RAPS 2022 Convergence

Health Authority Forum – Japan

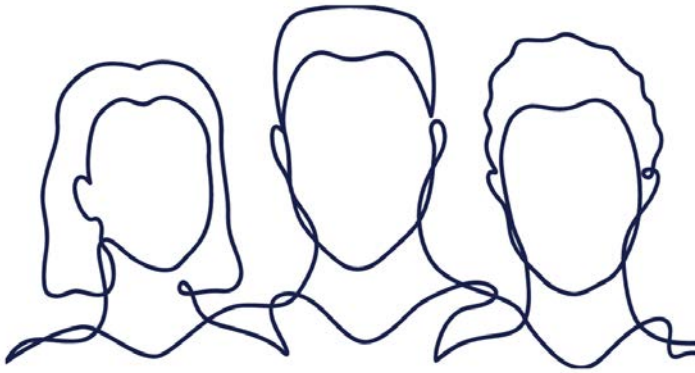
Fundamental concepts of the review regarding SaMD and AI/ML-enabled Medical Devices

Kuniki Imagawa

Principal Officer

Division of Standards for Medical Devices

Pharmaceuticals and Medical Devices Agency



Medical Devices Regulatory Authorities in Japan

MHLW

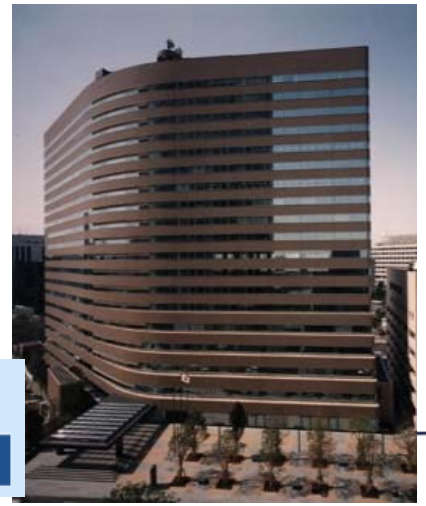
Ministry of Health, Labor and Welfare

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

PMDA

Pharmaceuticals and Medical Devices Agency

- Scientific Review for Drugs & Medical Devices
- GCP, GMP and QMS Inspection
- Consultation on Clinical Trials, etc.



Medical Devices Regulations in Japan

GHTF Classification		PMD Act classification		
		Category	Regulatory requirements	Japanese MD Nomenclature※
Class A	Extremely low risk e.g., X-ray film	General MDs (Class I)	Self declaration Approval of the product is not required, but marketing notification is necessary.	1,217
Class B	Low risk e.g., MRI, digestive catheters	Controlled MDs (class II)	Third party Certification Certification by a registered certification body is required. ・Certification Criteria	2,011 (1,518 for 3rd Party)
Class C	Medium risk e.g., dialyzer	Specially Controlled MDs (class III & IV)	Minister's Approval (Review by PMDA) The Minister's approval for the product is required. ・Approval Criteria ・Review Guideline	815 (43 for 3rd Party)
Class D	High risk e.g., pacemaker			375

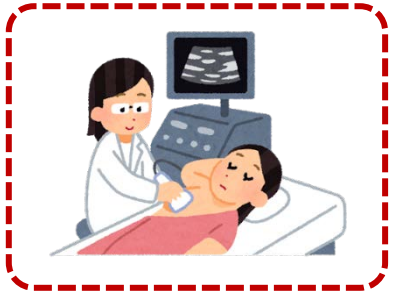
※ JMDN is based on Global Medical Device Nomenclature (GMDN): 2003

Transition of regulations for Software as a Medical Device (SaMD) in Japan

before November 2014

program which determines performance of medical device

install



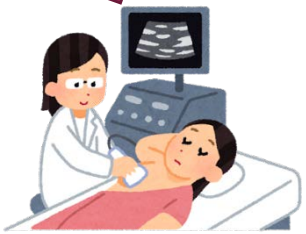
Medical device（tangible object including software）

after November 2014

program which determines performance of medical device

Medical device（software itself）

install



Reasons of Approval Rejection 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 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

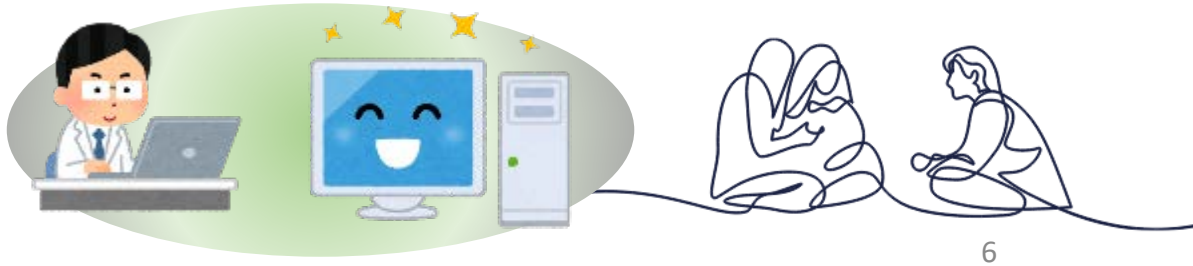
Perform appropriately
for clinical data

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

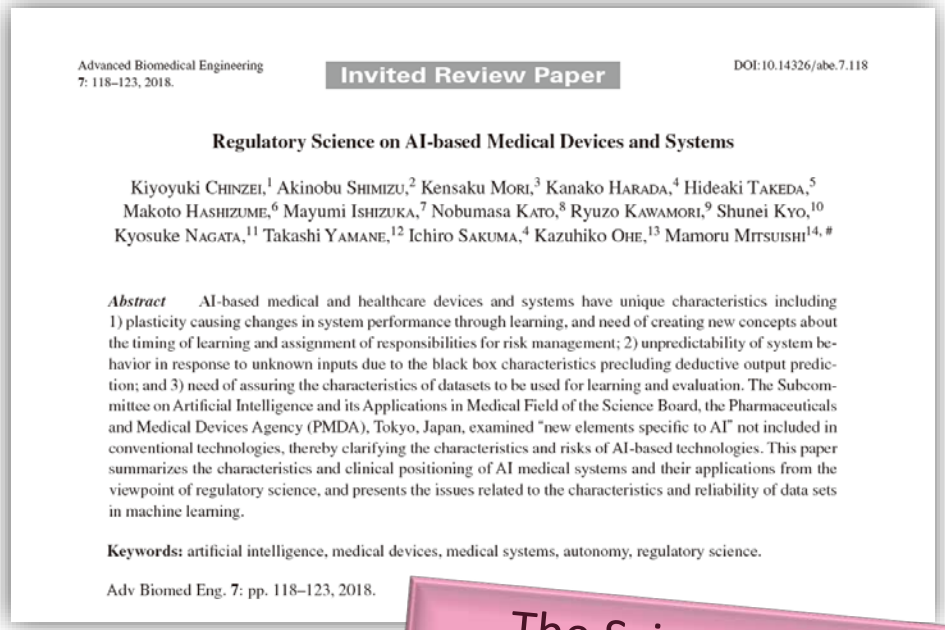
Basic Function

Verify to work appropriately
as designed

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



Outcome document and Guidance regarding AI/ML-enabled SaMD



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

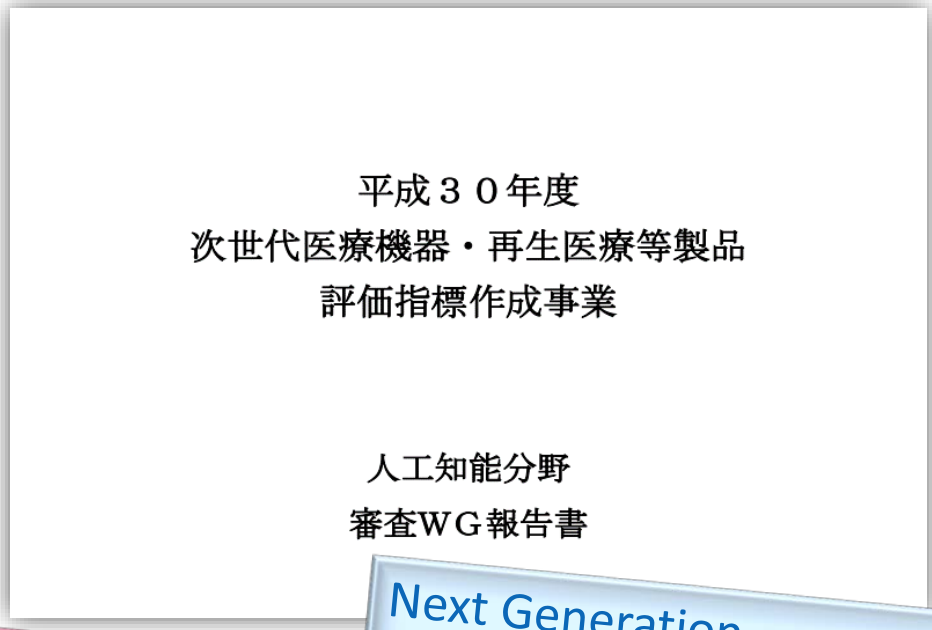
Kiyoyuki CHINZEI,[1] Akinobu SHIMIZU,[2] Kensaku MORI,[3] Kanako HARADA,[4] Hideaki TAKEDA,[5] Makoto HASHIZUME,[6] Mayumi ISHIZUKA,[7] Nobumasa KATO,[8] Ryuzo KAWAMORI,[9] Shunei KYO,[10] Kyosuke NAGATA,[11] Takashi YAMANE,[12] Ichiro SAKUMA,[4] Kazuhiko OHE,[13] Mamoru MITSUISHI[14, #]

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 data	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

【Approval Product 】

- The majority of them are CAD by 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.

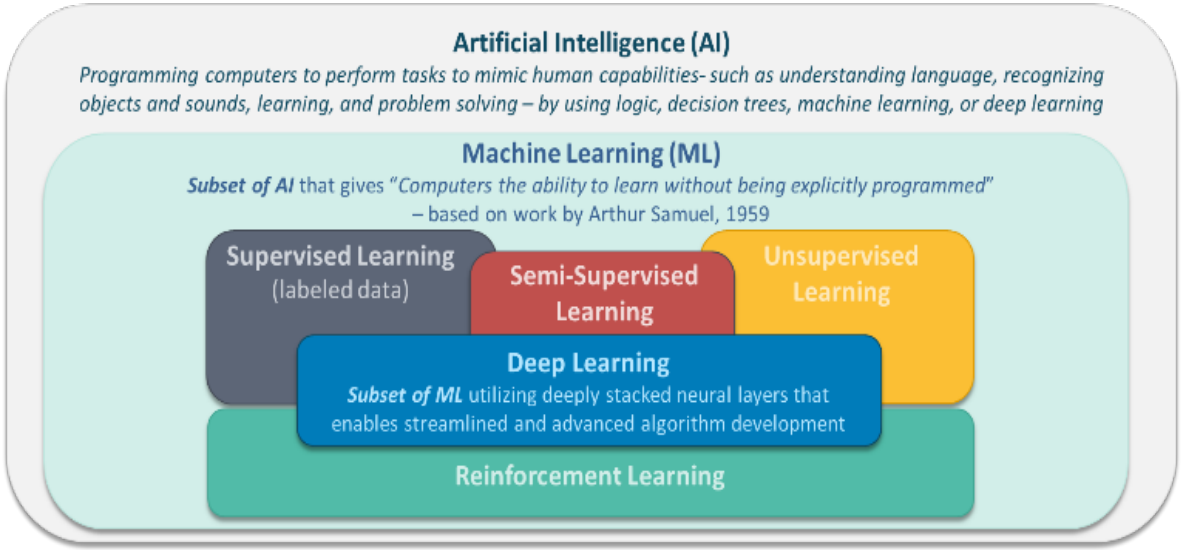
The Definition regarding Artificial Intelligence and Machine Learning

- There is no definition regarding Artificial Intelligence and Machine Learning in Japanese regulation.

- IMDRF defines these definitions as is follows;

  5.1. Machine Learning-enabled Medical Device (MLMD)

  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：Changes 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 such as IMDRF、ISO/IEC standards.

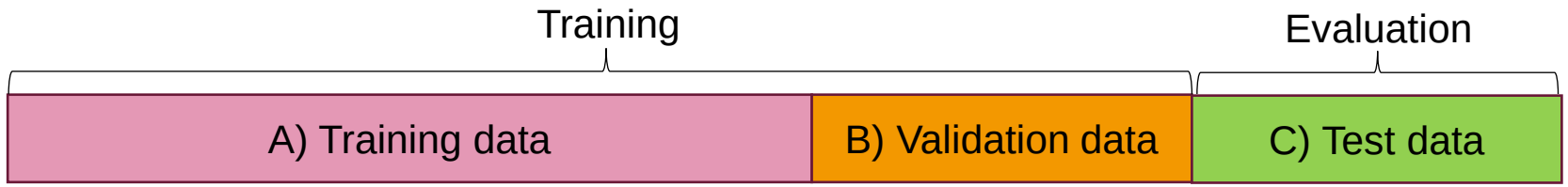
The type of clinical data（Standalone Performance Test）

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

The Algorithm Design and Function are described in the application material, such as.

- Processing, Features, model and classifiers
- How are algorithm parameters selected, etc.

※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 used 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

Manage for bias especially for retrospective study

- Despite the practical value, retrospective study generates some potential sources of bias.
- Bias should be managed to minimize or mitigate through study design.
- Some example potential source of bias are as is follows;
  - Selection Bias: The sample of object is not representative of the target population.
  - Imperfect Reference Standard Bias : The reference procedure is not 100% accurate classifying subjects by presence or absence of the condition of interest.
  - Reading-Order Bias: When comparing two or more test, the reader's interpretation is affected by his or her memory of the results from the competing test , etc.

Reference Standard is used as training and evaluation when conducting a supervised learning.

The example of Reference Standard（Gold Standard）

How is disease presence/absence determined ?

- An established clinical determination (e.g., biopsy, PCR, specific laboratory test)
- A follow-up clinical imaging examination;
- An interpretation by a reviewing clinicians ;
  - Clinicians participating in the labelling process should not be the same as those who participate in the clinical performance assessment
  - Clarify the labelling process accounts for any inconsistencies between reviewing clinicians.
  - Clarify the background of reviewing clinician;
    - ✓ The number of clinicians
    - ✓ Their qualification
    - ✓ Levels of experience and expertise, etc.

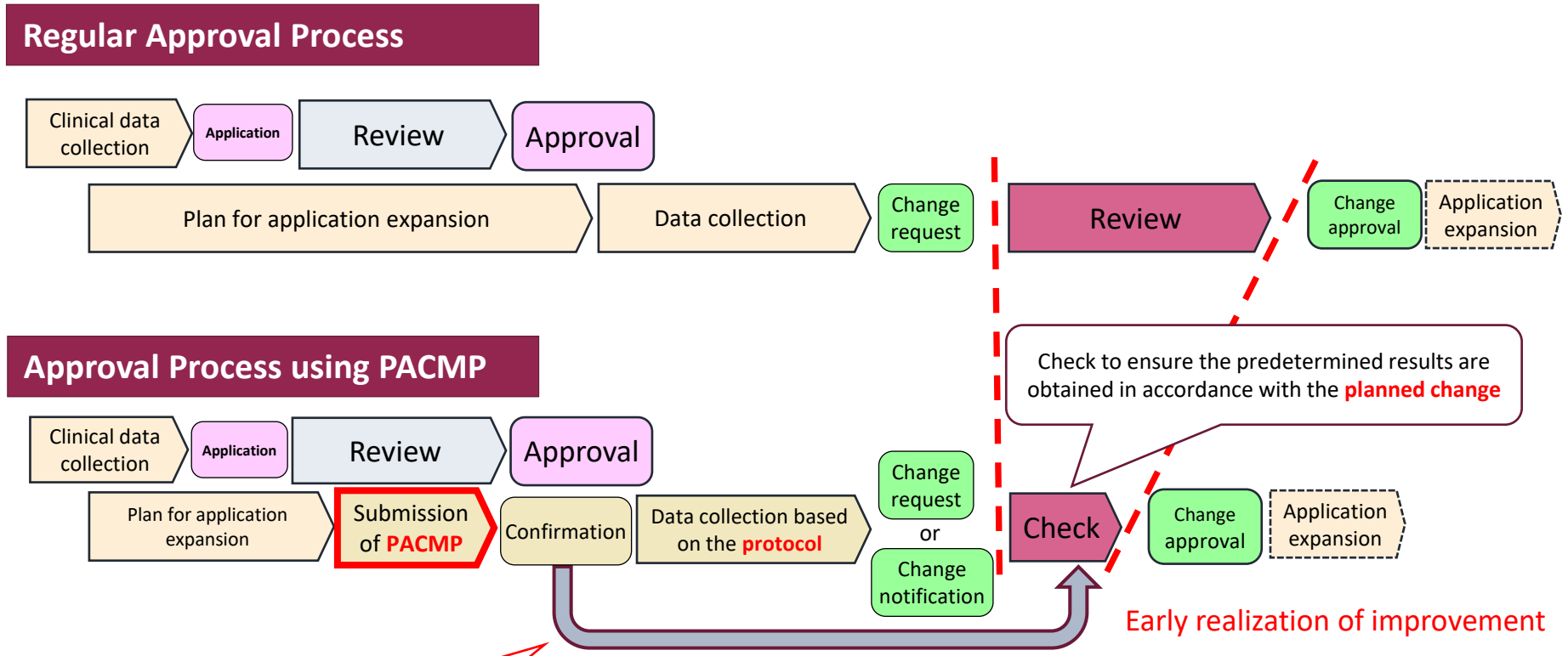
Reference Standard ※

An objectively determined benchmark that is used as the expected result for comparison, assessment, training, etc.

※ *IMDRF/AIMD WG (PD1)/N67:2021*

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

PMDA Science Board

Universities
Research Institutes

Medical institutions

Collaboration

pmda

- 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.

"DASH for SaMD"

DX(Digital Transformation) Action Strategies in Healthcare for SaMD

1. Early recognition of research seeds and publication of the review guide

a. Assess seeds of technology in the early stage of research.
b. Organize and publish the review guide regarding characteristics of SaMD.

2. Centralization of the consultation contact desk

c. Centralize consultation service (April 1, 2021)
d. Marshal and publish consultation case examples
https://www.mhlw.go.jp/content/11120000/000836443.xlsx

3. Review system applicable to unique characteristics of SaMD

e. Carry out efficient review based on characteristics of SaMD
f. Utilize the Post-Approval Change Management Protocol (PACMP) scheme
g. Consider establishing the innovative SaMD designation program

4. Enhancement of structure for early realization

h. Establish new office specialized in SaMD in MHLW and PMDA (April 1, 2021)
i. Establish Expert Examination Committee for SaMD in the Pharmaceutical Affairs and Food Sanitation Council (April 1, 2021)
j. Establish collaborative forum among regulator, academia and industry (February 4, 2022)
k. Enrich published database of approval cases
https://www.pmda.go.jp/PmdaSearch/kikiSearch/