Updated Regulatory Strategies for Innovative Medical Devices in Japan

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The importance is…

- EARLY ACCESS of patients for effective and safe medical device with guaranteed quality

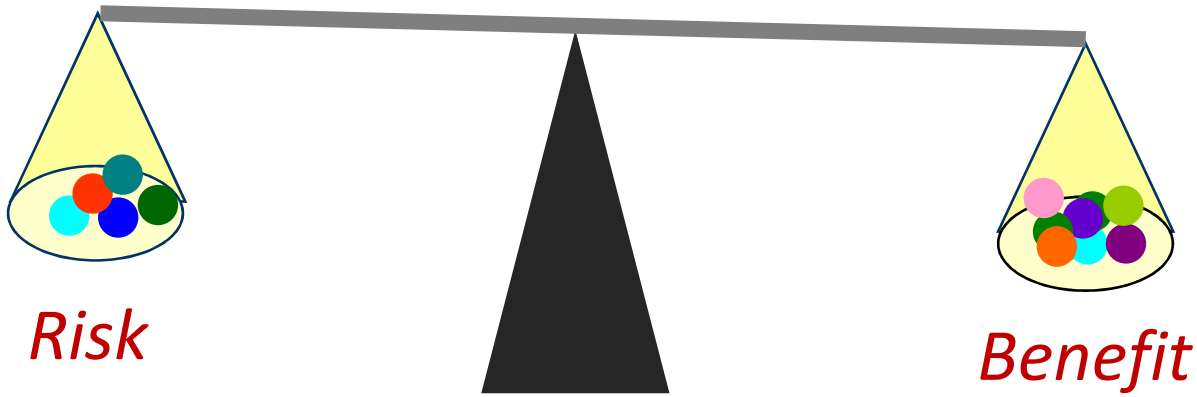
EXPEDITING OF REVIEW/DEVELOP PROCESS

1. *Evolving early access scheme*
2. *Use of real world data*

Basic concept of reviews

- *To evaluate safety and performance (efficacy), then examine the benefit and risk balance.*

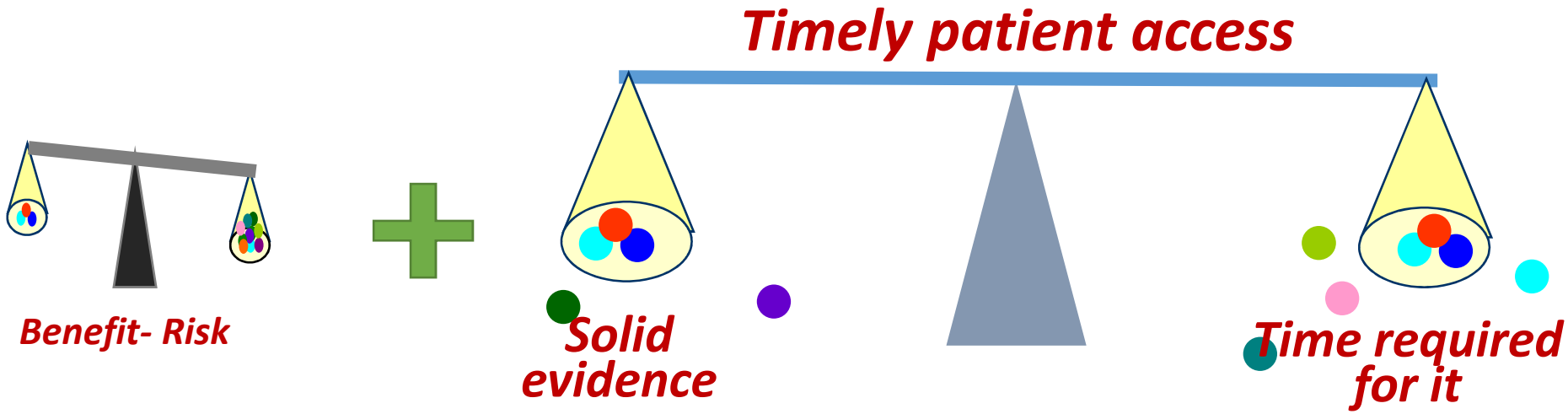
- *Also examine the appropriateness of the description of device's characteristics and the labelling that define usage circumstances.*
  (intended use, instruction for use, precautions etc.)



Additional thinking

- *It is demanded to reconsider the balance between **patient's timely access** to MDs and **considerable amount of time** required to conduct clinical trials in order for much more robust evidence.*

- *Also it's required to examine further the balance of what should be required **in pre- and post-market stage**.*



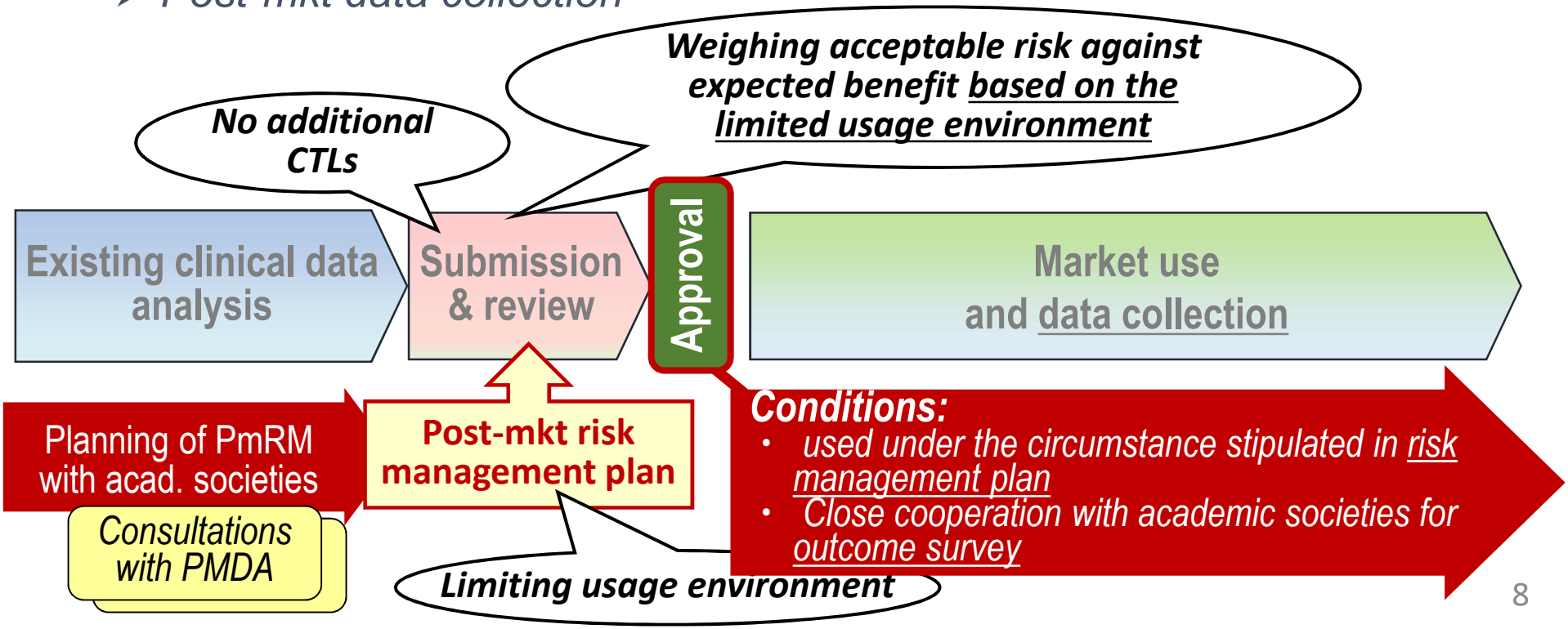
1. Evolving Early Access schemes

- *MHLW implements following measures to accommodate patient access demand.*

Type	Measures
Priority	Priority review, orphan designation
Conditional approval	**Conditional and Accelerated Approval Scheme**
Rolling submission	**Forerunner (*SAKIGAKE*) Review Assignment**

(1) Conditional and Accelerated Approval Scheme

- *MHLW clarified circumstances where new MD can be approved with exploratory trial data.* (July 2017)
  - MDs for life-threating disease that has no effective treatment
  - Extraordinary difficulties in conducting confirmatory trial within reasonable time frame (eg. Too long period of time due to very small number of Pts)
  - Post-mkt risk management plan developed in conjunction with related academic societies (eg. Dr/hospital qualification, rules for proper use)
  - Post-mkt data collection



(2) SAKIGAKE Review Assignment*

(* Forerunner, pioneer)

Since 2015, MHLW assigns the world's first products currently being developed with high expectation.

Assignment criteria

- *Prominent effectiveness and dire medical needs for the therapy*
- *Technological innovativeness*
- *World's first submission in the future* (incl. simultaneous submissions)

Supports from RAs

" feel like I'm riding a train going to approval, while others struggle to find their way there "

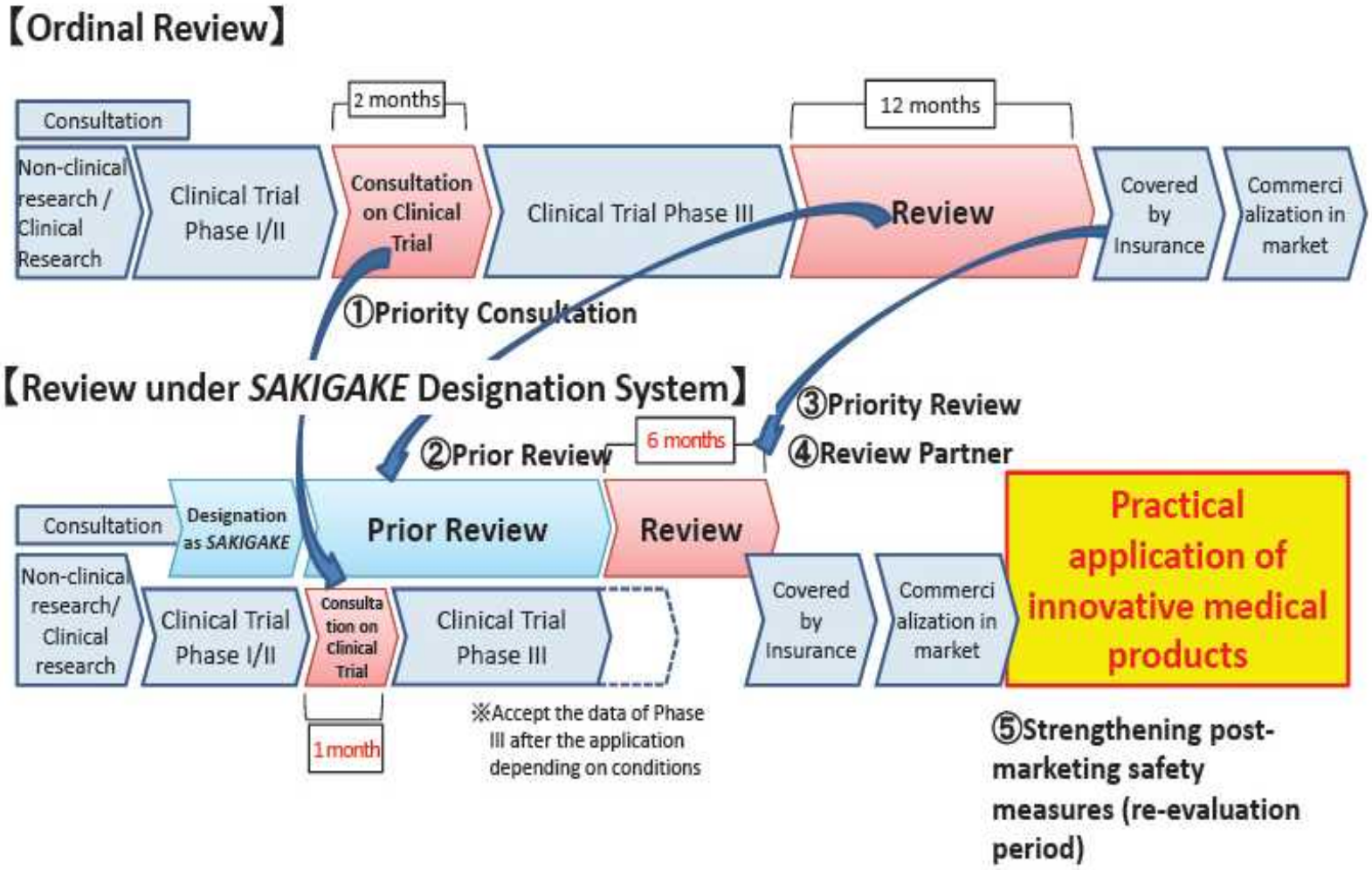
1. Review partner ***[A PMDA manager as a concierge]***

2. Prioritized consultation

3. Substantialized pre-submission assessment

4. Prioritized review

SAKIGAKE Designation System



SAKIGAKE Assignment for MD/IVD

(Feb. 2016(#1), Feb.2017(#2-5))

	Name	Proposed indication	Sponsor
#1	**Titanium Bridge** (Hinge-type titanium plates) 【2017 Dec.15 approved (1st in Sakigake designated products)】	Adduction-type spasmodic dysphonia	Nobelpharma
#2	**Tracheal prosthesis** (made of polypropylene mesh and collagen sponge)	Aiding reconstruction of tracheal while maintaining intratracheal structure after partial removal.	Daiichi Medical
#3	**Boron neutron capture therapy system** (Neutron irradiation system for BNCT)	Glioblastoma, head and neck cancer (Selective destruction of tumor cells marked by boron agents)	Sumitomo Heavy Industries, Ltd.
#4	**UT-Heart** (Software to aid CRT)	Higher accuracy prediction of effectiveness of cardiac resynchronization therapy for patients with serious heart failure.	Fuji Film
#5	**Cancer-related gene panel examination system**	Collective examination of cancer-related genes to aid decisions on cancer treatment strategies	Sysmex

SAKIGAKE Assignment for MD/IVD

(Mar. 2018(#6-7))

	Name	Proposed indication	Sponsor
#6	**Cardiac-repair patch(OFT-G1(tentative name))** (combination of bioabsorbable and stretchable non-bioabsorbable synthetic polymeric threads and a bridging gelatin membrane)	A Cardiac-repair patch used during cardiovascular intervention - Applied to correct blood flow, maintain hemoperfusion, and to construct/reconstruct surrounding tissues	Teijin limited
#7	**CliniMACS CD34 System** (CD34 positive cell selective isolation system)	Product capable of facilitating synostosis - Administered to the site of non-union bone fracture with collagen-containing soft-tissue injection materials as a scaffold	Miltenyi Biotec K.K.

2. Use of real world data

- *MHLW is developing regulatory systems supporting pragmatic trials using registries/health records.*

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph
and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MAN
trials did not adequately inform practice because they were optimized t
determine efficacy.[1] Because such trials were performed with relatively sma

An attractive alternative to trials in which **electronic health records** are used can be found in trials of alternative interventions involving patients who are already enrolled in **disease-specific or intervention-specific registries** that incorporate detailed patient phenotypes and long-term follow-up data. This framework provides **an efficient and low-cost opportunity for conducting pragmatic trials** (e.g. the TASTE trial)

Ford I. et al. NEJM 375;5, 454-463, 2016
http://www.nejm.org/doi/full/10.1056/NEJMra1510059?query=featured_clinical-trials

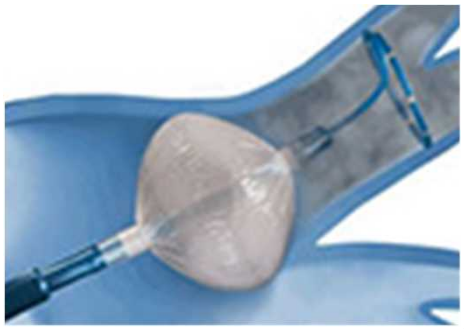
Examples of use of registry outcome for approval review

- **Da Vinci Surgical System**
  (Additional application of MVP & ASD)

  Comparison with results using conventional methods from the Society of Thoracic Surgeons (STS) National Database.

- **SATAKE Hot Balloon Catheter**
  (Paroxysmal atrial defibrillation therapy for high-frequency ablation catheters)

  Comparison with results using conventional methods from the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF) of the Japanese Heart Rhythm Society (JHRS).



Examples of use of registry outcome for approval review

- Kawasumi Najuta Chest Stent Graft System
  (Stent graft for prevention of aortic aneurysm rupture)

  Comparison with results from surgery from the historical control group of the Japan Adult Cardiovascular Surgery Database （JACVSD).

- EXCOR Ventricular assist system (VAS)

  Comparison with the matching patient group survival rate from the ECMO treatment registry: Extracorporeal Life support Organization (ELSO).

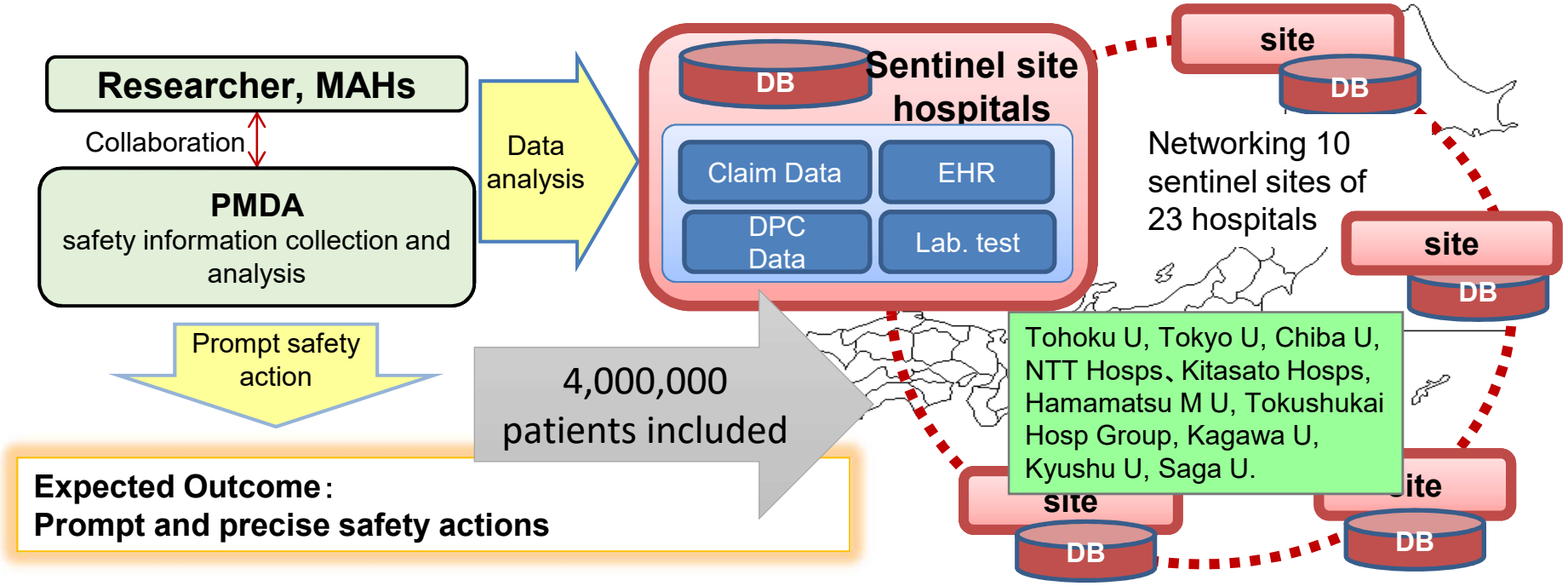
Use of electronic medical records for regulatory submission

- *MHLW published/will publish followings in 2017 as to develop the standards and general considerations for ensuring the reliability of electronic medical records (EMR) used for post-marketing studies / surveillances.*

- **Revision of Good Post-marketing Study Practice Ordinance** (Oct. 2017)
  - To address contract relations, Medical institution, DB providers and MAH to specify the information sources and responsibilities
- **General Considerations on using EMR for Drug PMS** (June 2017)
  - Scope of usable data and general consideration on study designs
  - Scientific consideration, characters of DB for PMS purposes
- **General Considerations on data reliability of EMR DBs for PMS** (tba)
  - Describe the range of data to be verified and preserved in terms of guaranteeing the reliability when using application data.

Medical Information Database Network（MID-NET）

- Promote safety measures by pharmaco-epidemiological method using medical information database.
- MHLW/PMDA have established a medical information database for collecting large-scale medical data at sentinel site hospitals and have constructed analytical systems at PMDA since FY 2011.



【History and way forward】

- ●April 2010 : 「Revision of pharmaceutical administration etc. to prevent recurrence of pharmaceutical disasters (final recommendation) 」
- ● April 2011 - : Start construction of MID-NET system
- ● April 2013 - : Start data quality validation to assure precision and comprehensiveness of the collected data
- ● April 2015 - : Start trial operations by PMDA and sentinel sites
- ● April 2015 - : Setting utilization rules for full-scale operation and framework of operation cost / user fees.
- ● in FY 2018 : Full scale operation, enable MAHs and researchers to use MID-NET

CONSIDERATION FOR EMERGING TECHNOLOGIES

Software as a Medical Device (SaMD) is regulated in PMD Act

Example of Medical Device with embedded program

Image Diagnostic Apparatus

It processes, stores and displays image data from CT, MRI etc.

Data from CT scanning

Processing by program

3D image of a skull

PAL

Software (program)

Hardware

Combination of hardware and software is regulated as a total system.

MD Regulation

PMD Act

SaMD

Software (program)

Software itself is independently regulated

Category of SaMD in the cabinet ordinance on PMD Act

1. SaMD for diagnosis of disease and its recording medium

2. SaMD for treatment of disease and its recording medium

3. SaMD for prevention of disease and its recording medium

- Class I SaMD is not subject to approval/certification under PMD Act.

Establishment of the Science-Based

Basic Research

Seeds of New drug/medical devices/regenerative medicine product

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

Practical use

Innovative medical products

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

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

Office of Review Innovation

Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.

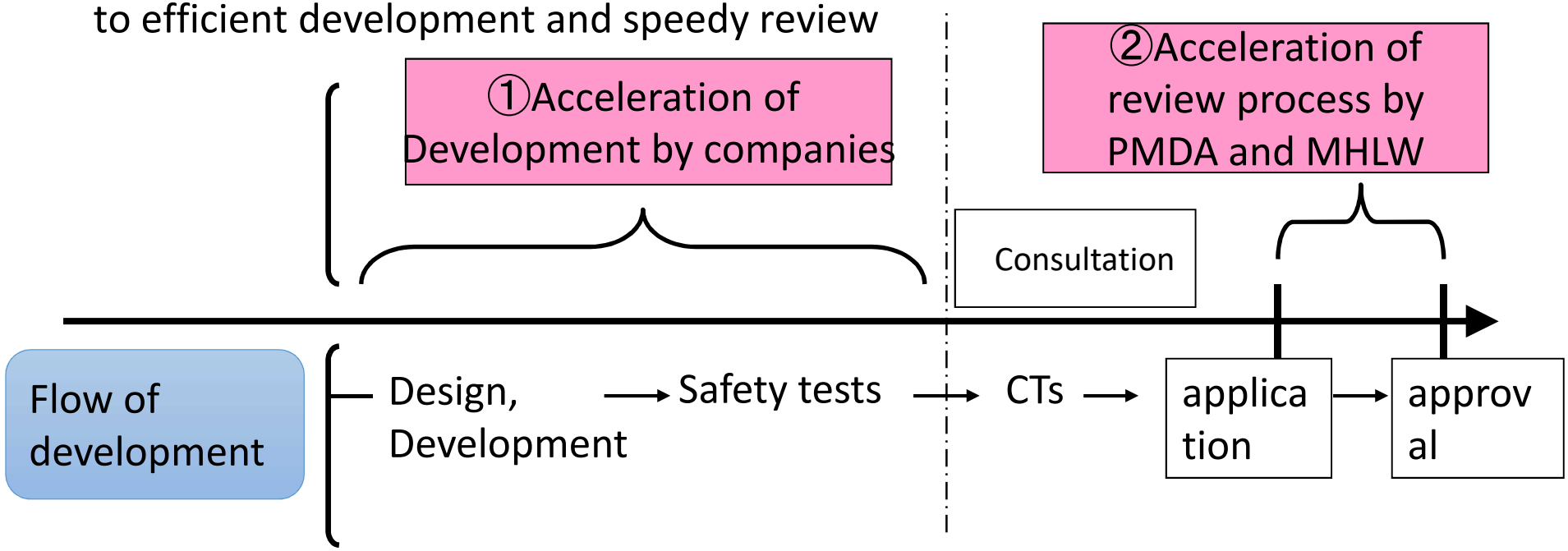
Board members

Academia

Review guidance for Next-generation regenerative medicine products

Purpose

To facilitate development of diverse innovative regenerative medicine products, publishing review guidance for regenerative medicine products with extensive medical needs and practicability , which is expected to enable to efficient development and speedy review



Results

more than 10 review concepts for cell sheets, regenerative cartilage and iPS have been published

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