Regulatory Updates on Medical Devices in Japan

- Our efforts to deliver safe and innovative medical devices to patients-

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Coordinator, Office of International Programs

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Today’s Agenda

1. Overview of PMDA and regulation on medical devices in Japan

2. Utilization of RWD for approvals and post marketing measures

3. Regulatory updates for SaMD

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1. Overview of PMDA and regulation on medical devices in Japan

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3. Regulatory updates for SaMD

Japanese Regulatory Authorities in Pharmaceutical and Medical Devices Affairs

Pharmaceutical Safety and Environmental Health Bureau, MHLW
厚生労働省　医薬生活衛生局

MHLW

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

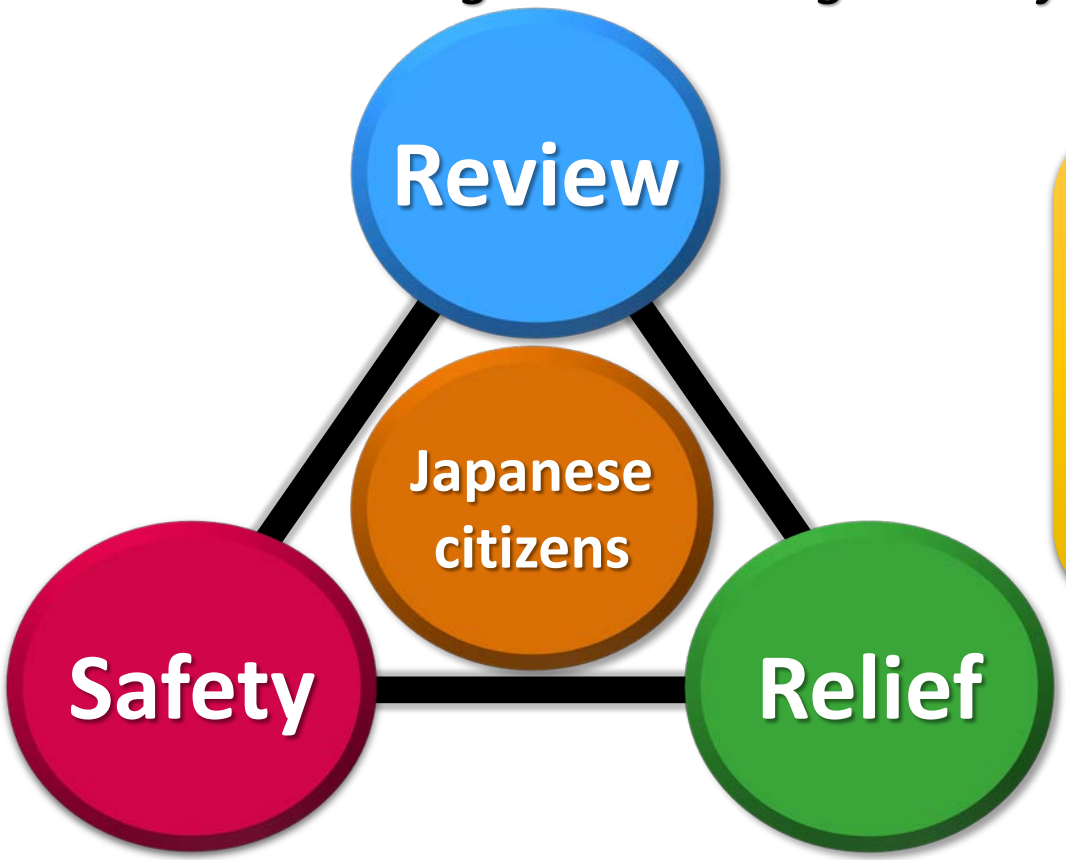
Pharmaceuticals and Medical Devices Agency
医薬品医療機器総合機構

PMDA

- **Scientific Review for Drugs, Medical Devices and Regenerative Medicines.**
- **GCP, GMP, QMS Inspection**
- **Scientific Advice for Clinical Trials etc.**

PMDA’ s Three Major Services - Safety Triangle -

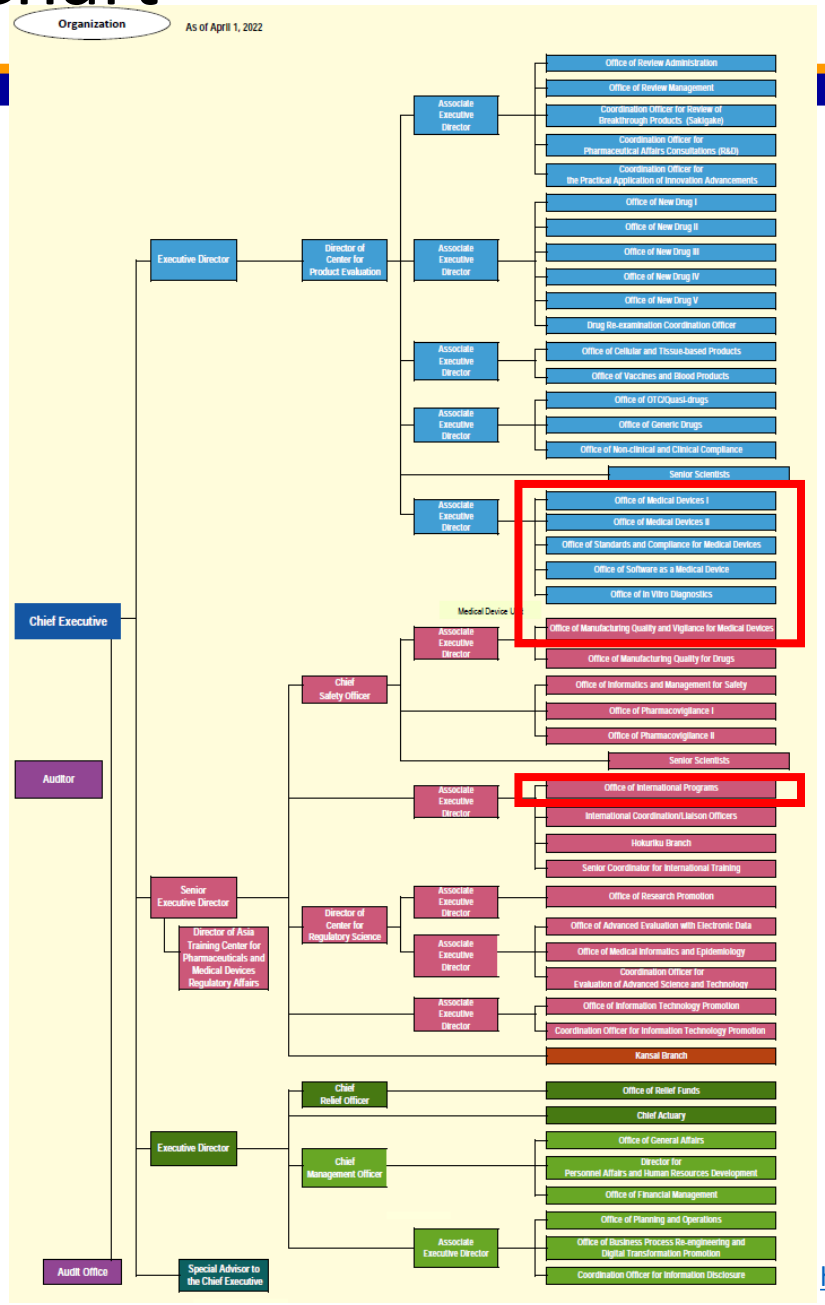
Comprehensive Risk Management through the 3 functions



World-class pharmaceutical regulatory system for protecting the safety of the people

As the only regulatory authority in the world which plays three roles in an integrated manner, PMDA contributes to improve the standard of medical care by delivering safer and higher quality products faster to medical practice based on regulatory science

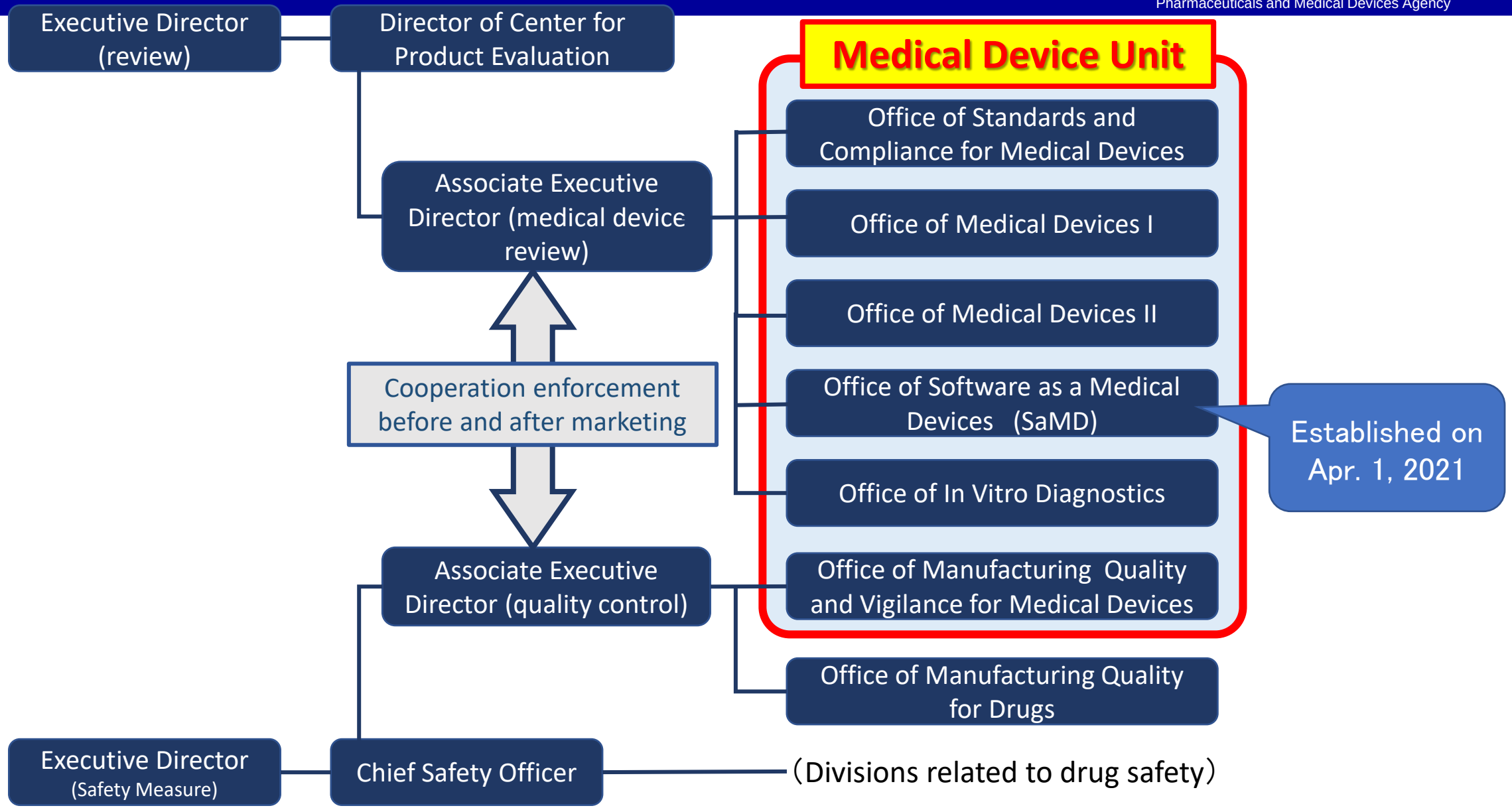
PMDA's Organization Chart



As of April 1, 2022

https://www.pmda.go.jp/english/about-pmda/outline/0003.html

PMDA's Medical Device Unit



Legal Structure for Medical Device Regulations

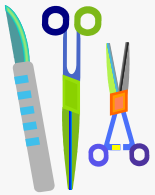
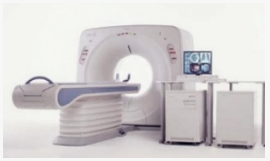
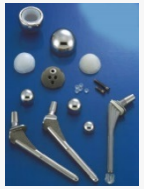
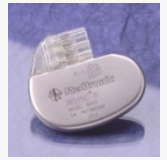
Act	Pharmaceuticals and Medical Devices Act (**PMD Act**), 1960
Cabinet Order	Cabinet Order on PMD Act, 1961
Ministerial Ordinance	Ministerial Ordinance on PMD Act, 1961 GCP/GLP for medical device, 2005 Good Vigilance Practice (GVP) Quality Management System (QMS) etc.
Ministerial Notification	Essential Principles Certification criteria for class II/III devices Classification of medical devices List of orphan designation etc.
Notification	Information on application procedures Guidelines for clinical evaluation etc.

Definition of Medical Device under PMD Act

The term “medical device” as used in the Act refers to appliances or instruments, etc. which are **intended for** use in the diagnosis, treatment or prevention of disease in humans or animals or **intended to** affect the structure or functioning of the bodies of human or animals, which are specified by Cabinet Order

~ PMD Act Article 2.4

Medical Device Regulations in Japan

Classification	Class I	Class II	Class III	Class IV
Category	General MDs	Controlled MDs	Specially controlled MDs	
Premarket regulation	Self-declaration	Third party certification	MHLW approval (PMDA review)	
Example		 	 	  
Post market safety (vigilance/surveillance)	PMDA and MHLW			

Review Period by category of New Medical Devices

【New Medical Devices（regular review）】

Target review times: 14 months

	FY2019	FY 2020	FY 2021
Percentile	80%	80%	80%
Total review times(months)	11.1	10.8	11.9
No. of approved applications	27	19	33

【Improved Medical Devices with Clinical Data】

Target review times: 10 months

	FY2019	FY 2020	FY 2021
Percentile	60%	60%	60%
Total review times(months)	8.6	8.6	8.8
No. of approved applications	43	48	43

【Improved Medical Devices without Clinical Data】

Target review times: 6 months

	FY2019	FY 2020	FY 2021
Percentile	60%	60%	60%
Total review times(months)	5.5	5.6	5.7
No. of approved applications	206	263	209

【Generic Medical Devices】

Target review times：4 months

	FY2019	FY 2020	FY 2021
Percentile	60%	60%	60%
Total review times(months)	3.6	3.4	3.6
No. of approved applications	719	731	736

The Targets were achieved in all category

※For FY 2021, preliminary data is used

Device Lag between the U.S. and Japan

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY2018	FY 2019	FY 2020
Development lag (years)	**1.2**	**1.2**	**0.8**	**1.9**	**2.6**	**1.4**	**0.6**	**2.3**
Review lag (years)	0	0	0	0	0	0	0	0
Device lag (years)	1.2	1.2	0.8	1.9	2.6	1.4	0.6	2.3

median time (years)

- Development lag：
Differences in timing which the medical companies submit marketing applications to the regulatory agencies in the United States and Japan
- Review lag：
Differences in the review time (from submission to approval of marketing applications) between the United States and Japan
- Device lag ：Sum of Development Lag and Review Lag

Current challenge is to shorten development lag

Promoting conduct of international clinical trial and utilization of RWD is important

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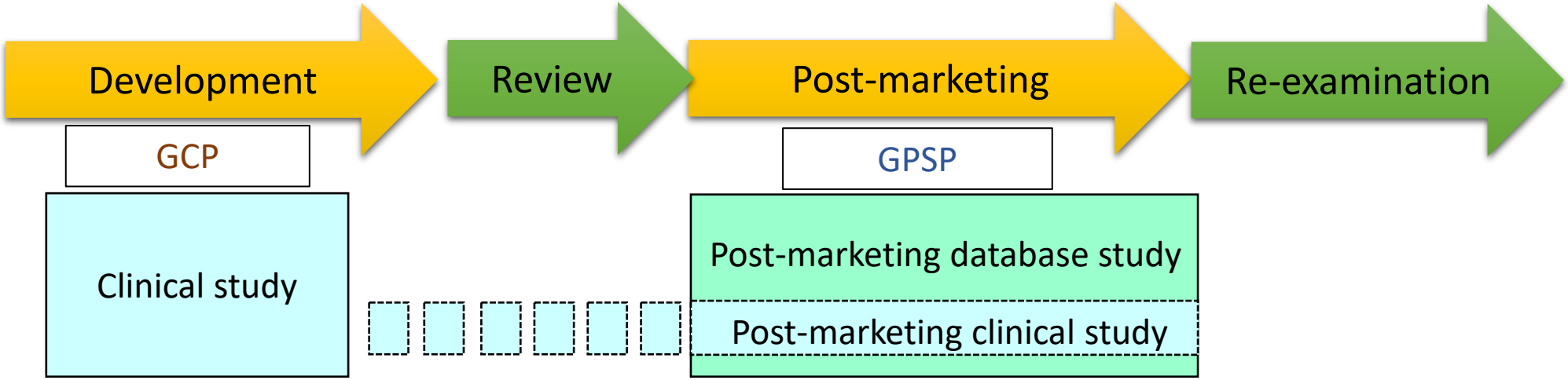
3. Regulatory updates for SaMD

PMDA's Efforts Toward Utilization of Real-World Data (RWD)



Utilizing registries in medical device development in cases where traditional randomized clinical trials are not feasible (such as for orphan devices)

Utilizing registries in post-marketing surveillance for safety assessments

April, 2019 **New Consultation Category : Utilization and Reliability of Registry Data for Registry Holders and Product Developers**

March, 2021 **Two guidelines were released (PHEHB/PED,PHEHB/MDED Notification No.0323-1, 0323-2)**

- **Basic principles for utilizing registries for applications**
- **Points to consider for ensuring the reliability of registry data for applications**

Basic Principles on Utilization of Registry for Applications (PSEHB/PED Notification No.0323-1, Mar. 23, 2021)

The GL was developed on the utilization of registry data for the following cases

1. Utilization of registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications
2. Utilization of registry data as complement or substitute of clinical study for efficacy and/or safety evaluation in applications
3. Utilization of registry data in evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional time-limited approval
4. Utilization of registry data in post-marketing efficacy and/or safety evaluation

The GL also provides Points to Consider on the following items when utilizing registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications

- Registry Patient Population
- Evaluation Period
- Endpoints
- Statistical Method
- Type of observational study for natural history (prospective or retrospective)

Case 1: External control of clinical studies for efficacy/safety evaluation in application

EXCOR Pediatric: External LVAS for children

（Marketing Authorization Holder in Japan: Cardio, inc.）

Blood Pumps of EXCOR Pediatric

- A one-arm clinical study was conducted in the US
- The external control group was formed with pts of similar severity extracted from the registry database of Extracorporeal Life Support Organization (ELSO) by using propensity score matching method
- Survival rate and survival period were compared between clinical study pts and external control pts

(Ref：PMDA Review Report)

Case 2: Complement/substitute of clinical study for efficacy/safety evaluation in application

Paxman Scalp Cooling System Orbis
（Marketing Authorization Holder in Japan:
Century Medical, Inc.）

- A domestic clinical trial was conducted with breast cancer pts
- In the clinical evaluation for other solid tumors than breast cancer, data from foreign registries used as a reference data
- Intended use was set for pts with solid tumors other than breast cancer

(Ref : PMDA Review Report)

Examples of Utilization of Registry for Approval in JAPAN

Name of Product	Type of Utilization	Registry Used
EXCOR Pediatric VAS	**External Control**	ELSO-DB：ECMO patient registry（**US**）
Kawasumi Najuta Thoracic Stent Graft System	**External Control**	JACVSD：Adult cardiovascular surgery DB（**Ja**）
HVAD	**External Control**	INTERMACS（**US**）
daVinci Surgical System	**External Control**	STS-DB：Thoracic surgery DB（**US**）
MitraClip NT System	**External Control**	Duke Medical Center DB（**US**）
SATAKE・HotBalloon Catheter	**External Control**	J-CARAF DB: AF catheter ablation registry（**Ja**）
Heart Mate 3	**External Control**	INTERMACS（**US**） J-MACS (Japanese ver. of INTERMACS)（**Ja**）
Paxman Scalp Cooling System	Supportive Data	Netherlands Cancer Registry（**Holland**）
Edwards SAPIEN3	Supportive Data	STS/ACC TVT Registry（**US**）
Core Vulve Evolut R	Supportive Data	STS/ACC TVT Registry（**US**）
Edwards SAPIEN3	Supportive Data	STS/ACC TVT Registry（**US**）

(Ref: PMDRS, 52(5), 318～324（2021）)

Case 3: Post-marketing efficacy/safety evaluation

- When using **“disease registry”**, it may be able to evaluate device efficacy and/or safety by comparing pts who used certain device with those who did not (ex. CCISC etc.)
- When using **“device registry”**, while all the registered pts have devices used, it may be able to compare the efficacy/safety or different models (ex. INTERMACS etc.)

Caution:

In Japan, a post-marketing survey covering all cases may be imposed. In this case, the regulator may require that all patients for whom the medical device are used be registered in the registry to be utilized for PMS.

Examples of Utilization of Registry for PMS in JAPAN

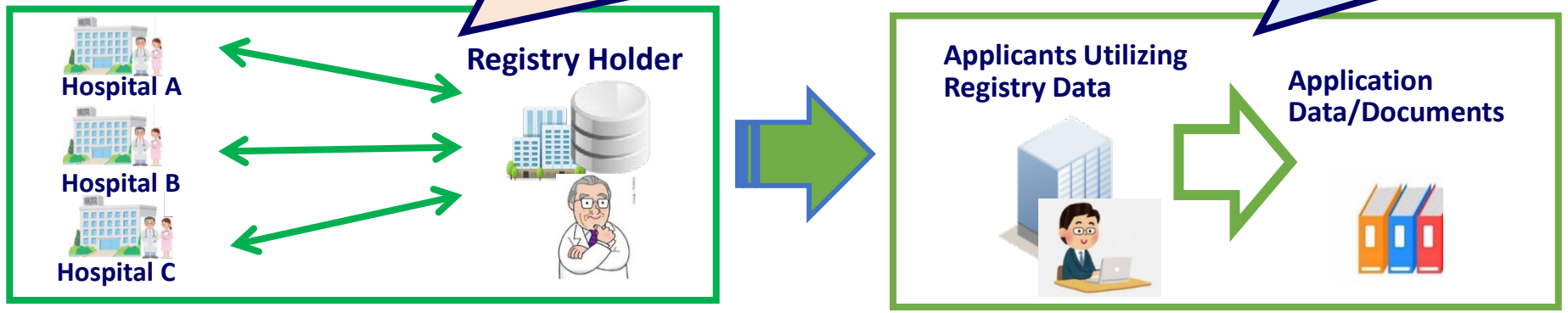
Name of Product	Summary of Product	Affiliated Societies（Registry）
AMPLATZER Piccolo Occluder	Occlusion device for PDA	Japanese Society of Pediatric Cardiology and Cardiac Surgery etc.（J-CIC Registry）
Edwards SAPIEN3	TAV for congenital heart diseases	
Woven EndoBridge Device	Embolization device for intracranial ANs	Japanese Society for Neuroendovascular Therapy（JSNET-DB）
PULSERIDER	Embolization device for intracranial ANs	
Pipeline Flex Flow diverter system	Embolization device for intracranial ANs	Japan Neurosurgical Society（NCD-DB）
Edwards SAPIEN XT	TAV for severe aortic stenosis	Council for Transcatheter Heart Valve Therapy Related Academic Societies（TAVI Registry）
Edwards SAPIEN3		
Core Valve	TAV for severe aortic stenosis	
Core Valve Evolut R		
Core Valve Evolut PRO		
EVAHEART	Implantable ventricular assist system	Japanese Associasion for Thoracic Surgery etc.（J-MACS）
DuraHeart		
Jarvik2000		
HeartMate Ⅱ		
HeartMate 3		

(Ref: PMDRS, 52(5), 318～324（2021）)

Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications (PSEHB/PED Notification No.0323-2, Mar. 23, 2021)

- Governance by Registry Holders
- Quality Management (QM) and Security of Computerized System
- Consideration for Protection of Personal Information
- QM and QA of Registry Data etc.

- Contracts with Registry Holders
- Confirmation of Data QM Implemented by Registry Holders
- Preparation of Application Data/Documents
- Storage of Records etc.

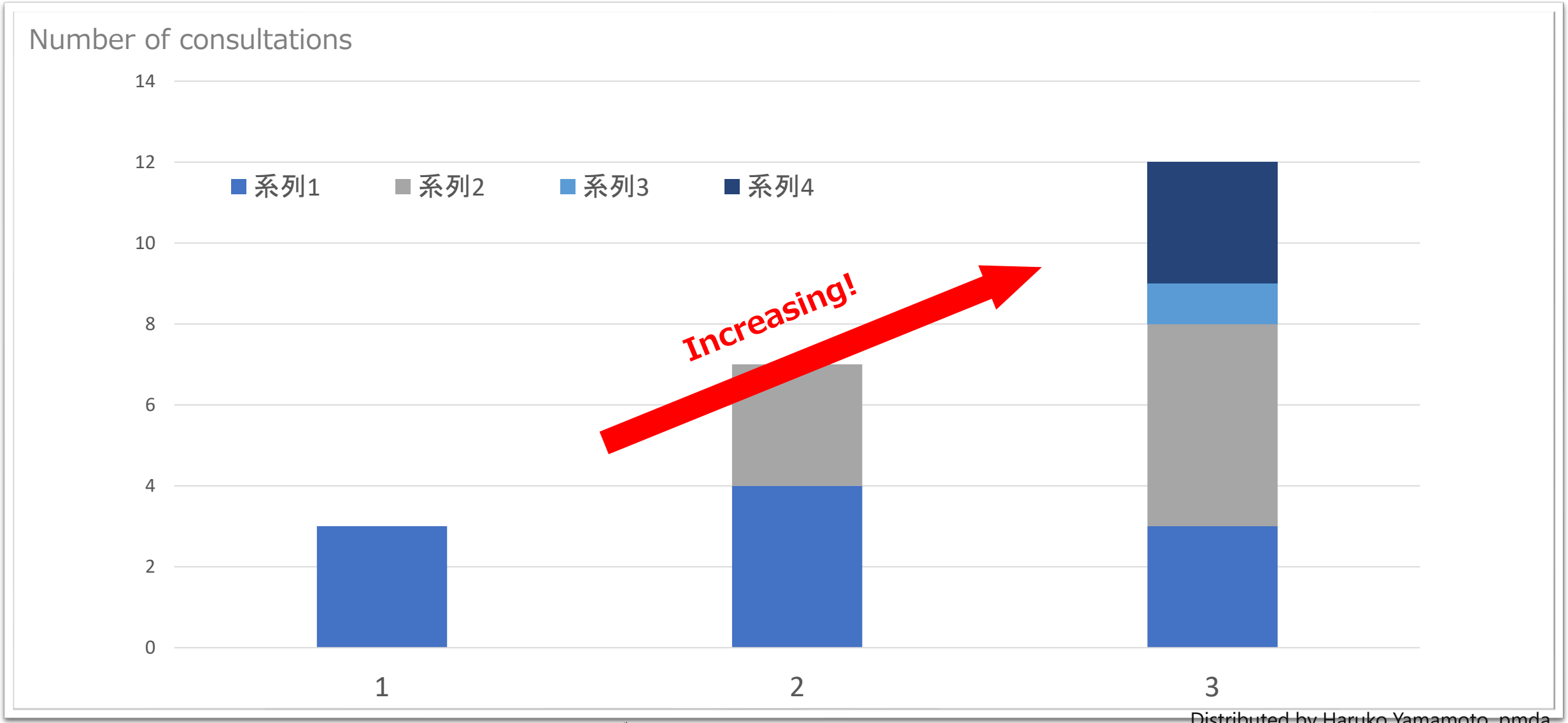


- The scope of this notification includes not only the registries to be newly constructed but also the registries that have been constructed with accumulated data
- As the level of reliability required for the registry data may vary depending on the purpose of utilization, **an applicant is encouraged to consult PMDA** in the case of utilization of registry data as Application Data/Documents, etc.

PMDA Consultation Services on Patient Registries/Databases

Type of Consultation	Contents
Consultation on Registry Utilization	- Advice on the plans of utilization of the registries in filing applications for regulatory approval or re-examination of drugs, medical devices and reproductive medical products - Advice on regulatory points of view on ensuring data integrity and reliability - For registry holders (mainly academic)
Consultation on Registry Use Plan	- Advice on plans for use of the relevant registry, particularly focusing on appropriateness of use, adequacy of outcome measures, etc. - For applicants who wish to utilize patient/disease registries for evaluation of the efficacy and safety of individual products in filing applications for regulatory approval or re-examination
Consultation on Compliance Assessment of Registries to be used for regulatory purposes	- Advice on the data integrity of the registries to be used, before the relevant applicant files the application or initiates post-marketing surveillance - For individual products for which application for regulatory approval or re-examination is planned to be filed utilizing data from patient/disease registries
Consultation on Medical Information Database Utilization	- Advice on the plans of utilization of the databases in filing applications for regulatory approval or re-examination of drugs - Advice on regulatory points of view on ensuring data integrity and reliability - For database operators
Consultation on Compliance Assessment of Databases to be used for regulatory purposes	- Advice on the data integrity of the databases to be used, before the relevant applicant files the application or initiates post-marketing surveillance - For individual drugs for which application for regulatory approval or re-examination is planned to be filed utilizing data from databases

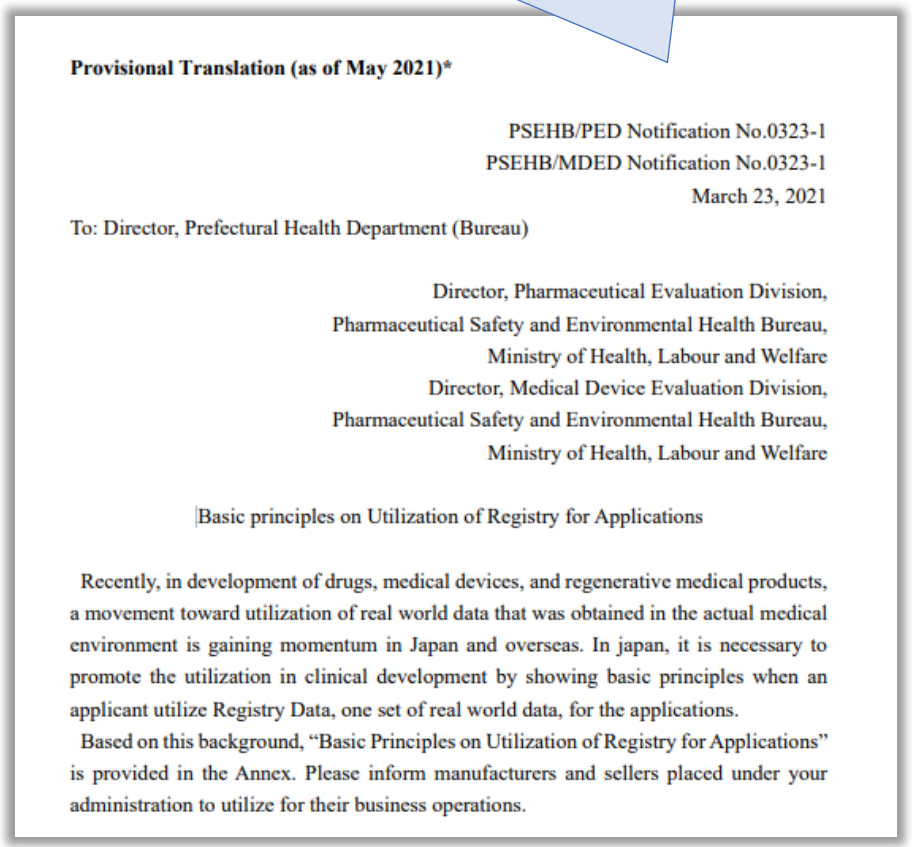
The Number of Consultations on Registry & Database Conducted by PMDA



PMDA's Efforts Toward Utilization of Real-World Data (RWD)

PMDA published the following two guidelines on March 23, 2021.

Basic principles on Utilization of Registry for Applications



Provisional Translation (as of May 2021)*

PSEHB/PED Notification No.0323-1
PSEHB/MDED Notification No.0323-1
March 23, 2021

To: Director, Prefectural Health Department (Bureau)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
Director, Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

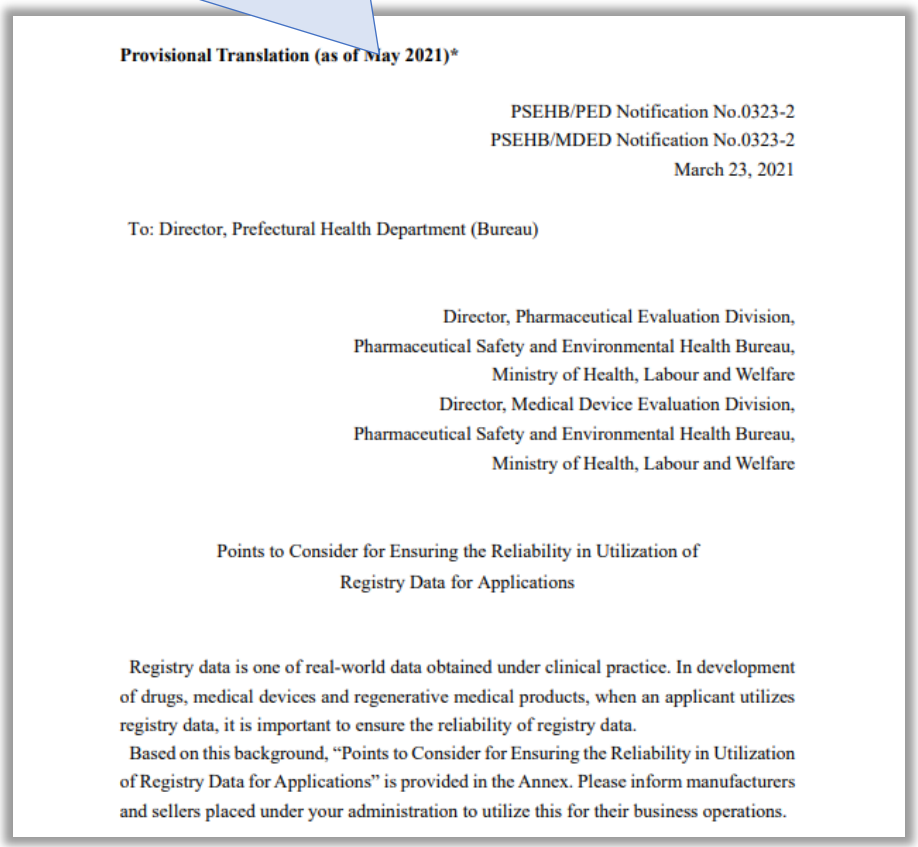
Basic principles on Utilization of Registry for Applications

Recently, in development of drugs, medical devices, and regenerative medical products, a movement toward utilization of real world data that was obtained in the actual medical environment is gaining momentum in Japan and overseas. In japan, it is necessary to promote the utilization in clinical development by showing basic principles when an applicant utilize Registry Data, one set of real world data, for the applications.

Based on this background, "Basic Principles on Utilization of Registry for Applications" is provided in the Annex. Please inform manufacturers and sellers placed under your administration to utilize for their business operations.

https://www.pmda.go.jp/files/000240810.pdf

Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications



Provisional Translation (as of May 2021)*

PSEHB/PED Notification No.0323-2
PSEHB/MDED Notification No.0323-2
March 23, 2021

To: Director, Prefectural Health Department (Bureau)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
Director, Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications

Registry data is one of real-world data obtained under clinical practice. In development of drugs, medical devices and regenerative medical products, when an applicant utilizes registry data, it is important to ensure the reliability of registry data.

Based on this background, "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" is provided in the Annex. Please inform manufacturers and sellers placed under your administration to utilize this for their business operations.

https://www.pmda.go.jp/files/000240811.pdf

Projects Across Multi-Offices in PMDA
Newly Established RWD WG (in April 2021)

RWD WG

- Implementation of the guidelines on patient registries
- Sharing experiences and knowledge on patient registries

- Discuss all subjects on RWD comprehensively
  - ➢ General principles on RWD utilization and data reliability in regulatory setting

Data reliability SWG

Discuss reliability standards on RWD utilization in clinical development etc.

Utilization SWG

Discuss general principles on RWD utilization for efficacy and safety assessment

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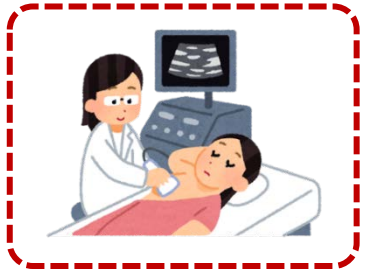
3. Regulatory updates for SaMD

What is Software as Medical Device (SaMD) ?

Previous legislation

program which determines performance of medical device

install



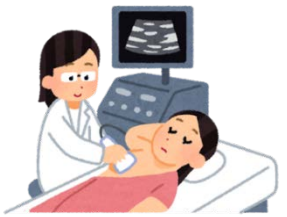
Medical device
（tangible object including software）

Current legislation

program which determines performance of medical device

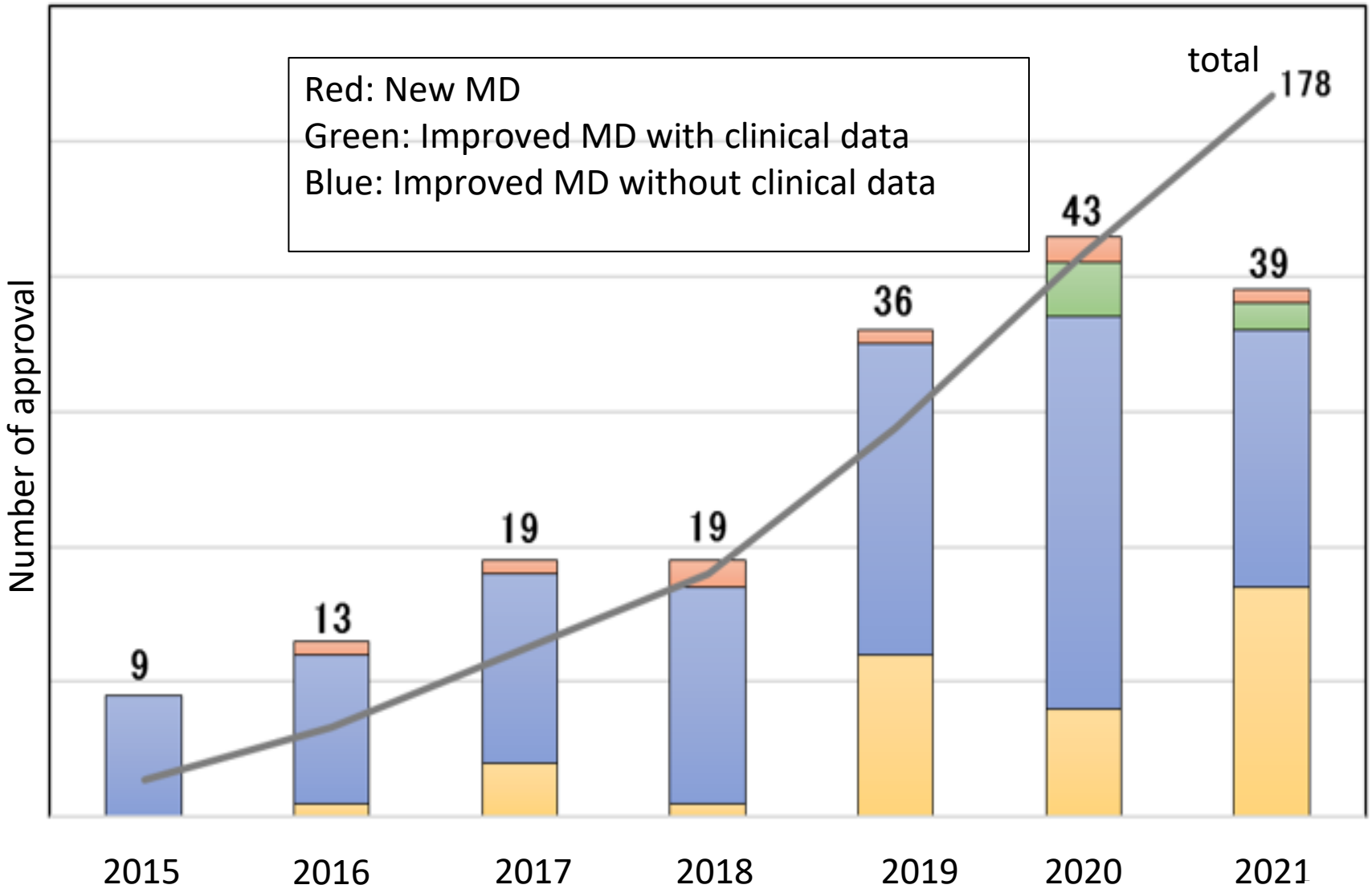
Medical device（software only）

install



MD software classified as Class I is **NOT** subjected to regulations on PMD-Act

Transition of number of approved SaMD



https://www.mhlw.go.jp/content/11124500/000826476.pdf

as of March 31, 2022

DX(Digital Transformation) Action Strategies in Healthcare for SaMD "DASH for SaMD"

1. Early grasp of research seeds and publication of the review policy

a. Grasp research seeds in the early stage of development

b. Organize and Publish the review policy based on characteristics of SaMD

2. Unification of the consulting contact point

a. Unify consultation service

b. Publish consultation case examples as many as possible

3. Review system based on characteristics of SaMD

a. Carry out efficient review based on characteristics of SaMD

b. Utilize the Post-Approval Change Management Protocol (PACMP/IDATEN) scheme

c. Consider establishing the innovative SaMD designation system

4. Enhanced structure for early realization

a. Establish new office which specialized in reviewing SaMD in PMDA and MHLW

b. Establish an expert examination committee for SaMD in the Pharmaceutical Affairs and Food Sanitation Council

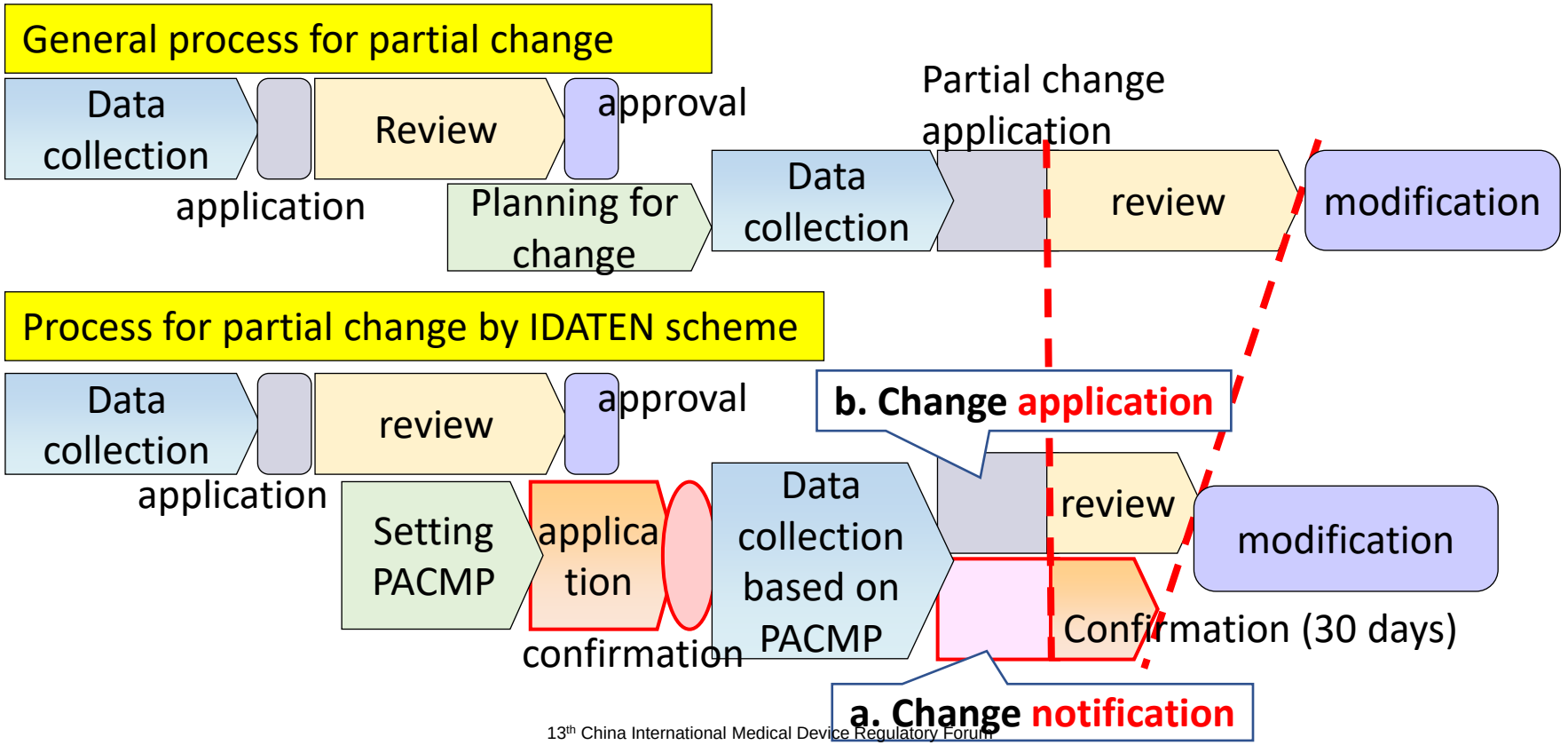
c. Establish a collaborative forum among regulator, academia and industry

d. Enrich published database of approval cases

Utilization of Post-Approval Change Management Protocol (PACMP) ～Challenge to accept “Plasticity” in regulation～

IDATEN （Improvement Design within Approval for Timely Evaluation and Notice）

a. Modification can be made by submitting the change notification and is not required approval review if it follows the PACMP which has been reviewed and confirmed by PMDA.
b. If the modification needs clinical evaluation based on the PACMP, manufacturer needs to submit change application but the application goes under streamlined review.



Consultation for SaMD

Comprehensive consultation for SaMD

Determine whether the product is MD or Non MD

MHLW, Compliance and Narcotics Division

Consultation regarding the determination of whether or not software under development is classified as a medical device under the PMDA Act.

Review the developed product

PMDA, Office of SaMD

Pre-consultation before each consultation (pre-development consultation, clinical trial protocol consultation, etc.) conducted by PMDA.

Consult the reimbursement prices

MHLW, Economic Affairs Division

Various consultations regarding medical insurance.

Take Home Message

PMDA make efforts to deliver safe and innovative medical devices to patients.

✓Utilization of RWD

✓Regulation update of SaMD

Thank you for your attention!

多謝