2 Brazil: Memorandum of Cooperation (MOC) has been signed on cooperation of pharmacopoeia.

Cooperation in Global and High-Level Frameworks

- **Summit of Heads Medicines Regulatory Agencies :** Information and opinion exchange by heads of regulatory authorities on pharmaceutical regulation
- **ICMRA (International Coalition of Medicines Regulatory Authorities**): A leadership role in planning and coordination among regulatory authorities, e.g. crisis management and pharmacovigilance.
- **Japan will host the 12th Summit and ICMRA in 2017.**

ICH and its Reform

(International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use)

About ICH

- International harmonization project of technical requirements involving the Regulators and research-based Industries
- Accomplished through the development and implementation of harmonized Guidelines

ICH Reform (Oct 2015)

- MHLW/PMDA is a permanent member in Management Committee
- **New membership application is now open for regulators and industries in global society**

All the players in good harmony

Thank you for your attention