# Regulatory framework for innovative medical devices（ex. SaMD, AI）

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# The definition of Medical Devices in Pharmaceuticals and Medical Devices Act（PMD Act）

Medical devices are machinery or apparatus, etc. **intended for use** in the diagnosis, treatment or prevention of disease in humans or animals or **intended to** affect the structure or functions of the human or animal body, which are specified by Cabinet Order

Article 2.4, PMD Act

| | |
|---|---|
| Intended use | Diagnosis, treatment or prevention of disease<br>or<br>Affect the structure or functions |
| Condition | Specified by Cabinet Order |

# Medical Devices Specified by Cabinet Order

- Medical appliances
  — （85 items： e.g. Medical disinfector, Respiration assisting apparatus, Physioclinic appliance, thermometer, Blood pressure or Pulse wave appliance, Electrosurgical, Medical Scissors , Injection needles, Syringe, Dental unit, Vision corrective lens, etc.）

- Medical supplies
  — （6 items： e.g. radiographic film , suture , Orthopedic Appliances, etc. ）

- Dental materials
  — （9 items ：e.g. dental metal , dental crowns , etc. ）

- Sanitary goods
  — （ 4 items ：e.g. Menstrual tampon , condom , contraceptive device , etc. ）

- Program
- Recording media on which programs are recorded
  — （6 items ： e.g. Program for diagnosis of disease ）

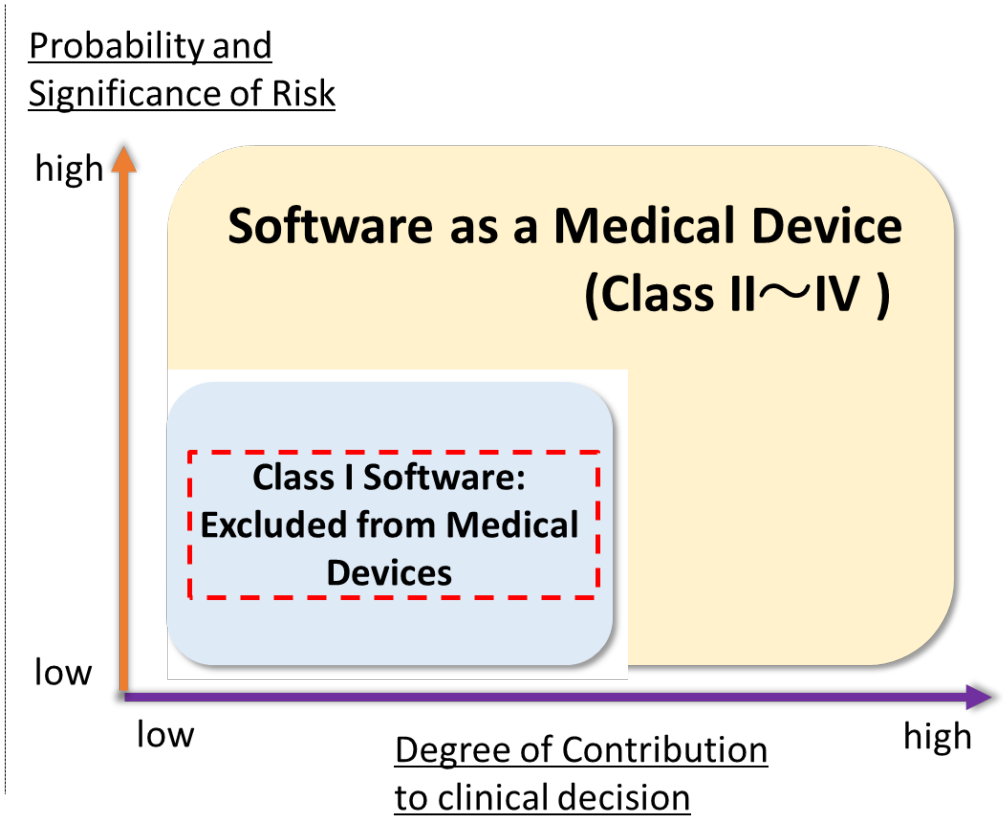
*Software as a Medical Device (SaMD） has been regulated in PMD Act since 25th Nov. 2014*

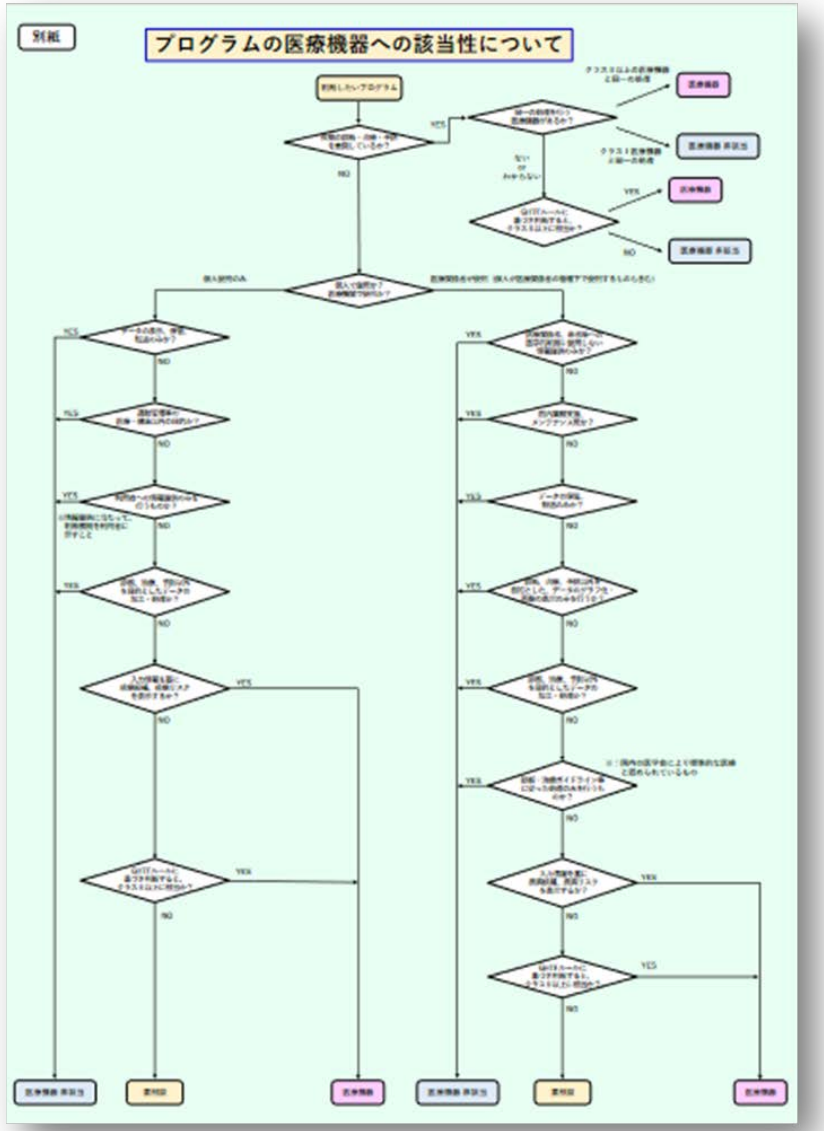
- Medical Devices designated for animal— （12 items ）

# The kind of Software treated as a Medical Device（SaMD）in Japan

Not Medical Device

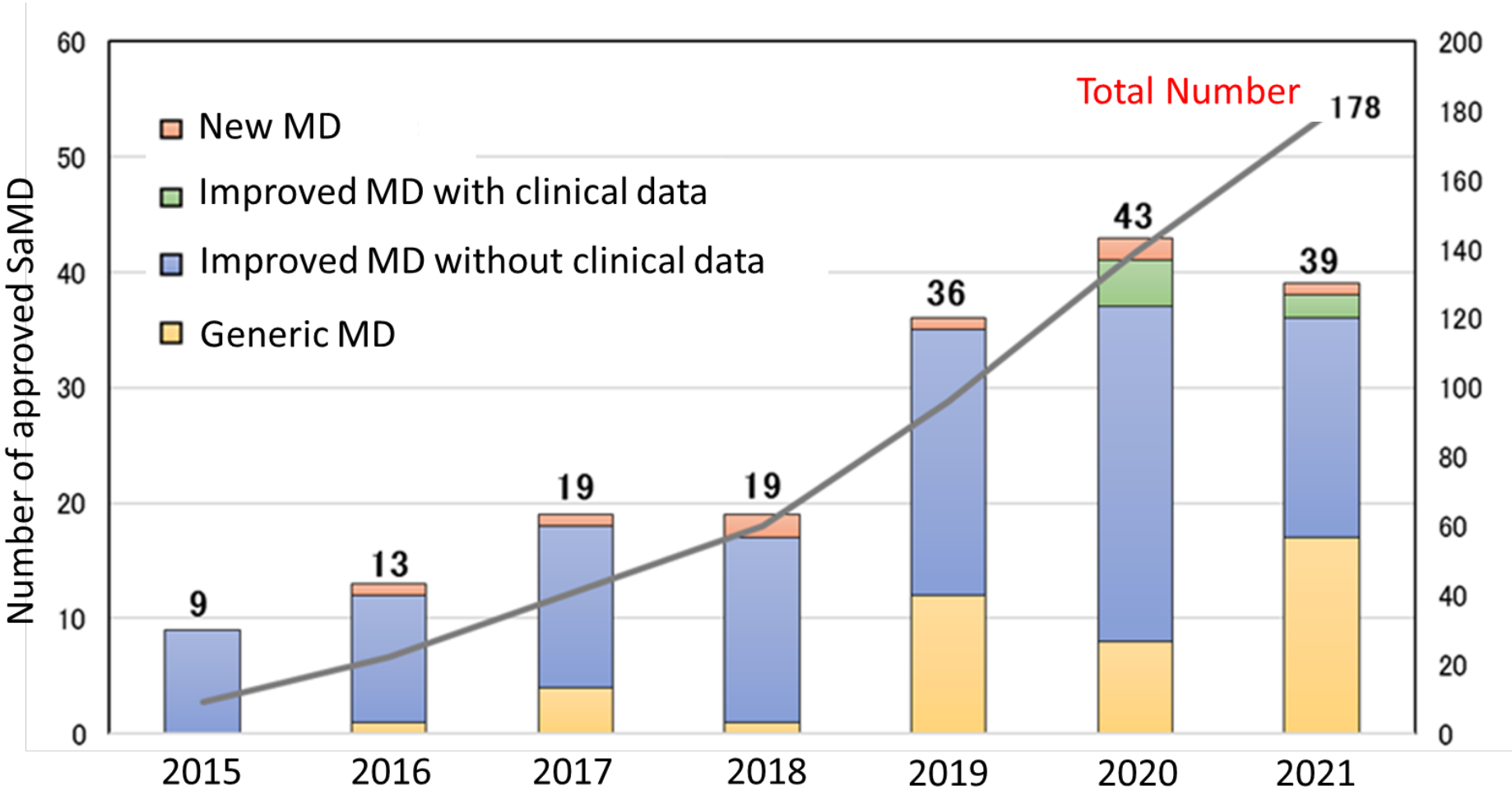
Not used for prevention, diagnosis or treatment of diseases




*https://www.pmda.go.jp/files/000240233.pdf*

# The number of approved SaMD in Japan※




※ The number of certified SaMD isn't included in this figure.

As of 31st Mar. 2022

# Rejection Reasons of Application for all type of Medical Devices

(a) The given device is judged that it does not have its own efficacy, effectiveness and/or performance as to be concerned in the application.
(b) The given device is judged of no value for medical use because its adverse effect(s) far exceed its efficacy, effectiveness and/or performance.


PMD Act, Article 23-2-5
paragraph(2), item(iii), (a) &(b)

# Example of evaluation of SaMD （Computer- Aided Diagnosis；CAD）

What is the development concept ?

Prevention of oversight by a radiologist

What is the design concept ?

Detection capability equivalent to a radiologist

## Clinical effectiveness

Contribute to clinical outcome

e.q.
Evaluate whether CAD can improve reader performance;
- Reading with CAD
- Reading without CAD

## Clinical performance

Perform appropriately for clinical data

e.q.
Evaluate the sensitivity and specificity for clinical image data

## Basic Function

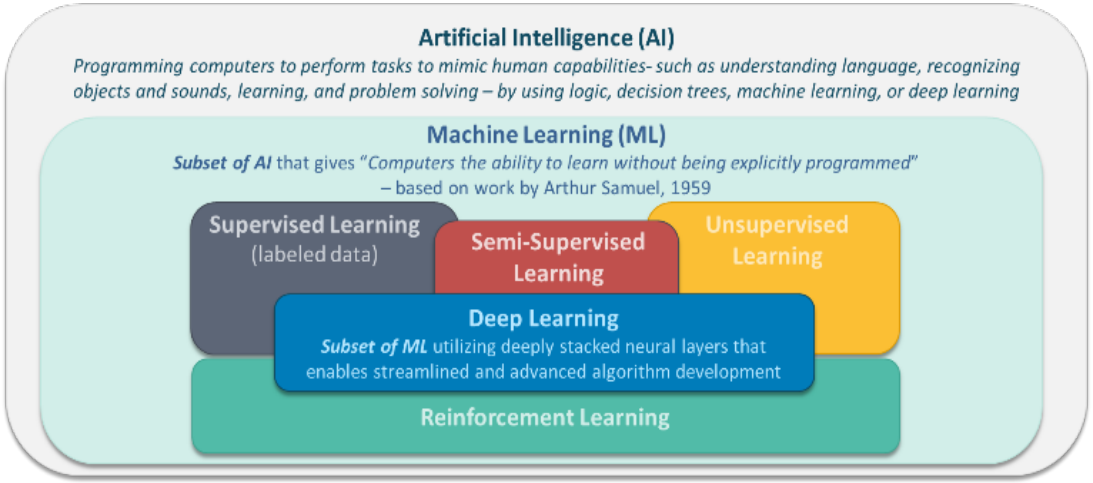
Verify to work appropriately as designed

e.q.
Conduct the bench test for the verification of implemented functions

# Artificial Intelligence and Machine Learning Definition

- There is no definition regarding Artificial Intelligence or Machine Learning in Japanese regulation.
- IMDRF defines Machine Learning-enabled Medical Device (MLMD) as

  “A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose.”※




※ The descriptions within the diagram are not definitions, and are included to convey a general sense of the technology.

※ *IMDRF/AIMD WG (PD1)/N67:2021*

# The type of MLMD considering plasticity

- Locked type：These have only included algorithms that are “locked” prior to marketing.
  - The fundamental review concept is same for general medical devices.

- Adaptive type：Change its behavior using a defined learning process
  - The first performance review is same for general medical devices.
  - Post-Approval Change Management Protocol (PACMP) was introduced in September, 2020 in Japan for medical devices to enable continuous improvements through product lifecycle.
  - In generally, this PACMP system is expected to be utilized.

- These is no clear definition regarding Locked type and Adaptive type in IMDRF or ISO/IEC standards.

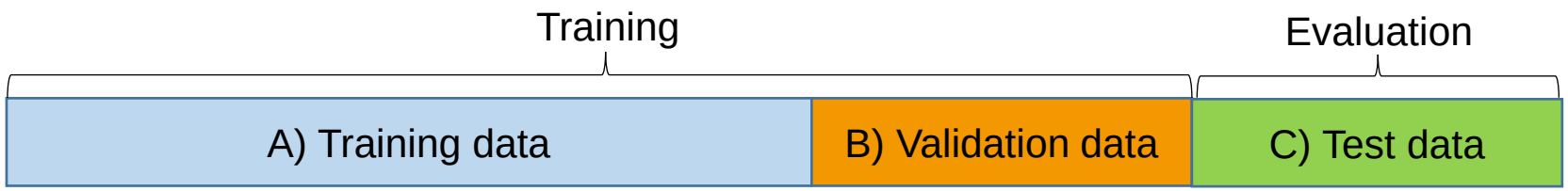
# The type of clinical data（Standalone Performance Test）

Standalone Performance Assessment for clinical data

- To confirm a proper performance against clinical data
  （Evaluation for learning algorithm and learning model）

Clinical data

A) Training data※：Data used to train a *machine learning model*
B) Validation data※：Validation data can be used to tune hyper parameters or to validate some algorithmic
C) Test data※ ：Data used to assess the performance of a final model




**Training data should be independent of Test data**

※ISO/IEC 22989：2022

# The type of clinical data（Clinical Performance Assessment）

Clinical Performance test for clinical effectiveness

- To confirm a contribution clinical outcomes considering the role in Clinical Practice
  C) Test data※ ：Data used to assess the performance of a final model

The results through this test data are treated as MLMD performance because the difficulty of interpretability and explainability.

Need to the rational explanation for comprehensive (various) data

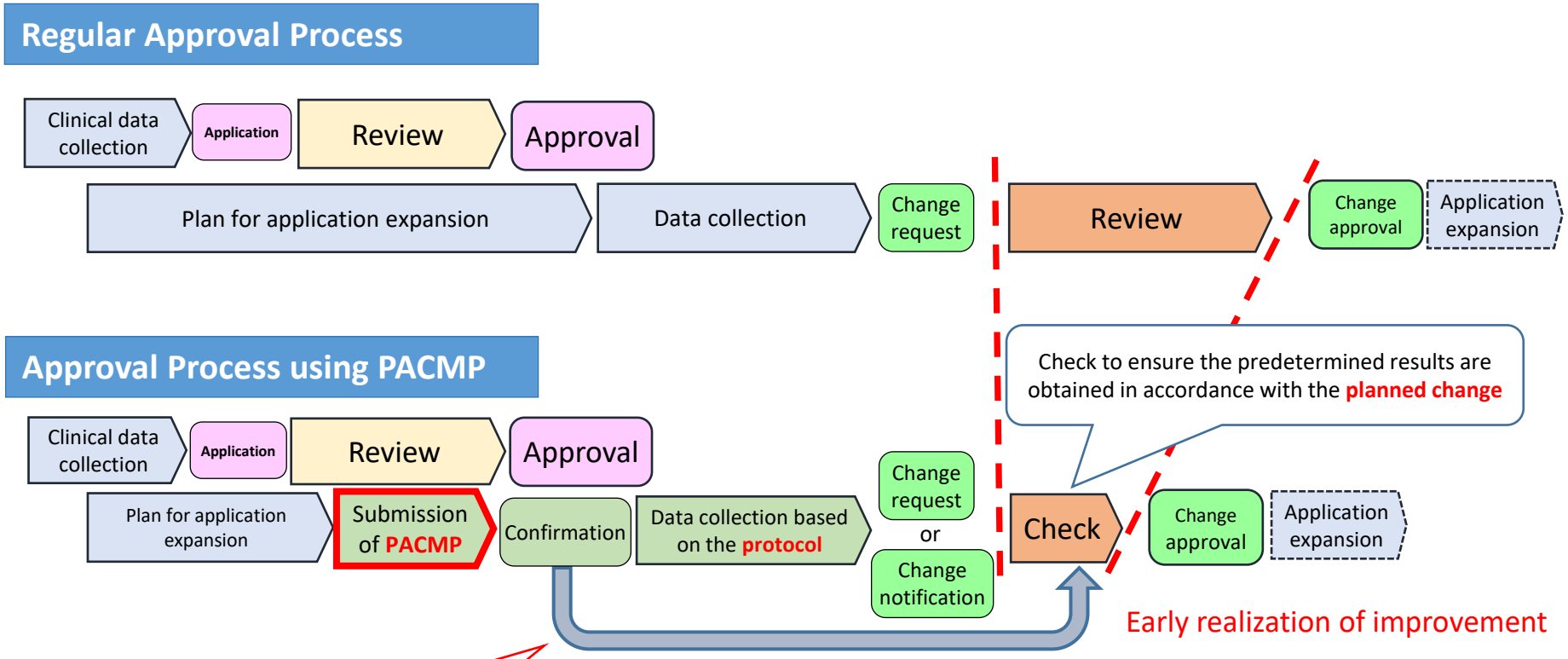
This test data should be comprehensive (various) data considering intended use and the role in clinical practice, such as ;

・Image and scanning protocol ・Target patient demographic ・Disease status
・Lesion size/ type/ location ・Collection site ・Ratio of disease and normal cases

※ISO/IEC 22989：2022

# Post-Approval Change Management Protocol (PACMP)

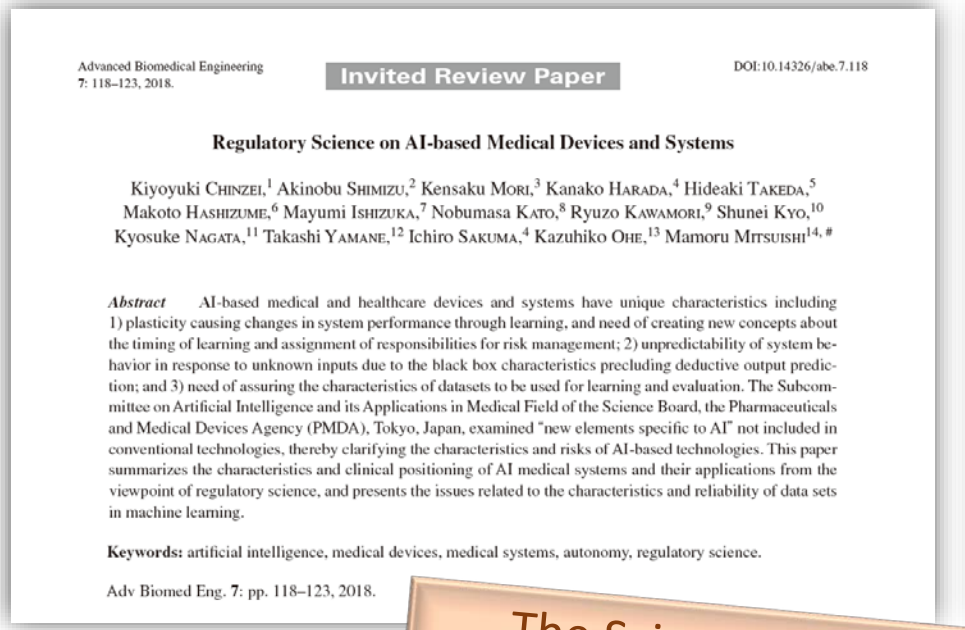
Post-Approval Change Management Protocol (PACMP) is introduced for medical devices to enable continuous improvements through product lifecycle.




Following things are assumed ;

- Re-use the evaluation data used for approval
- Modify the MLMD algorithms and hyper parameters for same MLMD model

# Publication and Guidance regarding AI/ML-enabled SaMD in Japan



Advanced Biomedical Engineering
7: 118–123, 2018.

Invited Review Paper

DOI:10.14326/abe.7.118

**Regulatory Science on AI-based Medical Devices and Systems**

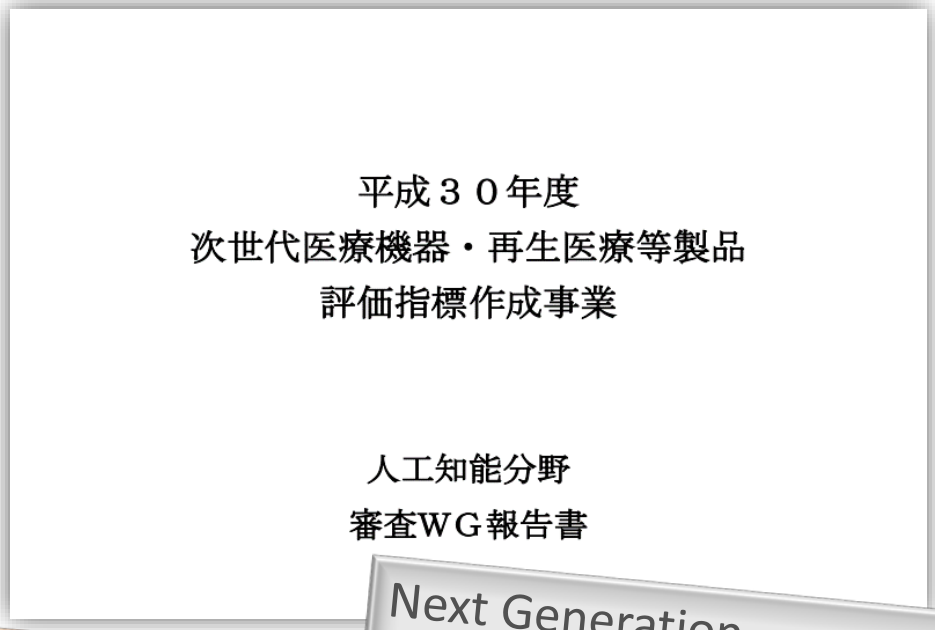
Kiyoyuki CHINZEI,[1] Akinobu SHIMIZU,[2] Kensaku MORI,[3] Kanako HARADA,[4] Hideaki TAKEDA,[5] Makoto HASHIZUME,[6] Mayumi ISHIZUKA,[7] Nobumasa KATO,[8] Ryuzo KAWAMORI,[9] Shunei KYO,[10] Kyosuke NAGATA,[11] Takashi YAMANE,[12] Ichiro SAKUMA,[4] Kazuhiko OHE,[13] Mamoru MITSUISHI[14, #]

***Abstract*** AI-based medical and healthcare devices and systems have unique characteristics including 1) plasticity causing changes in system performance through learning, and need of creating new concepts about the timing of learning and assignment of responsibilities for risk management; 2) unpredictability of system behavior in response to unknown inputs due to the black box characteristics precluding deductive output prediction; and 3) need of assuring the characteristics of datasets to be used for learning and evaluation. The Subcommittee on Artificial Intelligence and its Applications in Medical Field of the Science Board, the Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan, examined "new elements specific to AI" not included in conventional technologies, thereby clarifying the characteristics and risks of AI-based technologies. This paper summarizes the characteristics and clinical positioning of AI medical systems and their applications from the viewpoint of regulatory science, and presents the issues related to the characteristics and reliability of data sets in machine learning.

**Keywords:** artificial intelligence, medical devices, medical systems, autonomy, regulatory science.

Adv Biomed Eng. **7**: pp. 118–123, 2018.

The Science Board



平成３０年度
次世代医療機器・再生医療等製品
評価指標作成事業

人工知能分野
審査ＷＧ報告書

Next Generation Evaluation Guidance

**English Version;**
https://www.jstage.jst.go.jp/article/abe/7/0/7_7_118/_article/-char/en

**English Version;**
https://dmd.nihs.go.jp/jisedai/tsuuchi/Guidance_for_evaluation_of_AI_assisted_systems.pdf

# The example of approval AI/ML-enabled SaMD in Japan

| Approval date | Medical Device Nomenclature (JMDN) |
|---|---|
| 2018.12.6 | Supporting software for differential diagnosis with endoscopic imaging |
| 2019.9.17 | Software for MRI system workstation |
| 2019.12.25 | Software for general-purpose imaging system workstation |
| 2020.4.27 | Supporting software for differential diagnosis with endoscopic imaging |
| 2020.5.8 | Software for general-purpose imaging system workstation |
| 2020.6.3 | Software for diagnostic X-ray imaging system workstation |
| 2020.6.19 | Software for general-purpose imaging system workstation |
| 2020.6.29 | Supporting software for detecting lesion with endoscopic imaging |
| 2020.6.29 | Software for diagnostic X-ray imaging system workstation |
| 2020.7.15 | Supporting software for differential diagnosis with endoscopic imaging |
| 2020.8.20 | Software for diagnostic X-ray imaging system workstation |
| 2020.9.2 | Supporting software for differential diagnosis with endoscopic imaging |
| 2020.11.24 | Software for ultrasound imaging system workstation |
| 2020.11.30 | Supporting software for detecting lesion with endoscopic imaging |
| 2021.5.26 | Software for general-purpose imaging system workstation |
| 2021.7.7 | Software for general-purpose imaging system workstation |
| 2021.9.1 | Software for general-purpose imaging system workstation |
| 2021.10.11 | Software for diagnostic X-ray imaging system workstation |
| 2021.12.9 | Software for general-purpose imaging system workstation |
| 2021.12.24 | Software for diagnostic X-ray imaging system workstation |
| 2022.6.2 | Software for diagnostic X-ray imaging system workstation |
| 2022.9.20 | Supporting software for detecting lesion with endoscopic imaging |

【Approval Product 】

- The majority of them are CAD using Machine Learning（Locked type）

- **Type of Machine Learning :**
  Support Vector Machine, Deep Neural Network, Convolutional Neural Network, Cascade Classifier, etc.

- **Target Disease :**
  Lung nodules, Brain tumor, Breast tumor, Colorectal cancer, Covid-19, etc.

- **Modality :**
  X-ray, CT, MRI, Ultrasound, Endoscopy, etc.

As of 30th Sep. 2022

# PMDA Science Board

**Universities**
**Research Institutes**

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Collaboration


- Exchange opinions
- Between top-class researchers in Japan and PMDA reviewers
- Assess cutting-edge technologies

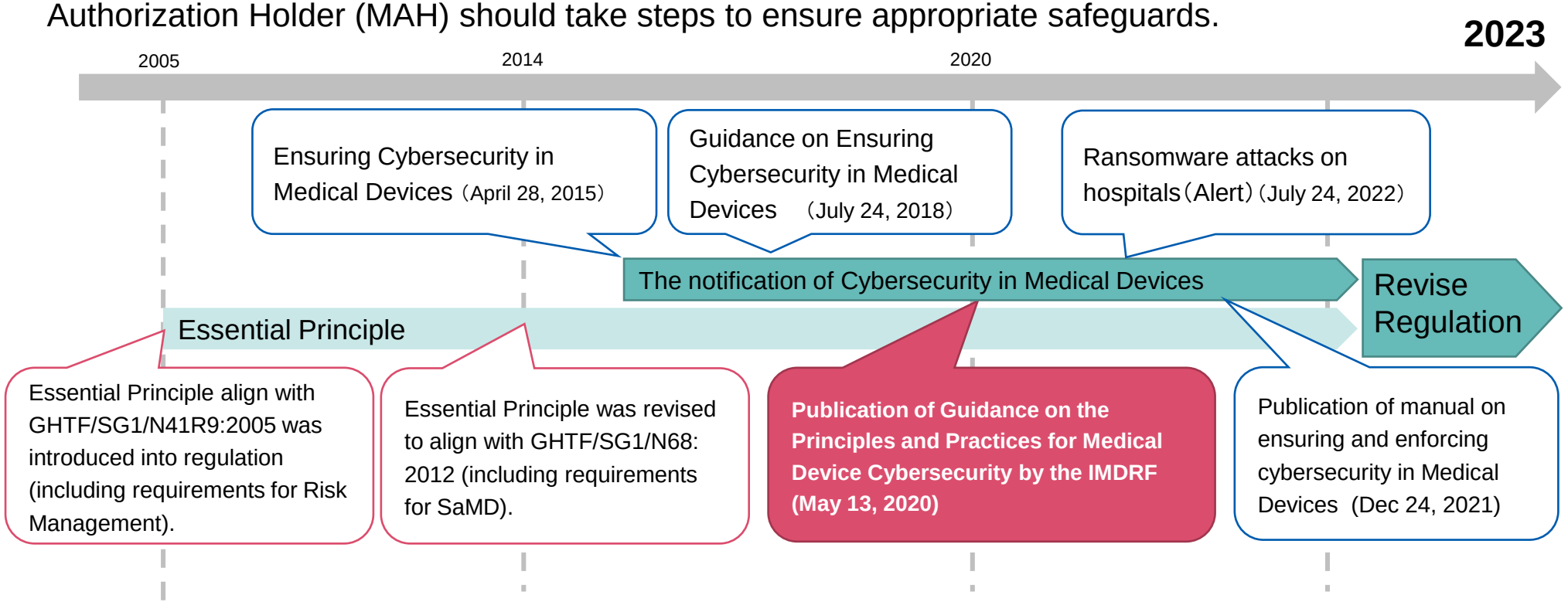
***Theme of on Science board in fiscal year 2022***

AI/ML-enabled Medical Device

- Re-use test data such as performance change at post-marketing.
- Comprehensive (various) test data considering intended use and clinical practice.
- How to review for adaptive AI.

# Cybersecurity in Japan

The notification regarding Cybersecurity in Medical Devices was published on 2015, and Marketing Authorization Holder (MAH) should take steps to ensure appropriate safeguards.




“Principles and Practices for Medical Device Cybersecurity”（IMDRF/CYBER WG/N60 FINAL:2020）was published on 20 April 2020.

⇒ Japan will introduce this IMDRF documents into regulation by March 2023