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# Japan Regulatory Update

IMDRF Sep. 2019 Ekaterinburg

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MHLW



## - Regulatory Authorities in Japan -

### MHLW

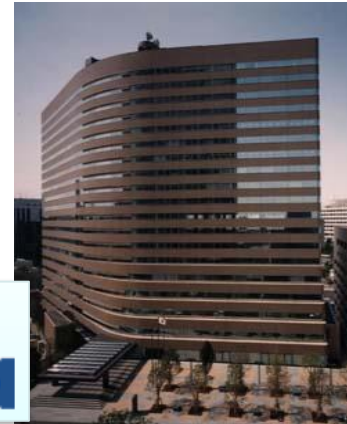
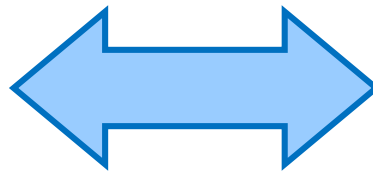
Ministry of Health, Labour and Welfare

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

### PMDA




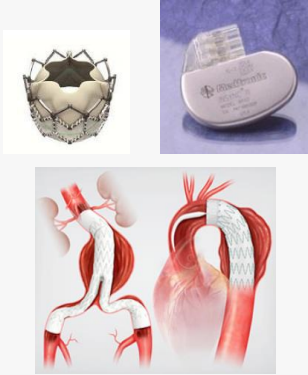
Pharmaceuticals and Medical Devices Agency

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





## 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			



# IMDRF

International Medical  
Device Regulators Forum

## Agenda

- Revision of PMD Act proposed
- 4<sup>th</sup> Round of Sakigake Designation
- Publication of Guidance for evaluating AI imaging system
- PMDA Asian Training Center on medical devices

# (update) Revision of Pharmaceutical and Medical Device Act

- The draft revision of Pharmaceutical and Medical Device Act (PMD Act) is currently under review in the National Diet.
- The revision includes the legislation of SAKIGAKE designation system.

## Current state

### Particularly high medical necessity

Orphan drugs<sup>※</sup>

others

SAKIGAKE products are handled in operations as a subject for priority reviews



## After revision

### Particularly high medical necessity

Orphan drugs<sup>※</sup>

SAKIGAKE drugs

Drugs for specific use

others

Legally clarify that it will be subject to priority reviews

(※) The number of patients who may use the drug should be less than 50,000 in Japan, or the drugs should be indicated for difficult-to-treat diseases.

# SAKIGAKE Designation System

## 【Ordinal Review】



① Priority Consultation

## 【Review under SAKIGAKE Designation System】



③ Priority Review

② Prior Review

④ Review Partner

※Accept the data of Phase III after the application depending on conditions

⑤ Strengthening post-marketing safety measures (re-evaluation period)

# 4th Round of *SAKIGAKE* Designated Products (newly designated on Apr. 8, 2019)

## - Medical Devices -

No.	Name of product	Applicant	Planned indication
1	<i>(tentative name)</i> Microwave mammography	Integral Geometry Science Inc.	Identify the tissues suspected to be breast cancer by microwave and provide the information to the doctor
2	<i>(tentative name)</i> Molds of vascular graft for lower extremity arterial bypass	Biotube Co., Ltd	Improvement of blood circulation failure below the knee by surgical reconstruction and maintenance of its long-term patency by self revascularization in patients with severe lower limb ischemia
3	<i>(tentative name)</i> Phosphorylated pullulan bioadhesive	BioARC Co., LTD.	Improvement of usability and retainability of the adhesive to bone defects with better formativeness and adhesiveness by mixing it with autologous bones, allogeneic bones, heterogeneous bones, artificial bones or their mixtures. Moreover, due to its volumizing effect, using this adhesive can reduce the amount of autologous bone to be collected.

# 4th Round of *SAKIGAKE* Designated Products (newly designated on Apr. 8, 2019)

## - In-vitro Diagnostic Drugs -

No.	Name of product	Applicant	Planned indication
1	<i>(tentative name)</i> Pancreas and biliary tract cancer test kit utilizing DNA chip technology MI-004	TORAY INDUSTRIES, INC.	Expression pattern analysis of microRNAs in RNA extracted from serum (diagnostic aids for pancreas and biliary tract cancer)

5<sup>th</sup> Round of *SAKIGAKE* Designation application process will be opened in Oct. 1 – Nov. 29, 2019.



## Guidance for evaluation of artificial intelligence–assisted medical imaging systems for clinical diagnosis

Annex 4 of MHLW MDED Notification No.2 May 23, 2019

English translation is available on the NIHS website (bottom of the page):

<http://dmd.nihs.go.jp/jisedai/tsuuchi/index.html>

### Section 1. Introduction

#### Issues:

- Algorithm for calculating output is “black box” nature in AI based on deep learning.
- Its performance, especially after post-market training, can only be evaluated by verification of the output.
- How to consider the source or type of the data, authenticity and bias in the learning data?

This guidance summarizes the issues and points to consider on evaluating the efficacy and safety of the medical imaging system for CAD utilizing AI technology in the approval review.

## Section 5. Open Problems and direction of their solutions:

### (1) Black box

- Approval review process should focus on the performance evaluation by confirming if the input yields the required output.
- Manufacturers should guarantee the performance by indicating that the systems always meet the specifications on performance.
- Functions that inform any unexpected outputs of the system to the users should be also required.

### (2) Changes in performance

#### 1. Continuous verification of performance:

The assistance systems should be validated every time when their performance changes to ensure their quality, safety, and efficacy.

#### 2. Quality assurance associated with performance changes:

Training algorithm and training data should be clarified.

#### 3. Principles on post-market approval process:

Necessity of taking the approval process should be determined in accordance with the magnitude of the associated changes in performance and risks.

## Section 5. Open Problems and direction of their solutions:

### (3) Assigning responsibility

- Manufacturers are responsible for the maintenance and troubleshooting of systems, and clarifying the use method of the system including by training for users
- Referring to the MHLW Health Policy Bureau notification that medical doctors are responsible for the final decision in diagnosis and treatment

Further technical considerations on the development and evaluation are discussed in **Section 6. Points to consider in evaluation.**

The potential type of AI for which users can perform post-market training to change their performance is discussed in **Annex.**

English translation is available on the NIHS website (bottom of the page):

<http://dmd.nihs.go.jp/jisedai/tsuuchi/index.html>

# Experience of PMDA-ATC Medical Devices Seminar

## 【Purpose】

- Learn basics of medical device regulations and regulatory organization
- Obtain updated information about utilization of GHTF/IMDRF documents, international standards, etc.



Group Discussion  
(PMDA-ATC Medical Devices Seminar 2018)

Date	Participants
November 7-11, 2016	28 from 13 countries/regions
November 6-10, 2017	30 from 12 economies
November 12-16, 2018	25 from 17 economies
November, 25-29, 2019	

# Outline of Medical Devices Seminar

**【Date】** November 25(Mon.)-29(Fri.),2019

**【Venue】** PMDA

## **【Target of training】**

- Get more knowledge of medical device reviewing and inspection with reference to GHTF/IMDRF documents and experiences of Japanese regulation.
- The training region:  
“Pre-market”, “Post-market” and “QMS”

## **【Participant】**

Regulators from APEC region and others economies

# Draft of program (Day1 – Day2)

Day 1	
	Opening CoE Pilot WS
AM	1 Outline of PMDA
	2 International Harmonization (IMDRF, APEC-LSIF-RHSC, etc.)
PM	3 Review and approval of medical devices (definition, classification, essential principle, review process, approval process, etc.)
	4 Regulations, legislative system and current effort for medical devices in Japan.
	5 Introduction of regulations by participants

Day 2	
AM	6 Consultation -from developing medical devices to getting marketing approval-
	7 Review of software
	8 Review of reprocessing system for single-use device
PM	9 Standards for medical devices
	10 Review of registered certifying bodies
	11 Selection and supervise of registered certification bodies
	12 Manufacture's expectation from third party certification system

# Draft of program Day3 – Day5

Day 3		Day 4	Day 5	
AM	13 GCP/GLP inspection and inspection based on standard of reliability for medical devices	17 Site visit to manufacturing facilities	AM	18 Group work on review of medical devices 2 (Review cases where preparation academic guidelines and/or training was required as conditions for approval, etc.)
	14 QMS for medical devices/ Outline of Medical Device Single Audit Program (MDSAP)			PM
PM	15 Review and approval of IVD Product		PM	
	16 Group work on review of medical devices 1 (Review cases requiring discussion on clinical data, etc.)			Closing Coe Pilot WS



# IMDRF

International Medical  
Device Regulators Forum

## Summary

- MHLW/PMDA is encouraging development of innovative products by operating SAKIGAKE Designation system and proposing its legalization.
- “Guidance for evaluating AI imaging system” is published to clarify the points of review of emerging technology.
- PMDA Asian Training Center annually provides seminar on the regulation of medical devices.