独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulations for QMS and SaMD in Japan

7th India-Japan Medical Products Regulatory Symposium

July 10th, 2024

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Pharmaceuticals and Medical Devices Agency

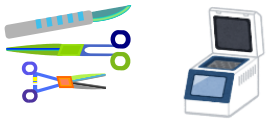
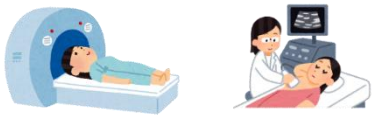
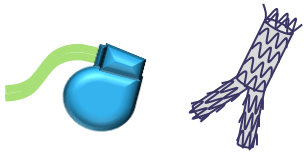
Agenda

1. QMS operation & inspection for grant of medical devices permission in Japan

2. Regulations and Licensing/Approval process for SaMD in Japan

Classification and Regulations of Medical Devices in Japan

Low ← Risk → High

Classification	ClassI	ClassII	ClassIII	ClassIV
Definition	Even if a malfunction occurs, the risk to the human body is considered to be extremely low. 	Even if a malfunction occurs, the risk to the human body is considered to be relatively low. 	Items that are considered to pose a relatively high risk to the human body in the event of a malfunction. 	Items that are highly invasive to patients and may directly lead to life-threatening problems if a malfunction occurs. 
Regulatory Classificaion	General Medical Devices	Controlled Medical Devices	Specially Controlled Medical Devices	
Premarket	Notification	3rd Party Certification		Ministerial Approval (PMDA's Review)
Postmarket	Adverse Event Report to PMDA			

Major Components of Medical Device Regulations

Marketing Authorization Holder:

Responsible for quality, effectiveness and safety of product.
License for Marketing Authorization Holder is required.

Product:

Quality, effectiveness and safety should be assured.

Submission/Certification/Approval for marketing is required.

Manufacturer:

Registration for manufacturer is required. **Compliance to QMS ordinance is required**.

QMS and QMS inspection

What is QMS?

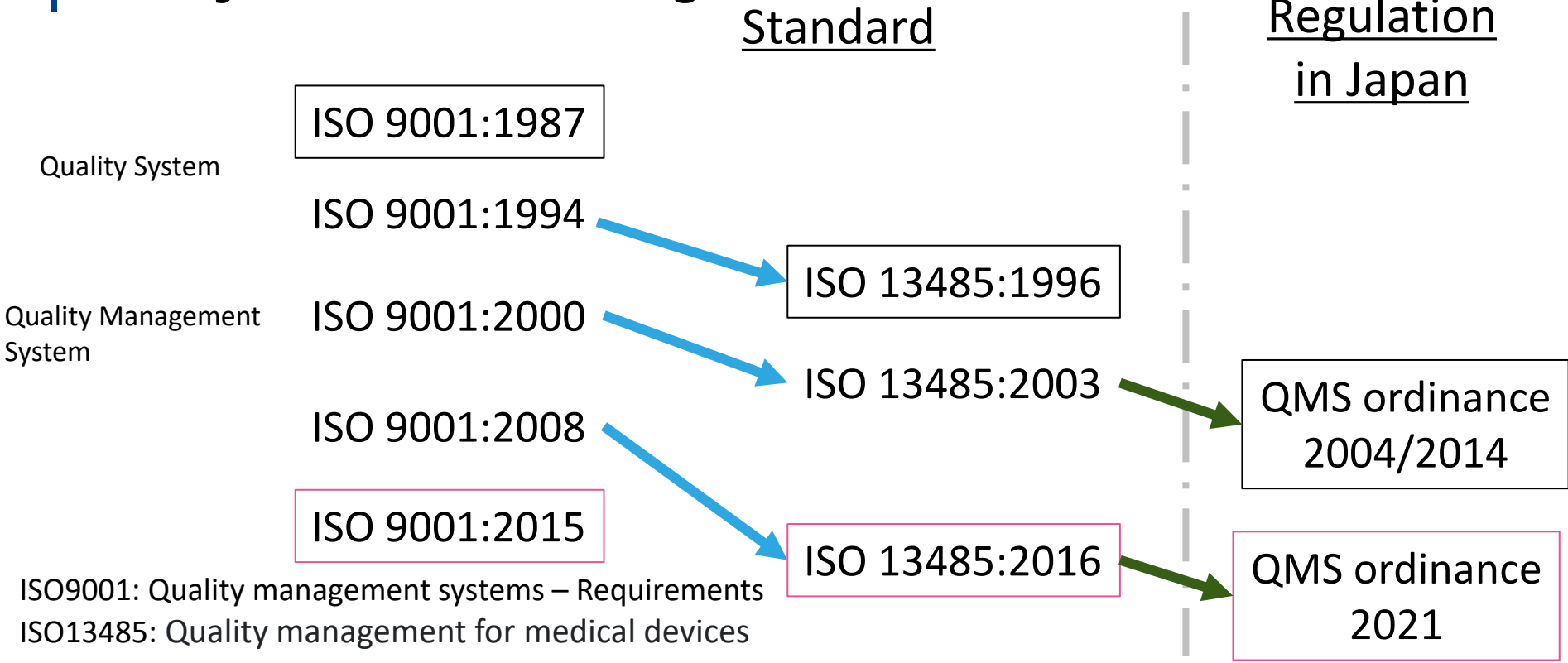
- Quality Management System. A management system for directing and controlling an organization regarding quality of the products.
- A QMS standard is a set of requirements for creating the rules, policies, processes, and procedures to provide products and services that meet customer needs, and improve customer satisfaction. The QMS standard is maintained by the Organization for Standardization such as International Organization for Standardization (ISO) and is agreed upon by a majority of member countries in this organization so that it can be recognized internationally and is accepted as the gold standard for the processes to be used worldwide for the QMS(ISO 13485).
- Under the Pharmaceutical and Medical Devices Act, QMS ordinance is incorporated as a standard for manufacturing control and quality control of medical devices, based on ISO 13485.

QMS and QMS inspection

What is QMS Inspection?

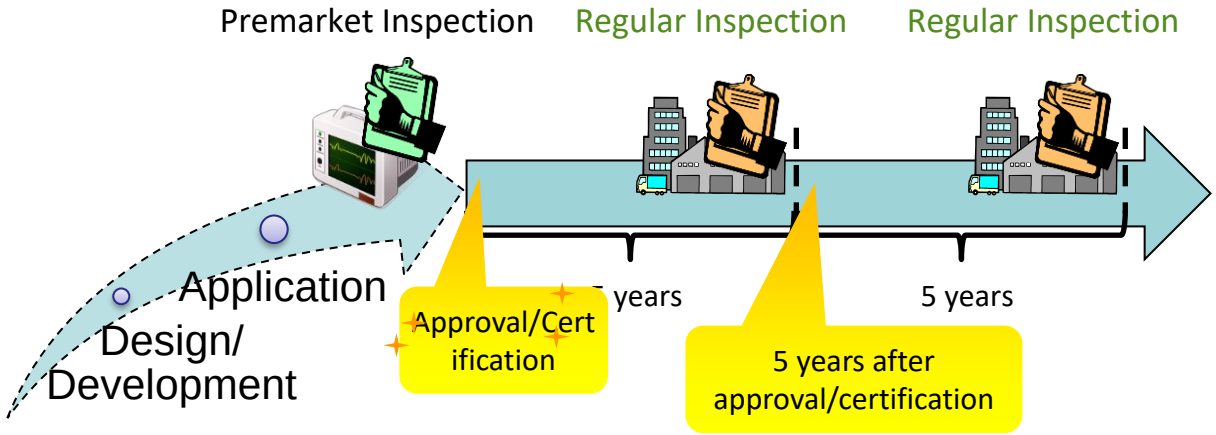
- An inspection to confirm whether the manufacturing control and quality control methods of medical devices, etc. at MAH, etc. comply with the QMS ministerial ordinance.
- If the product is not on the market, confirm that the product is not manufactured in a manner that differs from the approval application and that no defective products are being distributed on the market. After launch, confirm that no products with discrepancies with the approval documents are actually distributed on the market, and confirm that high-quality products are being manufactured continuously and that no defective products are distributed on the market.

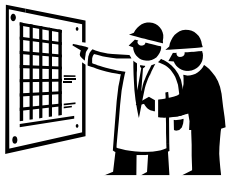
History of QMS standard/regulations



ISO9001: Quality management systems – Requirements
ISO13485: Quality management for medical devices

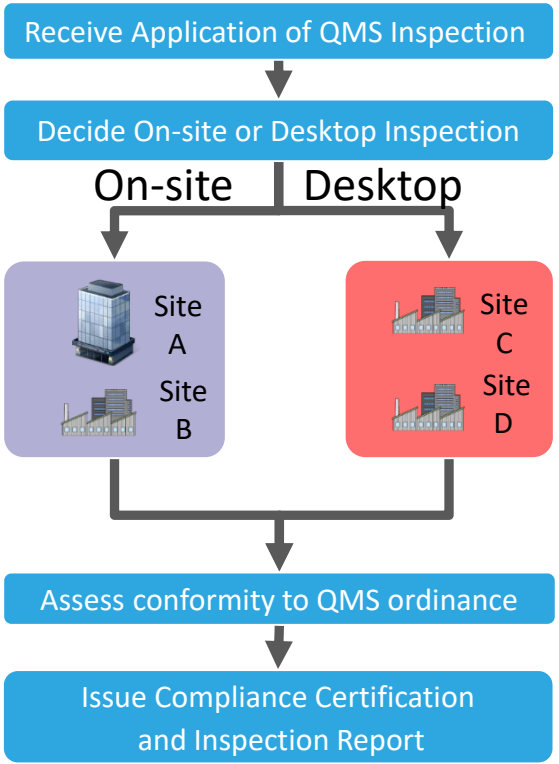
Timing of QMS inspection





Type of Inspection	Timing of Inspection
Premarket Inspection	Premarket, before approval/certification
Regular Inspection	Any day before “5 years after approval/certification (renewal deadline)”

QMS Inspection Flow



Input Information

Risk Assessment

Decision of On-site or Desktop

Input Information:

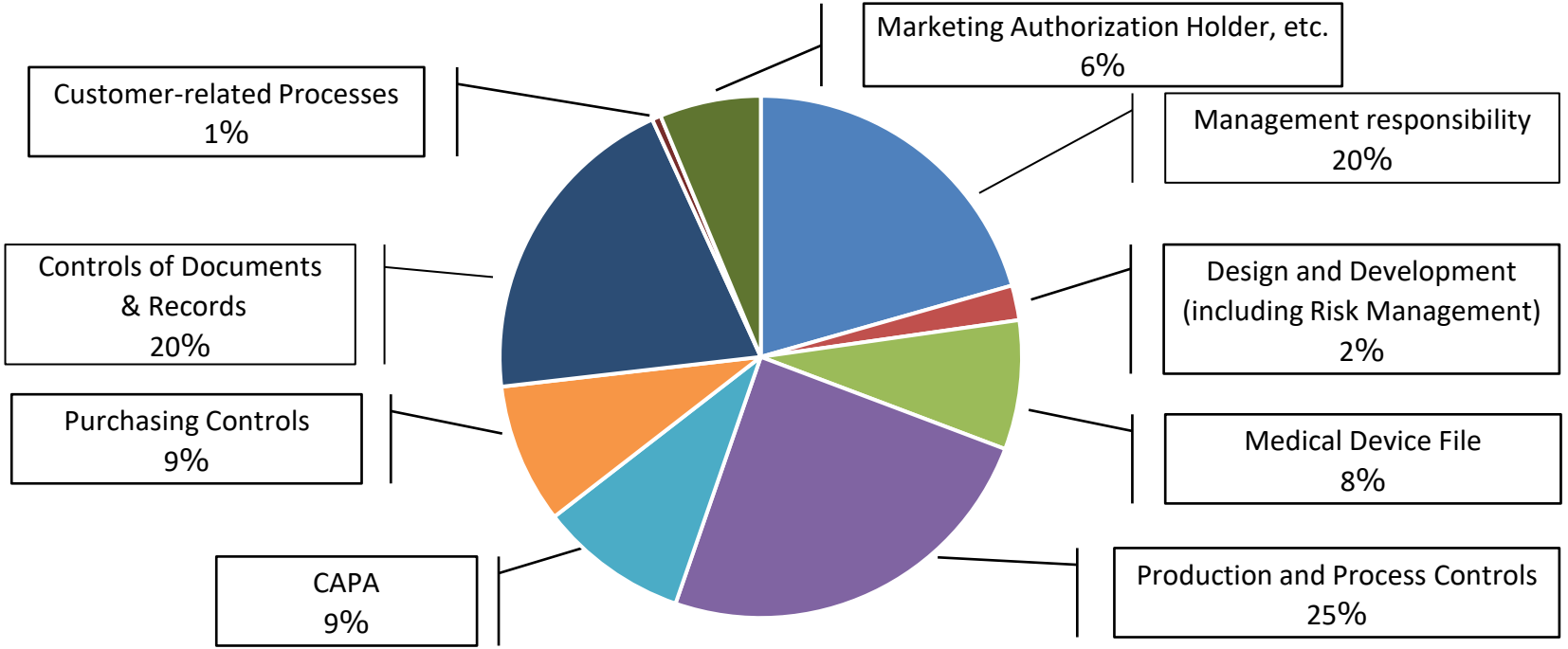
- **Submitted documents**
- **Reported adverse events**
- **Reported recalls**
- **Complexity of manufacturing processes**
- **Risks associated with the use of products**
- **Results and nonconformities of the previous inspections**
- **Audit results by other organizations**
- **Certificates of ISO13485 and the reports**
- **MDSAP reports inspection (Pilot phase in Japan).**

etc.

3-day On-site Inspection Schedule (Example)

Date	Time	Item
Day 1	9:30-12:00	1.Opening Meeting (1) Introduction of Inspection (2) Overview of Company and Products 2. Management QMS organization, Quality Manual, Quality Policy and Objectives, Management Review, Internal Audit, Training 3. Documentation and Records
	13:00-17:30	4. Factory tour
Day 2	9:30-12:00	5. Design and Development (including Risk Management) 6. Purchasing Control
	13:00-17:30	7. Product and Process controls
Day 3	9:30-12:00	8. Medical Device File 9. Customer Related Processes
	13:00-17:30	10. Corrective and Preventive Actions 11. Team Meeting of Inspectors 12. Confirmation on Findings and Closing Meeting

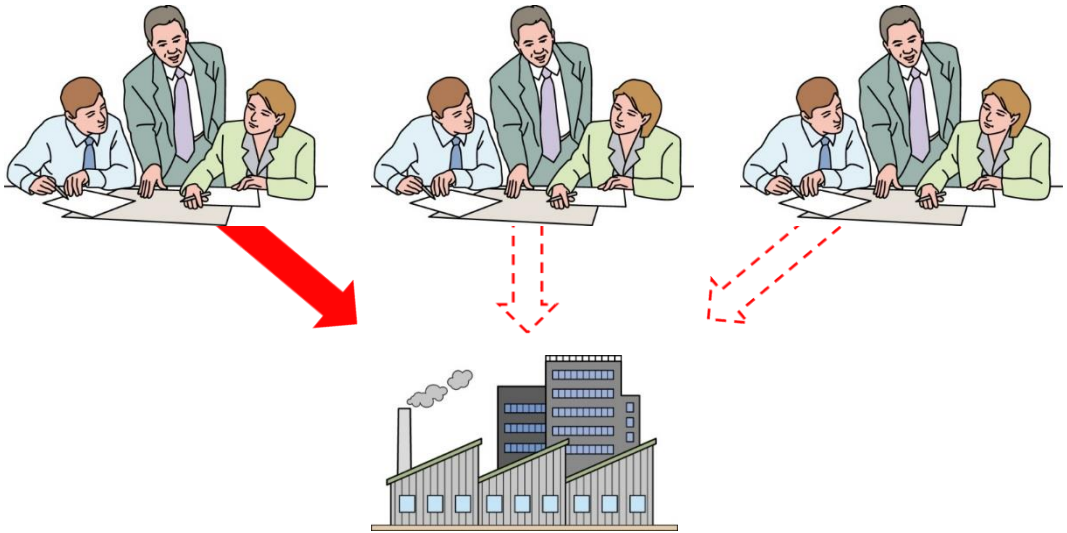
Nonconformities of On-site Inspections



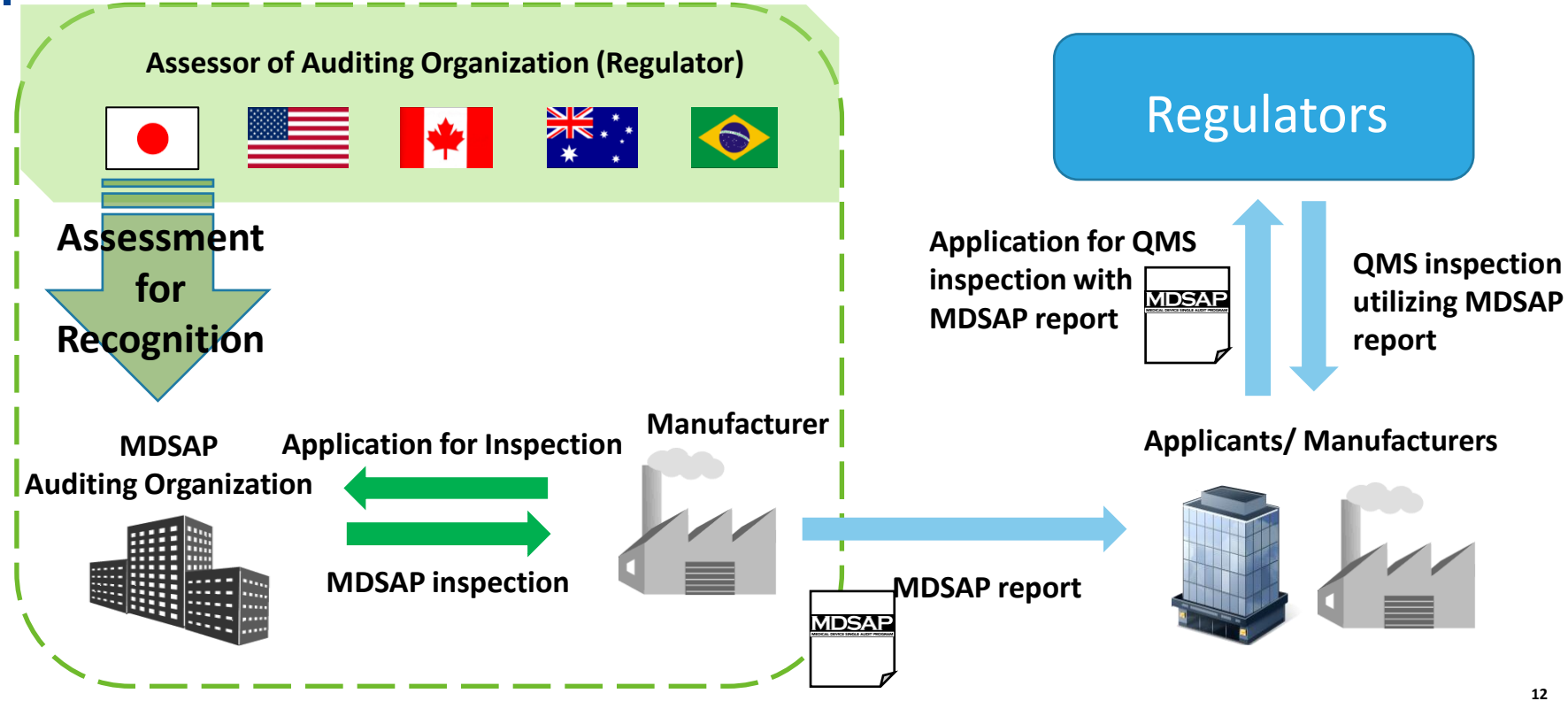
Aggregation period: October, 2016 – September, 2021

MDSAP: Multilateral effort for QMS inspection

Medical **D**evice **S**ingle **A**udit **P**rogram



Flow of MDSAP



Agenda

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SaMD Classification and Regulation

Risk based

Class II/Class III without Certification Standards, Class IV
->MHLW approval with PMDA review

Class II/Class III with Certification Standards
->3rd party Certification by Registered Certification Bodies

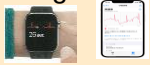
Novel Device

Software corresponded to Class I
Exempted from medical device regulations

(as of July 3, 2024)

Standards for medical devices		Those for SaMD
Japanese Medical Device Nomenclature	4461	193
Approval Standards	44	-
Review Guidelines	10	-
Review Points	7	5
Certification Standards	951	110

Overview of Approved/Certified SaMD

Non MD	MD	Class II	Class III
Software for heath management Software for education Software for supporting hospital operation Software corresponding to class I	For Home Use	Program for diagnostics assist for home use (2) 	
	For Diagnosis and examination	Program for computer assisted Imaging diagnostics (312)	
		Program for computer assisted diagnostics other than imaging (79)	
			Program for gene mutation analysis (10)
	For Treatment		Program for therapy planning support (59)
			Program for surgery support (1)
		Therapy support program (7)	
			Programmer for active implantable device (3)

Review of Software Products

In principle, it is not different from the review of non-software products.

Concept of development

↓

Intended use of SaMD

↓

Non-clinical evaluation
- Performance
- Safety

Clinical evaluation
- Clinical trials
- Literature investigation

Essential principle


GHTF/SG1/N68:2012

GHTF

FINAL DOCUMENT

Global Harmonization Task Force
(revision of GHTF/SG1/N41:2005)

Title: Essential Principles of Safety and Performance of Medical Devices

Authoring Group: Study Group 1 of the Global Harmonization Task Force

Date: November 2nd, 2012

Dr. Kazunari Asamura, GHTF Chair

This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide non-binding guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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IMDRF/GRRP WG/N27 FINAL:2018

IMDRF International Medical Device Regulators Forum

Final Document

Title: Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

Authoring Group: IMDRF Good Regulatory Review Practices Group

Date: 31 October 2018

Yuan Liu, IMDRF Chair

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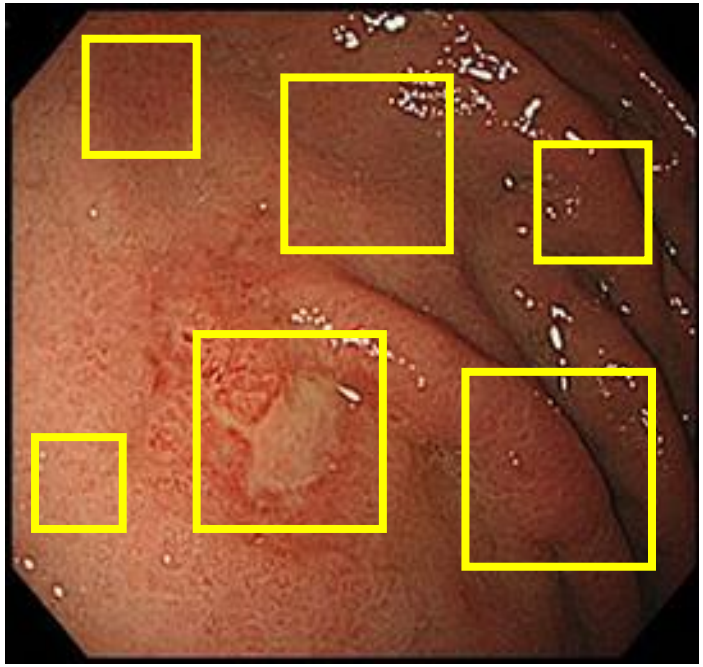
What's the risk of Software Products

Computer-aided detection on endoscope imaging



Review as Medical Device, Not just as Function

What is the medical utility of the product?

What RISKs are associated with the implementation of the product?

A function could be utilized in a various situation

→ Understanding of the function itself is not enough to determine the sufficiency of the evaluation.

It is important to understand
how the product can be implemented into the current medical practice
as a medical device.

e.g.

Relationship to current practice

- Combination with current practice
- Substitute for current practice
- Replace current practice
- Add new scheme/mean

etc…

Contribution to patient outcome

- Equivalent efficacy to current practice
- Higher efficacy to current practice
- Effect on patients not addressed by current practice

etc…

Consideration on bias regarding ML medical device

ML: machine learning

Applicants

【Appropriateness of performance test; **case 1**】

Training data was collected at institution A. The performance test was conducted using other data collected at institution A and the it's confirmed the performance of the SaMD is high enough.

【Question from PMDA】

The results could be affected by the patient population, equipment or medical practice specialized with Institution A and can not generalized for other institutions…

PMDA

Applicants

【 Appropriateness of performance test; **case 2**】

Performance test was conducted using dataset X from multiple institutions. A certain population shows not sufficient result so we re-train the SaMD then test again with dataset X. The result was good enough.

【 Question from PMDA 】

The SaMD could be just adjusted to dataset X by retraining…

PMDA

- Independence of training data and test data is ideal; ①appropriateness of data reuse、② separation of data collecting institute ,③Separation of annotator of Gold standard of training data and test data, etc.

Examples of AIML-enabled MDs approved in Japan

COVID-19 Pneumonia image analysis program FS-AI693

FUJIFILM Corporation

Nodoca

disease characteristic finding detection support software for endoscope
(influenza virus infection)

Aillis, Inc.

Major challenges in premarket review of AIML-enabled medical devices

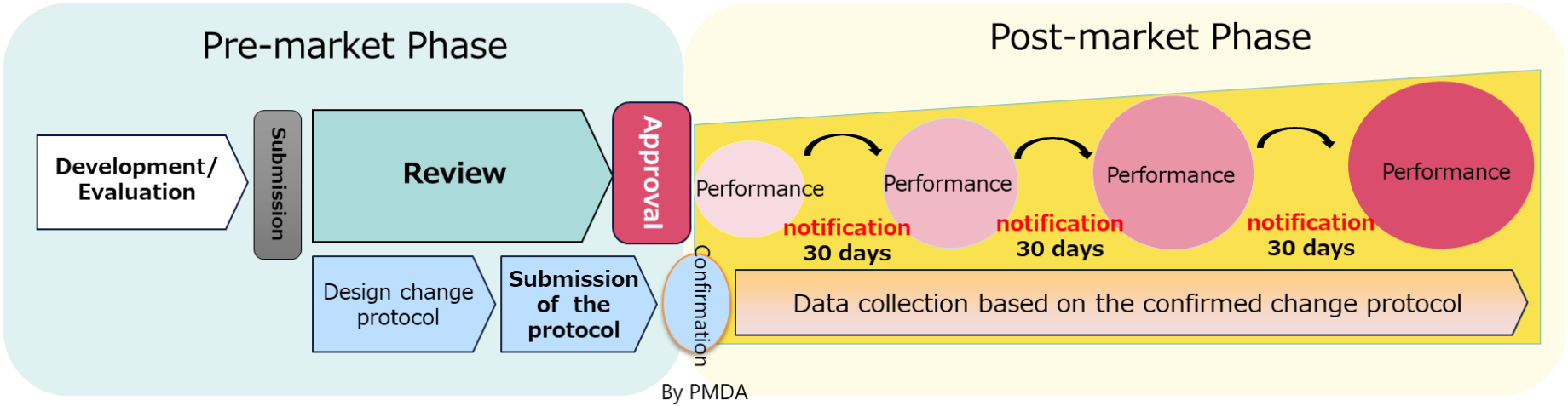
- Plasticity
  - Performance should be locked when regulators review the application
  - Performance can be changed in the post marketing phase

- Unpredictability
  - Bias of data could affect the performance of the software
  - Independence and completeness of data is critical

Plasticity

Post-Approval Change Management Protocol (PACMP/IDATEN) for MDs

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



Published in 2019, in force in 2020

Unpredictability

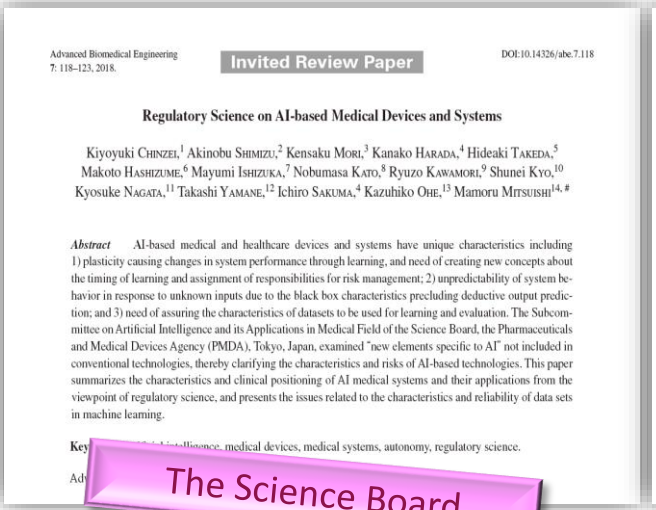
Publication of points to consider for some specific SaMD

- Supporting software for detecting lesion with endoscopic imaging
- Computer diagnostic support program aimed at supporting interpretation of medical images

(Japanese only)

Unpredictability

Outcome Document 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, #]

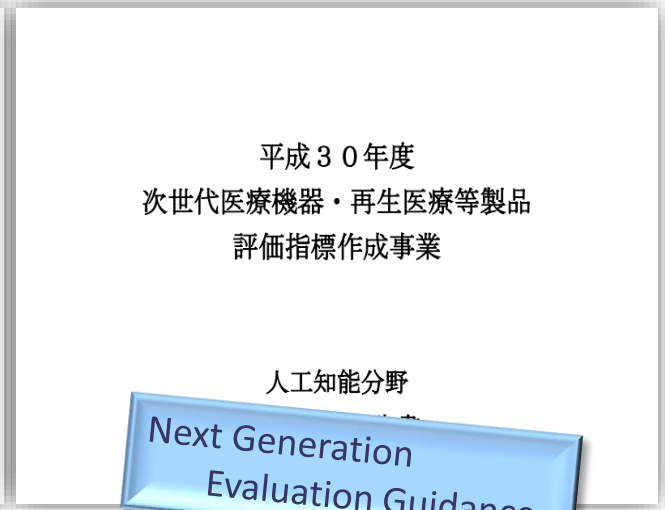
Abstract AI-based medical and healthcare devices and systems have unique characteristics including 1) plasticity causing changes in system performance through learning, and need of creating new concepts about the timing of learning and assignment of responsibilities for risk management; 2) unpredictability 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.

Key [illegible] intelligence, medical devices, medical systems, autonomy, regulatory science.

Ad[illegible]

The Science Board

2018

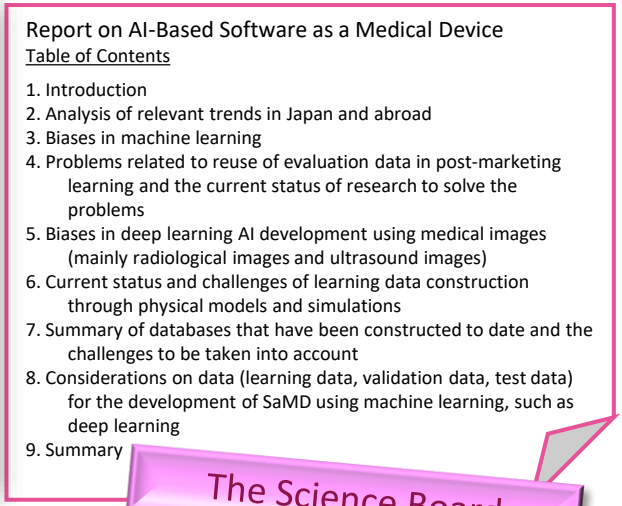


平成３０年度
次世代医療機器・再生医療等製品
評価指標作成事業

人工知能分野

Next Generation Evaluation Guidance

2018



Report on AI-Based Software as a Medical Device

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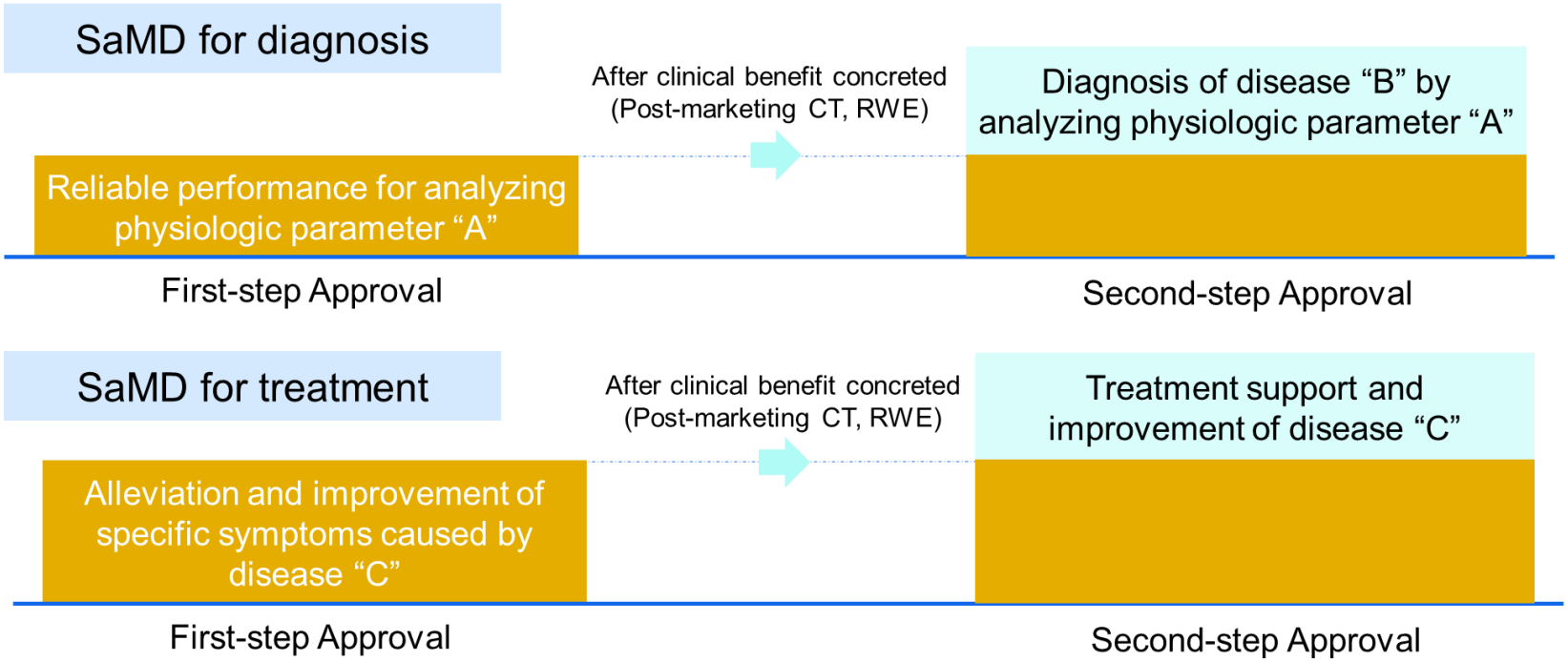
The Science Board

2023

Support for innovation

Two step Approval scheme for SaMD

November 16th, 2023



DASH for SaMD2

DASH for SaMD 2 （2023/9/6）

- Organize and publicize the two-step approval scheme for SaMD
- Develop guidelines for approval review and marketing procedures for SaMD for the general public
- Promotion of overseas acceptance of our review results (such as English translation of review reports)
- Subsidies for development funds for SaMD developers
- Support for SaMD developers to actively business overseas

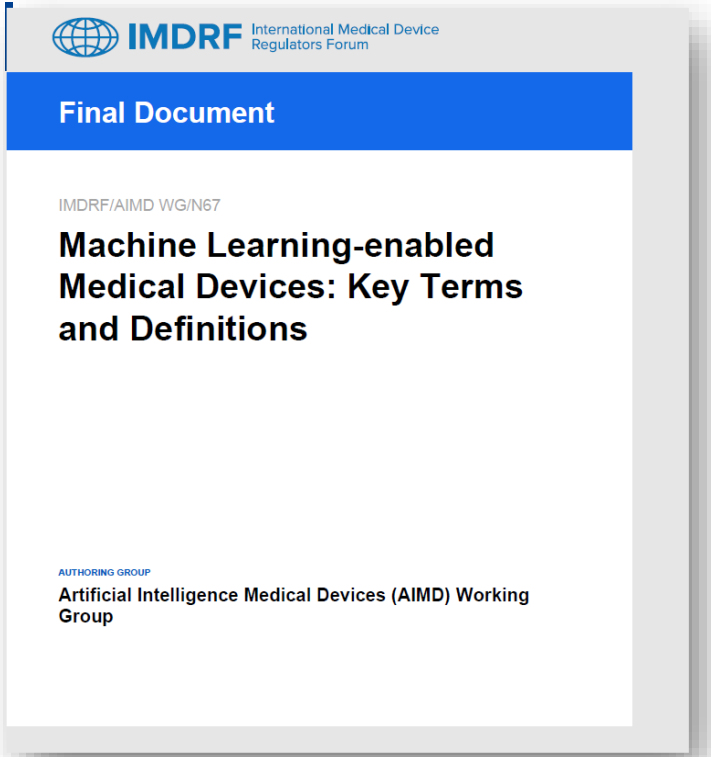
DASH for SaMD（2020/11/24）

- Setup an office to review SaMD in MHLW and PMDA
- Establishment of SaMD centralized consultation service
- Next-generation medical device evaluation index, development guidance, audit points, and certification criteria formulation
- Trial implementation of priority review, etc. for innovative SaMD
- Promote the use of IDATEN (Improvement Design within Approval for Timely Evaluation and Notice) and streamline procedures, etc.

<Expand and continue>

- Upgrade from office to Department for reviewing SaMD in PMDA
- Establishment of SaMD-specific consultation service
- (Continue)
- (Continue)
- (Continue)

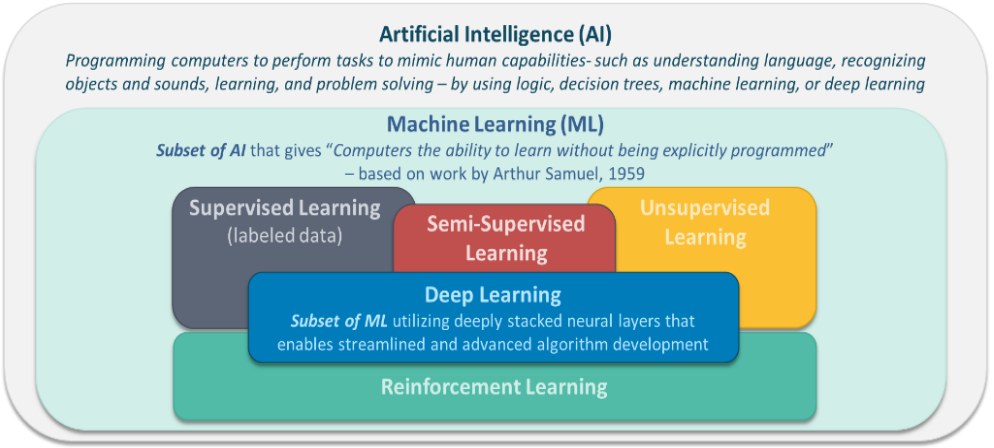
International Regulatory Harmonization



2022.5.6

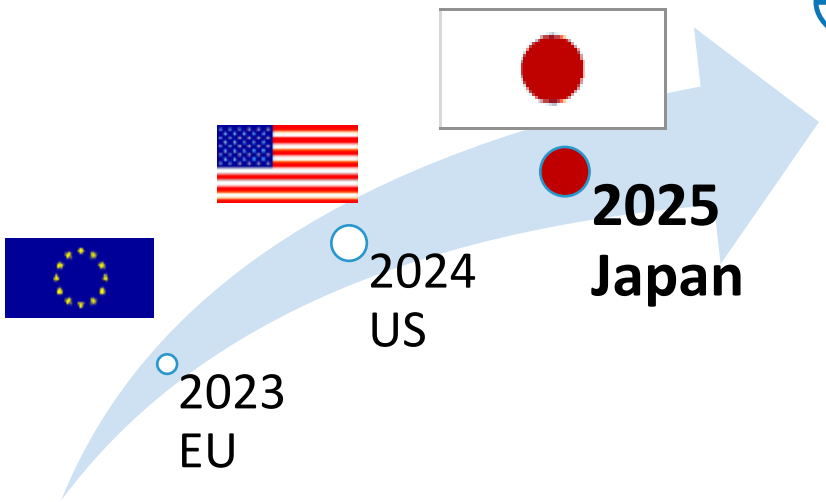
MLMD (Machine Learning-enabled Medical Device)

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.

The 2025 IMDRF Chair and Secretariat to be held by Japan



IMDRF International Medical Device Regulators Forum

The roles of IMDRF Chair and Secretariat

- Leading activities of IMDRF, including conducting all the IMDRF MC meetings
- Disseminating information
- Coordinating IMDRF MC meetings
- Maintaining a repository of documents and the tools of communication
- Leading to create strategic plan 2025-2030

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Thank You!
धन्यवाद