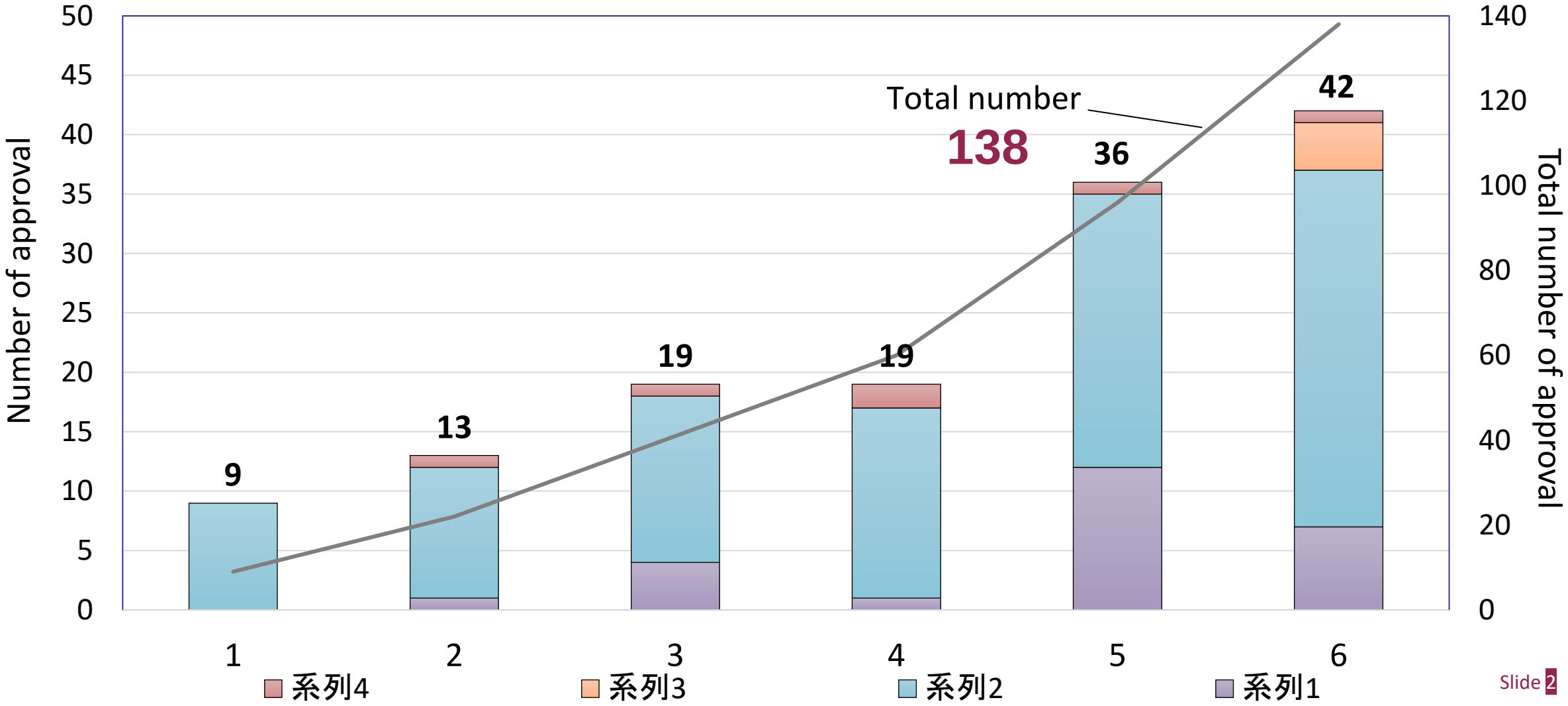
Regulation system and perspective for SaMD

Pharmaceuticals and Medical Devices Agency

Medical Devices Unit, Office of Software as a Medical Device, Reviewer

Takatomo Ezura

The annual number of approved SaMD



DX(Digital Transformation) Action Strategies in Healthcare for SaMD (Software as a Medical Device) "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 reinforcement for early realization

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

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

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

d. Enrich published database of approval cases

Outline

- Overview of regulation on SaMD product in Japan
- Evaluation and review of SaMD
- Activities for regulatory innovation in the Office of SaMD

Overview of regulation on SaMD products in Japan

Classification of non-IVD Medical Devices

GHTF Classification		Classification in Japan			
Class	Risk level	Class	# of JMDN**	Category	Pre-market regulation
A	**Low** Surgical retractors/ tongues depressors	I	1,214	General MDs	Self declaration***
B	**Low to Moderate** Hypodermic needles/ suction equipment	II	2,003	Controlled MDs + Designated Controlled MDs	Third party Certification (Review by RCB*) (**Designated** Controlled MDs and **Designated** Specially Controlled MDs)
C	**Moderate to High** Lung ventilator/ bone fixation plate	III	812	Specially Controlled MDs + Designated Specially Controlled MDs	**Ministerial Approval (Review by PMDA) (Controlled MDs and Specially Controlled MDs)**
D	**High** Heart valves / implantable defibrillator	IV	372		

*RCB: Registered Certification Bodies

**JMDN: Japanese Medical Device Nomenclature

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

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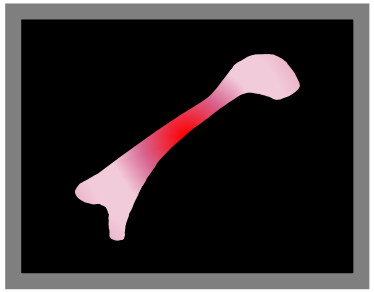
Intended use and claims of medical devices

Perform stress analysis in various objects



Diagnose the risk of bone fracture from the results of stress analysis

Not be intended to diagnose human disease

Be intended to diagnose human disease

Not MD

MD

Medical indications can not be claimed; such as diagnosis of bone fracture risk

Analytical performance to enable diagnosis of bone fracture risk should be evaluated

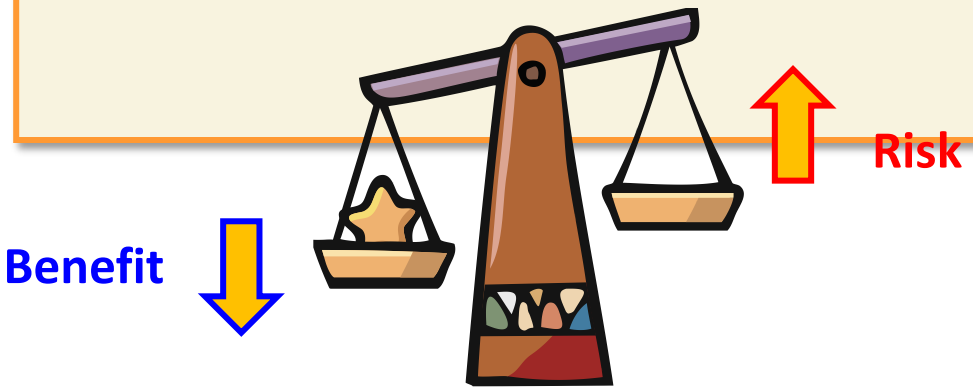
Evaluation and review of SaMD

Reasons of Approval Rejection

(a) The given device is judged that it does **NOT** have its own 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 effectiveness and/or performance.

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



Risk of SaMD

SaMD is trying to improve the user's decision better

Possibility to induce improper decision

【e.g.】

- CAD which provides doctors' reference information for diagnostic support
  ⇒ inducing improper diagnosis decision

- DTx promotes behavioral modification
  ⇒ promote excessive intervention and loss of treatment opportunity.

How to review

What is the concept of development?

What is the concept of design?

Clinical utility

Does it contribute to patient outcomes?

e.g. :
Shown that oversights were reduced by using CAD, comparing the diagnostic results between interpretation using CAD and without CAD

Clinical performance

Does it perform appropriately for clinical data?

e.g. :
Evaluate the sensitivity and specificity for clinical image data

Operation verification

Does it work as designed.

e.g. :
The basic bench test to validate performance of the function implemented

Summary of evaluation and review for SaMD

- Evaluate efficacy and risk, and explain that efficacy outweighs risk.
- Reviewers are trying to understand what kind of medical device it is first.
- Evaluation methods and criteria are depended on these concepts.
- SaMD also has risks.

Matters related to AI

The Science Board

- PMDA established the Science Board on May 14th 2012.
- As a high-level consultative body which discusses scientific aspects of pharmaceuticals and medical devices review.
- The purposes of the Science Board are, ***advancing regulatory science and evaluate products with advanced science and technology in appropriate manner*** by enhancing cooperation and communication with academia and medical institutions.

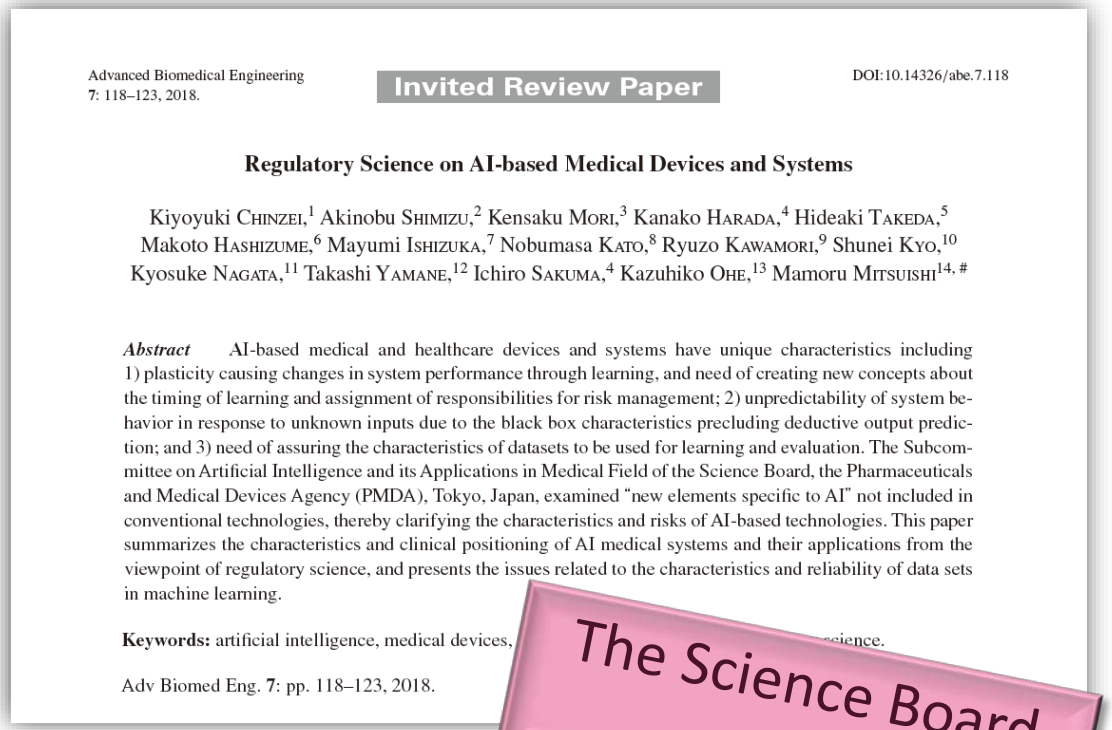
https://www.pmda.go.jp/english/rs-sb-std/sb/0001.html

Next Generation Evaluation Guidance

- "Next Generation Evaluation Guidance" is a guidance organized by specialists appointed by NIHS (National Institute of Health Service) and MHLW.
- The purpose of the guidance is to accelerate development and review process of much-needed innovative medical devices and bring the innovative medical devices into medical practice in a timely manner .
- More than twenty guidance for the medical device with cutting-edge technologies have been published.

https://dmd.nihs.go.jp/jisedai/

Artificial Intelligence



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

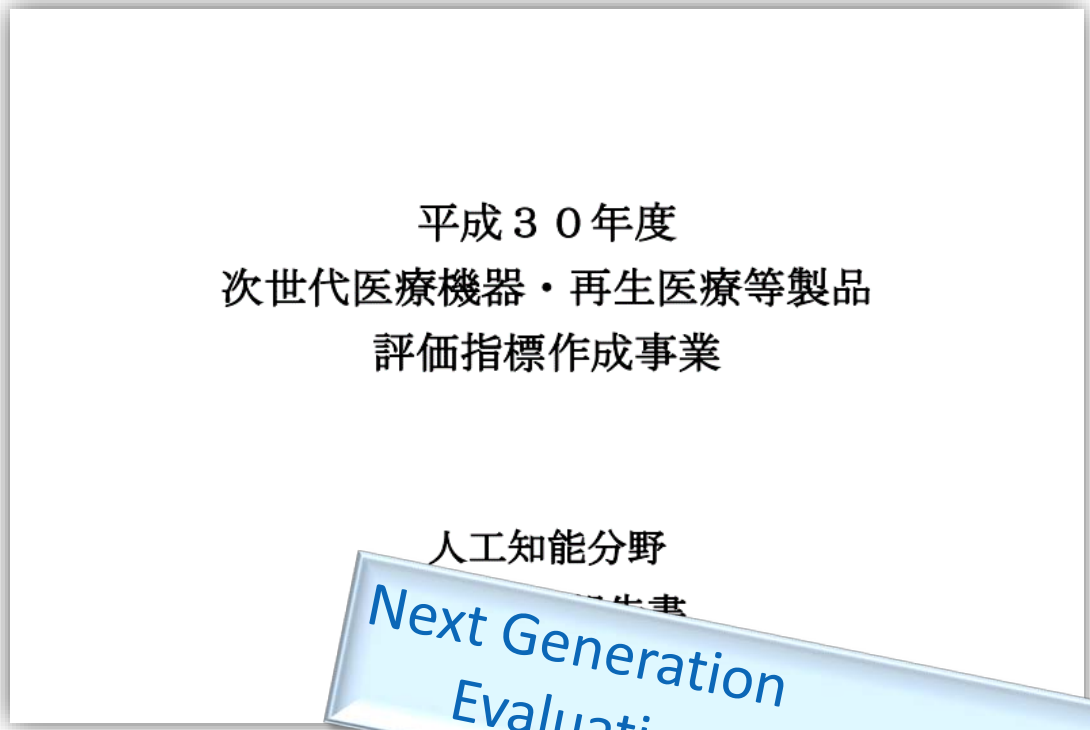
Kiyoyuki CHINZEI,[1] Akinobu SHIMIZU,[2] Kensaku MORI,[3] Kanako HARADA,[4] Hideaki TAKEDA,[5] Makoto HASHIZUME,[6] Mayumi ISHIZUKA,[7] Nobumasa KATO,[8] Ryuzo KAWAMORI,[9] Shunei KYO,[10] Kyosuke NAGATA,[11] Takashi YAMANE,[12] Ichiro SAKUMA,[4] Kazuhiko OHE,[13] Mamoru MITSUISHI[14, #]

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, ...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
...告書

Next Generation Evaluation Guidance

Chinzei et al.,
"Regulatory Science on AI-based medical Devices and Systems,"
Advanced Biomedical Engineering 7 2018

http://dmd.nihs.go.jp/jisedai/Imaging_AI_for_public/index.html

Uniqueness of AI products

Unpredictability

Developers cannot understand the meanings of the output

How do you estimate the situation in which error occur?

Plasticity

Post market learning may be worsen the performance of AI products

How do you keep its performance?

Unpredictability

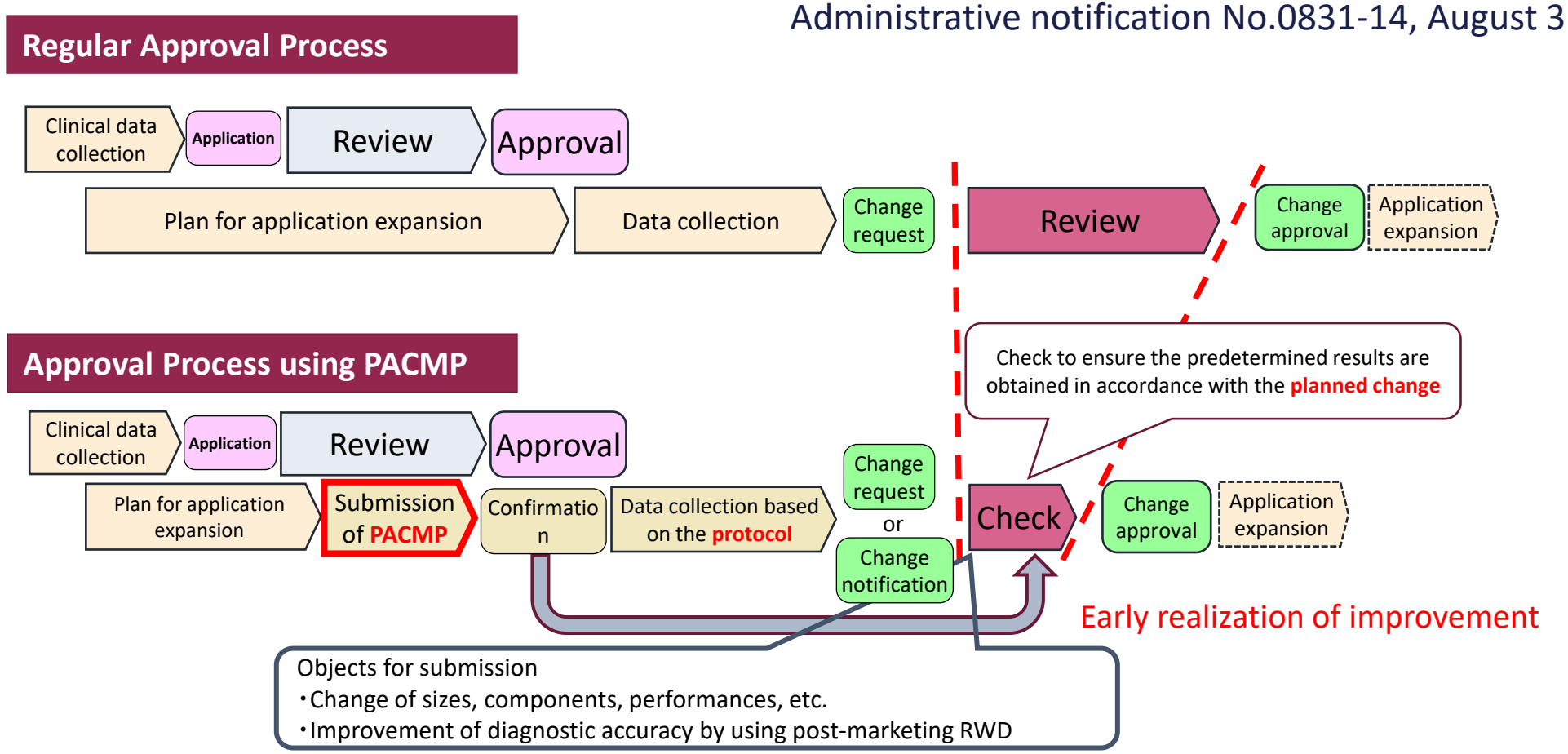
- It is difficult to limit the data set for evaluation because we do not understand where the weaknesses are in the output data.
- Comprehensive analysis of the results based on the clinical situation.
- Consider collecting data for evaluation as well as for development.

Plasticity

Post-Approval Change Management Protocol (PACMP) for Medical Devices

PACMP is introduced for medical devices to enable continuous improvements through product lifecycle.

Administrative notification No.0831-14, August 31, 2020



Summary of Matters related to AI

Unpredictability

- Since we don't know the weaknesses of AI, evaluation data must be exhaustively analyzed for possible clinical situations.
- Collect enough data to evaluate the performance of your product.

Plasticity

- The challenge of plasticity will be addressed through the utilization of PACMP.

This approach is not a drastic solution to the unpredictability of AI.

Activities for regulatory innovation in the Office of SaMD

Working group for SaMD

International:

IMDRF Working Group

Artificial Intelligence Medical Devices

WHO Working Group

WHO Meeting on Regulatory Consideration for Artificial Intelligence

Domestic:

NIHS and MHLW Review Working Group

Next Generation Evaluation Guidance
Medical device programs with promote behavioral modification

Japan Agency for Medical Research and Development (AMED)

Research on how to regulate pharmaceutical affairs for medical device programs using advanced technologies such as artificial intelligence

New 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 messages

If you are trying to market a medical device in Japan, you should

1. consider the intended use and claims for SaMD
2. know the special regulations of classification for SaMD
3. consider the risks of SaMD based on clinical performance
4. consider collecting data for evaluation as well as for development
5. consider utilizing PACMP
6. take advantage of the new consultation

Thank you for your kind attention!

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