# Pre Market Reviews:
# Conformity Assessment Concepts & Principles

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Regulatory Harmonization Steering Committee
APEC
Life Sciences Innovation Forum

# PMDA-Asia Training Center's Medical Devices Seminar

pmda

【Purposes】

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

| # | Date | Venue | Participants |
|---|---|---|---|
| 1 | Nov. 7-11, 2016 | Tokyo | 28 from 13 countries/regions |
| 2 | Nov. 6-10, 2017 | | 30 from 12 countries/regions |
| 3 | Nov. 12-16, 2018 | | 25 from 17 countries/regions |
| ***4*** | ***Nov. 25-29, 2019*** | | |

- Lectures on Pre-market review, QMS/GCP/GLP and Post-market safety
- Manufacturing site visits and session on R&D

# 1. OVERVIEW OF APPROVAL SYSTEM (taking Japan as an example)

# The regulation of MD in Japan

- ALL Medical Devices are under the regulation of the PMD Act
- One must take some action according to the PMD Act if one **markets** any Medical Device/IVD

Regulations on Marketing

# Definition of Medical Devices

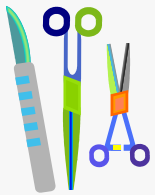
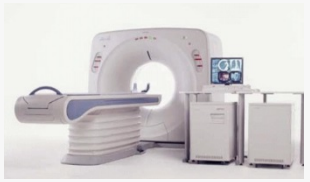
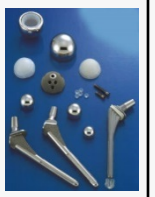
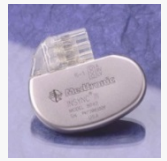
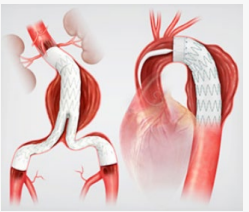
- …machinery or apparatus, etc. **intended for** use in the diagnosis, treatment or prevention of disease in humans or animals or **intended to** affect the structure or functions of the human or animal body, which are specified by Cabinet Order

~Pharmaceuticals and Medical Devices Act (PMD Act)

Article 2.4. Definition of Medical device

Not only matter of WHAT

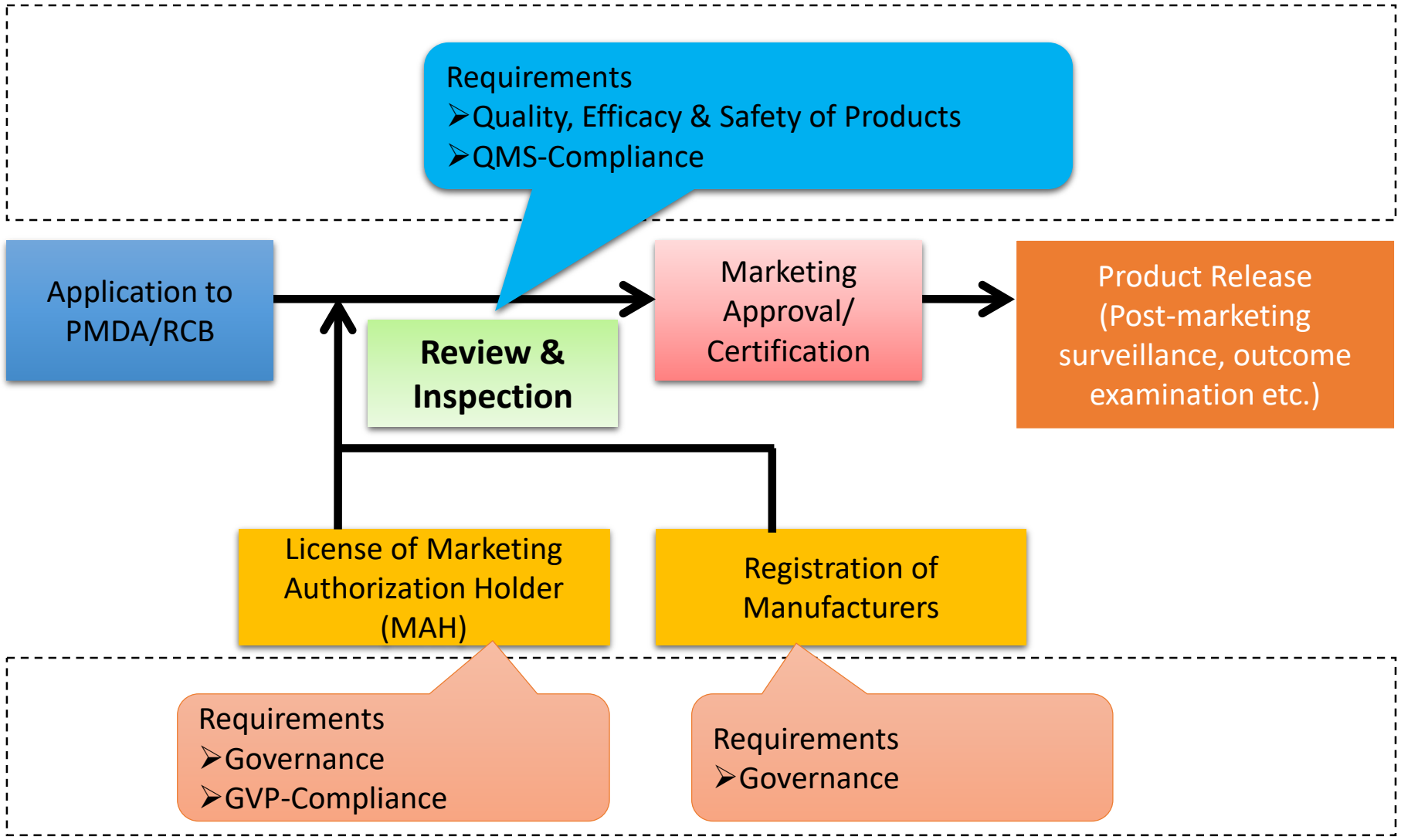
# Medical Device Regulations in Japan

| 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 | | | |



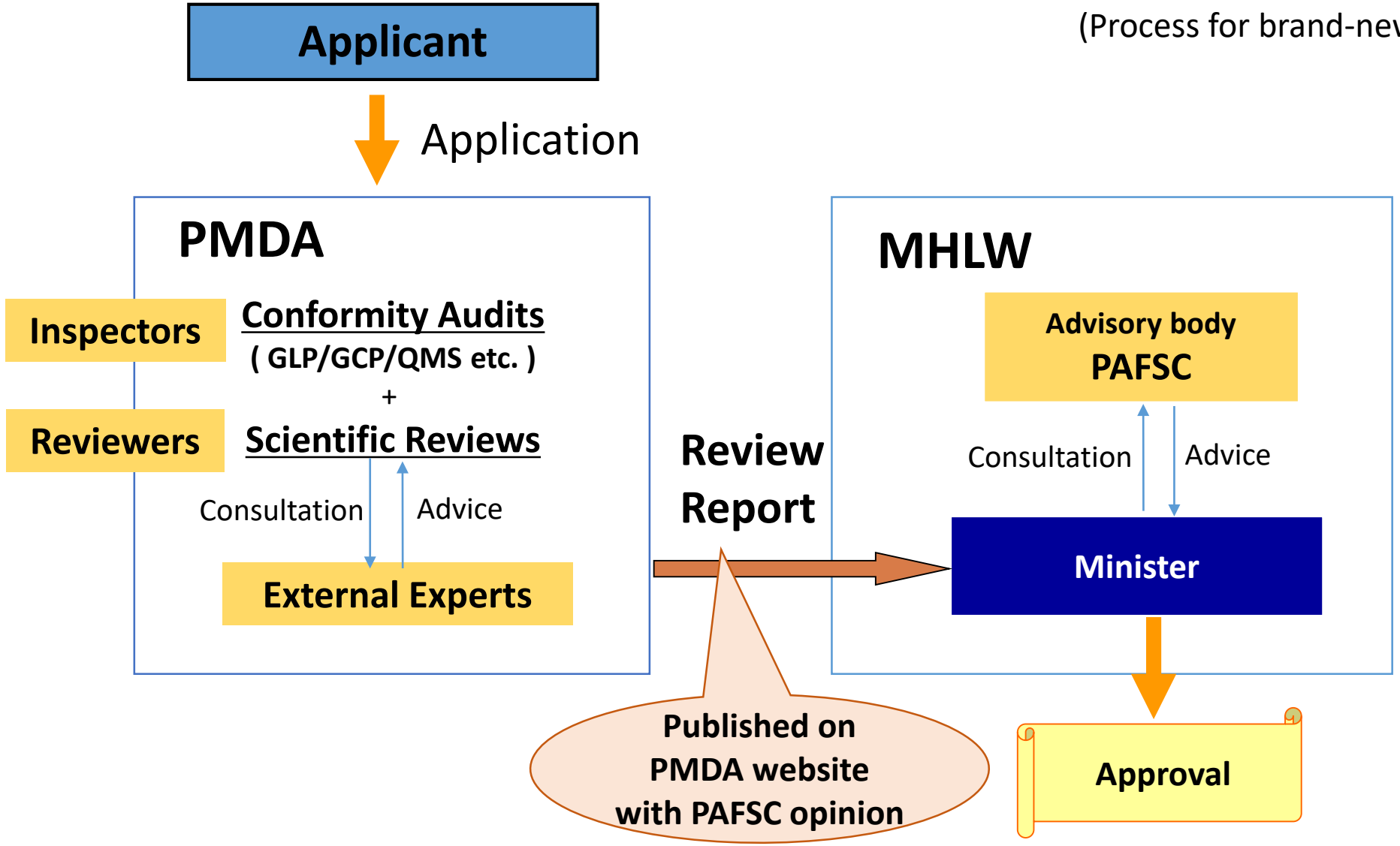
Nomenclature “JMDN” developed based on GMDN

# Approval/Certification system in Japan



# How to involve expert views in the process?

(Process for brand-new devices)

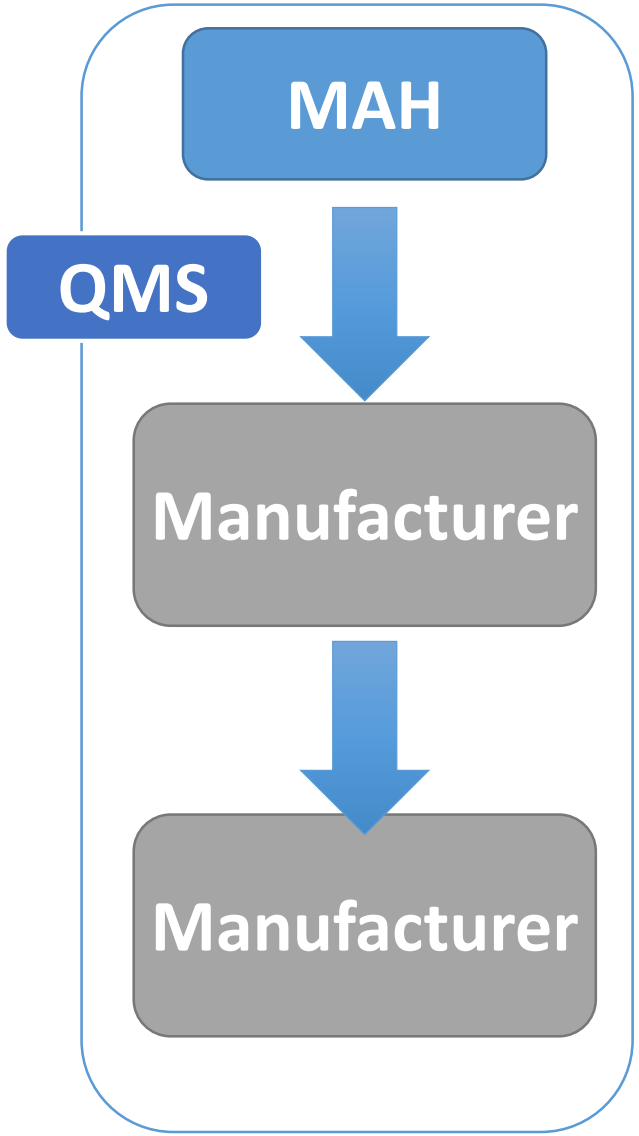



PAFSC:
Pharmaceutical Affairs and Food Sanitation Council

# How much different compared to marketed products?

| | |
|---|---|
| **Brand-new MD** | ● Medical devices whose structure, directions for use, effect or performance are clearly different from those already approved<br>● Clinical data required |
| **Improved MD** | ● Medical devices that are not categorized brand-new or generic<br>● To be required the clinical data if improved points are evaluated by the clinical data only |
| **Generic MD** | ● Medical devices whose structure, directions for use effect or performance are substantially equivalent to those already approved<br>● Clinical data not to be required |

# MAH is responsible for ALL




MAH License : From local government
Need for
1. Having marketing supervisor general, safety management supervisor and quality assurance supervisor
2. Having system for GVP (V: vigilance)
3. Having system for QMS

(They should follow QMS and GVP when they market products)

Manufacturer : JUST register
(They should follow QMS when they manufacture products)

# 2. PRE MARKET REVIEW PRINCIPLES

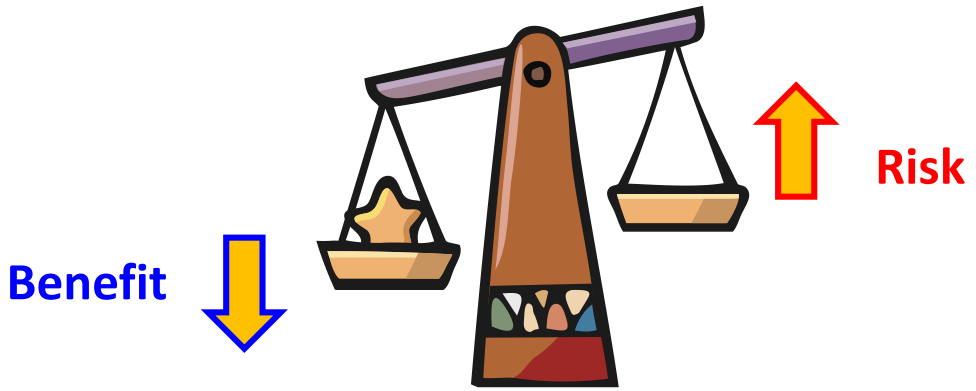
# What is approval review ?

## Reason of Approval Rejection

(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)*




**Risk < Benefit = Approvable**

# Review Standpoints

## -What evaluation is necessary?-

What subject for?

Higher efficacy, safety or usability?

**Purpose of development**

Novel treatment, comparable option, or for unmet medical needs?

**Intended use in clinical practice**


Design specifications

**Non-clinical test**

✓ Performance

✓ Safety

Appropriate evaluation based on its concept

**Clinical evaluation**

✓ Clinical trials – in what design?

✓ Literature investigation

Appropriate evaluation based on its place in the clinical practice

# Risk management of medical devices

ISO 14971 : 2007

**Risk management**

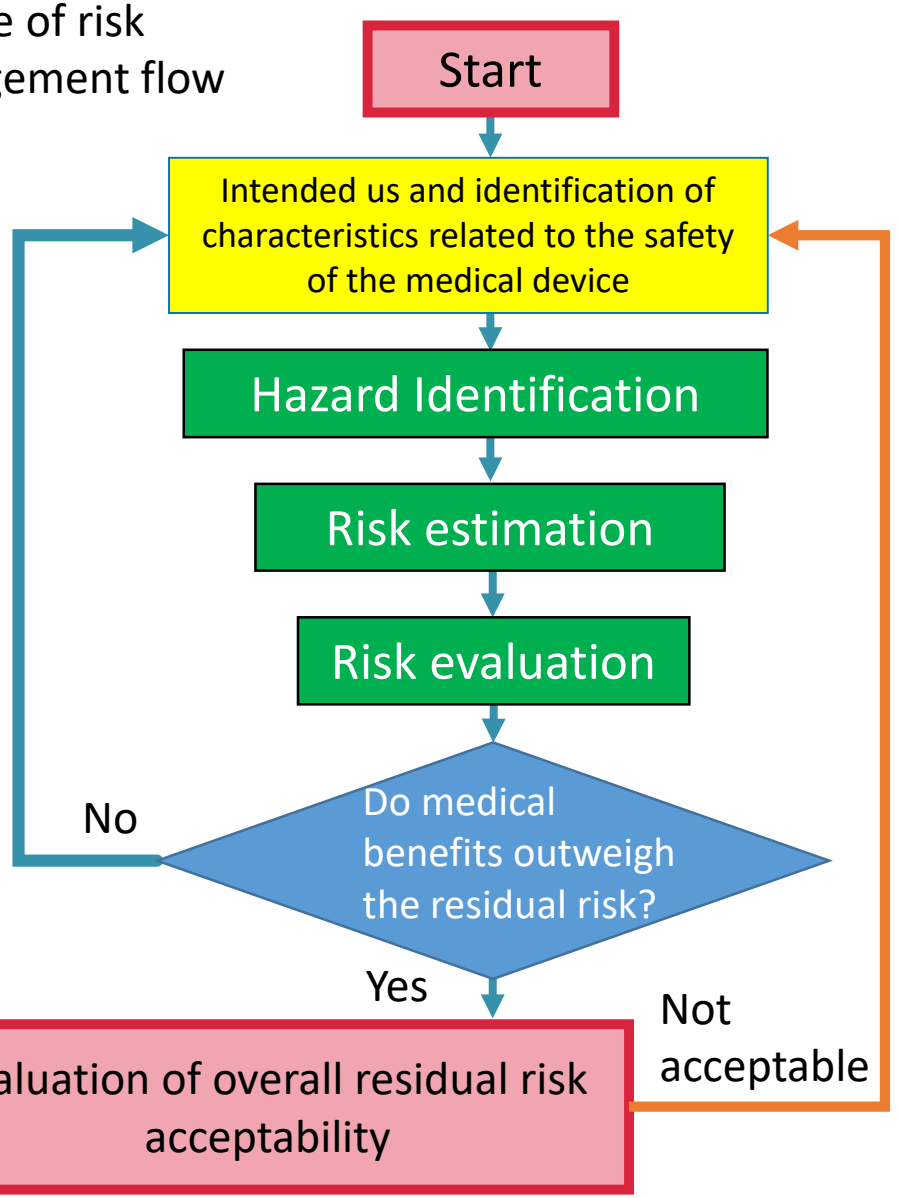
- **risk analysis**

  **Identify hazards and estimate risk**

- **risk evaluation**
- **risk control**

  Evaluate residual risk and implement risk control measures until the acceptable risk level attained

Outline of risk management flow




Need systematic review for production and post-production information

# How to mitigate risks

- ✓Reduce risks through ***safe design and manufacture***
- ✓Take adequate protection measures, ***including alarms if necessary***, in relation to risks that cannot be eliminated by safe design and manufacture
- ✓Provide ***post marketing measures*** including ***information for safety*** (warnings/ precautions/ contra-indications)

# Standards should be referred in the regulation

◆*Type of standards :*

- National Standards (e.g. JIS, ANSI, BSI, and DIN)
- International standards (e.g. ISO, IEC and ITU)
- Product standards (industry-proved standards) etc.

◆*Characteristics of standards :*

- Standards should be based on the consolidated results of science, technology and experience, … (ISO/IEC Guide2:2004, definition 3.2)
- Standards are characterized as the documents describing standardization requirements. (For example, evaluation methods and item specifications common in products.)
- A standard itself is generally a voluntary standard.

# Standards works as criteria in the evaluation

◆*Essential Principles*（*GHTF/SG1/N41R9:2005 ⇒ GHTF/SG1/N68:2012**）

- Fundamental design and manufacturing requirements are described.
- Essential Principles (EPs) was introduced in Japanese regulation and all devices shall be in conformity with the EPs.

◆*Role of Standards in the Assessment of Medical Devices (GHTF/SG1/N44:2008)*

- Recognized standards**:** Standards deemed to offer the presumption of conformity to specific Essential Principles of Safety and Performance.

The JIS, ISO and IEC standards used in Japanese regulation to show the presumption of conformity to specific Essential Principles.
⇒These standards meet recognizes standards defined in GHTF.

* The GHTF document was superseded as IMDRF document (IMDRF/GRRP WG/N47 FINAL 2018) with same title on 31st Oct. 2018. Medical devices which are conformed with the N47 document are acceptable in Japanese regulation.

# 3. APPLICATION DOCUMENTS

# Application Dossier

**Application Form**

**Identification of application items**

- **Type**
- **Name**
- **Purpose of use or effect**
- **Form, structure and principles**
- **Raw materials**
- **Specifications for performance and safety**
- **Method of operation**
- **Storage method and expiration period**

**STED with Supporting Data**

**Justifying data**

**Efficacy**
**Safety**
**Quality**

# Summary of the Technical Documents(STED) (GHTF/SG1/N063:2011)

Part1 Purpose of the STED

Part2 Contents of the STED

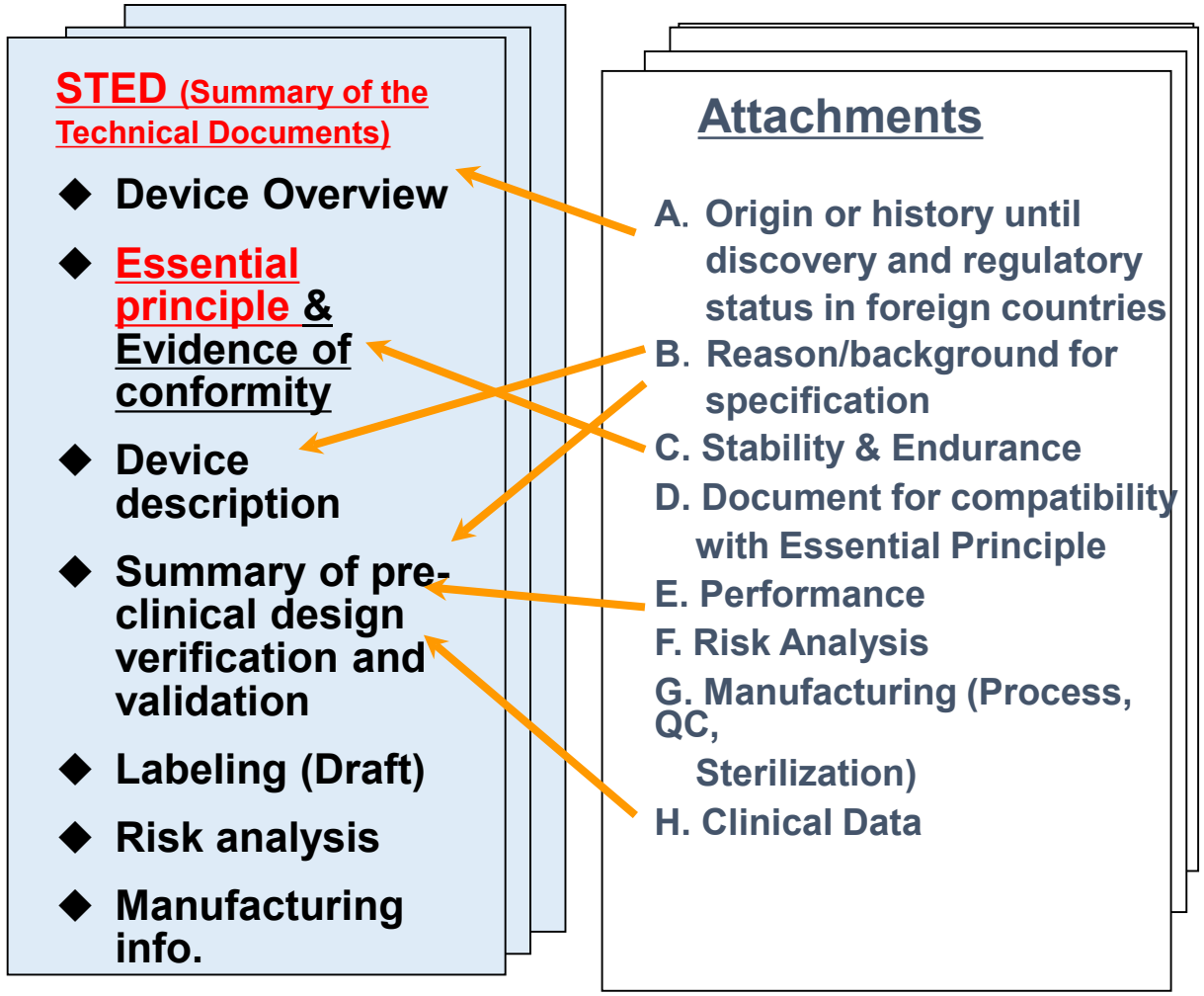
| No. | Contents |
|---|---|
| 6.0 | Device Description including Variants (Configurations) and Accessories |
| 7.0 | Essential Principles (EP) Checklist |
| 8.0 | Risk Analysis and Control Summary |
| 9.0 | Design and Manufacturing Information |
| 10.0 | Product Verification and Validation |
| 11.0 | Labelling |
| 12.0 | Format of the STED |
| 13.0 | Declaration of conformity |

Appendix A Essential Principles (EP) Checklist

# Package of Application Documents (Image)

**Application Format**

- ☐ Type
- ☐ Name
- ☐ Purpose of use or effect
- ☐ Form, structure and principles
- ☐ Raw materials
- ☐ Specifications for performance and safety
- ☐ Method of operation
- ☐ Storage method and expiration period
- ☐ ・・・




•Request for compliance of GCP/GLP
•Request for compliance to QMS (ISO13485 basis)

# Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (EPs)

IMDRF/GRRP WG/N47 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 Lin, IMDRF Chair

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(GHTF/SG1/N68:2012)→(IMDRF/GRRP WG/N47 FINAL:2018)

# The purpose of EPs

- ***To clarify fundamental design and manufacturing requirements*** for medical devices to provide assurance the devices is safe and performs to its specification are described

- ***The worldwide adoption*** of fundamental design and manufacturing requirements for medical devices that, when met, provide assurance the device is safe and performs to its specification, ***offers significant benefits*** to the manufacture, user, patient or consumer, and to ***Regulatory Authorities (RA)***

# Index of EPs

IMDRF/GRRP WG/N47 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 Lin, IMDRF Chair



Introduction

1. Scope
2. Reference
3. Definitions
4. Safety and Performance of MD-General Essential Principles
5. ***Essential Principle Applicable to all MD and IVD MD***
6. Essential Principle Applicable to MD other than IVD MD
7. Essential Principle Applicable to IVD MD

# 5. Essential Principles Applicable to all MD including IVD MD

| | |
|---|---|
| 5.1 | General |
| 5.2 | Clinical Evaluation |
| 5.3 | Chemical, Physical and Biological Properties |
| 5.4 | Sterilization and Microbial Contamination |
| 5.5 | Considerations of Environment and Conditions of Use |
| 5.6 | Protection against Mechanical, and Thermal Risks |
| 5.7 | Active Medical Devices and IVD Medical Devices and Medical Device Connected to Them |
| 5.8 | Medical Devices and IVD Medical Devices that Incorporate Software or are Software as a Medical Device |
| 5.9 | Medical Devices and IVD Medical Device with a Diagnostic or Measuring Function |
| 5.10 | Labeling |
| 5.11 | Protection against Radiation |
| 5.12 | Protection against the Risks posed by Medical Devices and IVD Medical Devices intended by the Manufacturer for use by Lay Users |
| 5.13 | Medical Devices and IVD Medical Devices Incorporating Materials of Biological Origin |

# What exactly happens during Review?

The application form and attachments are confirmed and the appropriateness of the evaluated contents are discussed

The appropriateness of the development concept, comparison with existing products, and method of use are explained

**Question and answer session about the contents of the application**

**Medical Device Review Team**

**Clinician** **Reviewers**

**Applicant**

**Discussions with experts from various fields (as necessary)**

**External expert committee**

**Review of application content and appropriate modification of the content based on the review results**

**Application package**

**●Application form**

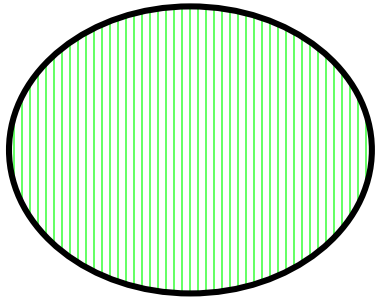
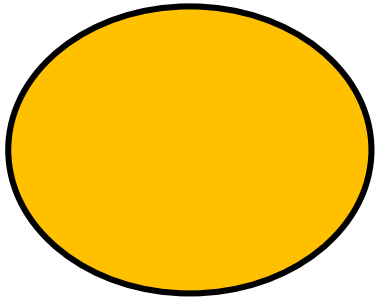
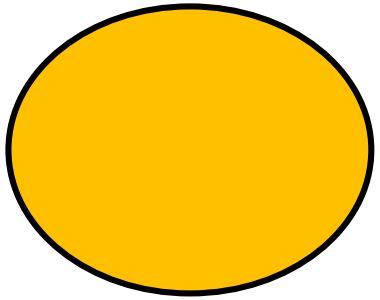
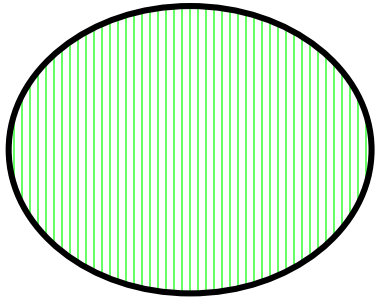
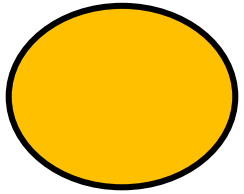
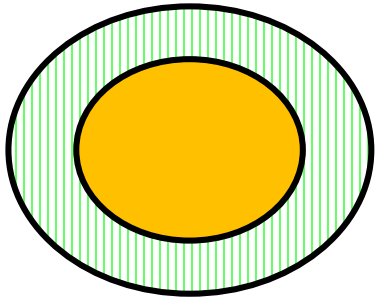
Intended purpose of use, structure, manufacturing and use methods, specifications, manufacturing process, etc.

**●Attachments**

Validation test materials, clinical trial documents, etc.

# Review Standpoints

## -Is the date sufficient ?-

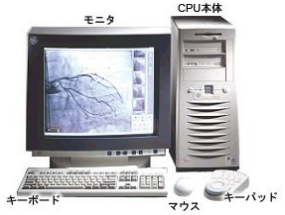
| Application Form | STED with Supporting Data | Approval |
| --- | --- | --- |
|  |  |  **Yes** |
|  |  |  **No** |

# 4. EMERGING TOPICS OF APPROVAL REVIEW

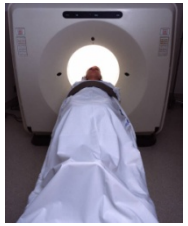
# Software as a Medical Device (SaMD) is regulated in PMD Act

Example of Medical Device with embedded program

## Image Diagnostic Apparatus

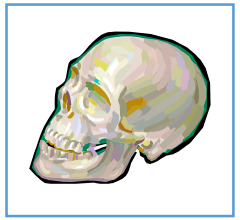



It processes, stores and displays image data from CT, MRI etc.



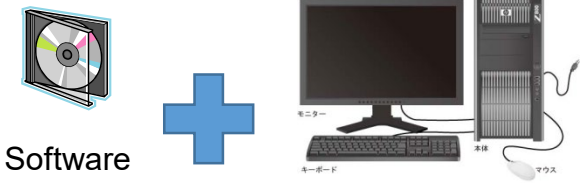
Data from CT scanning

Processing by program



3D image of a skull

## PAL



Software (program)

Hardware

**Combination of hardware and software is regulated as a total system.**

**PMD Act**

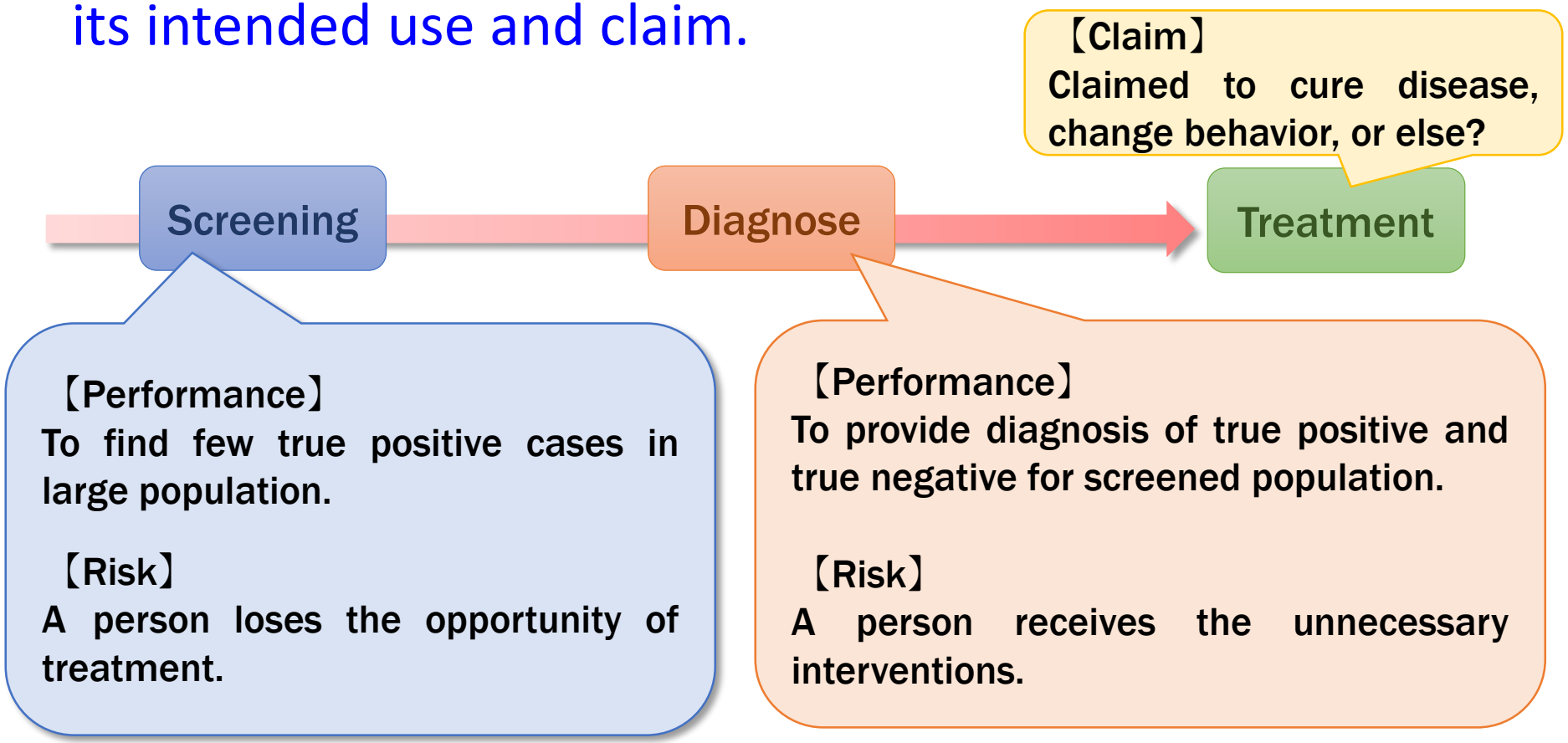
SaMD

Software (program)

**Software itself is independently regulated**

# Approval Review Principles of SaMD

Risk/benefit balance and evidence level are variable by its intended use and claim.




How much are false-positive and false-negative rates acceptable?
What sort of clinical evidence is needed to support its claim?

# Specific Considerations for review of MD/SaMD with **Artificial Intelligence**

**Unpredictability**

Users cannot understand the reasoning of output

How do you figure out difficult outputs?

**Plasticity**

Post market learning may be worsen the performance of AI products

How do you keep the performance of product?

# 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

Issues:

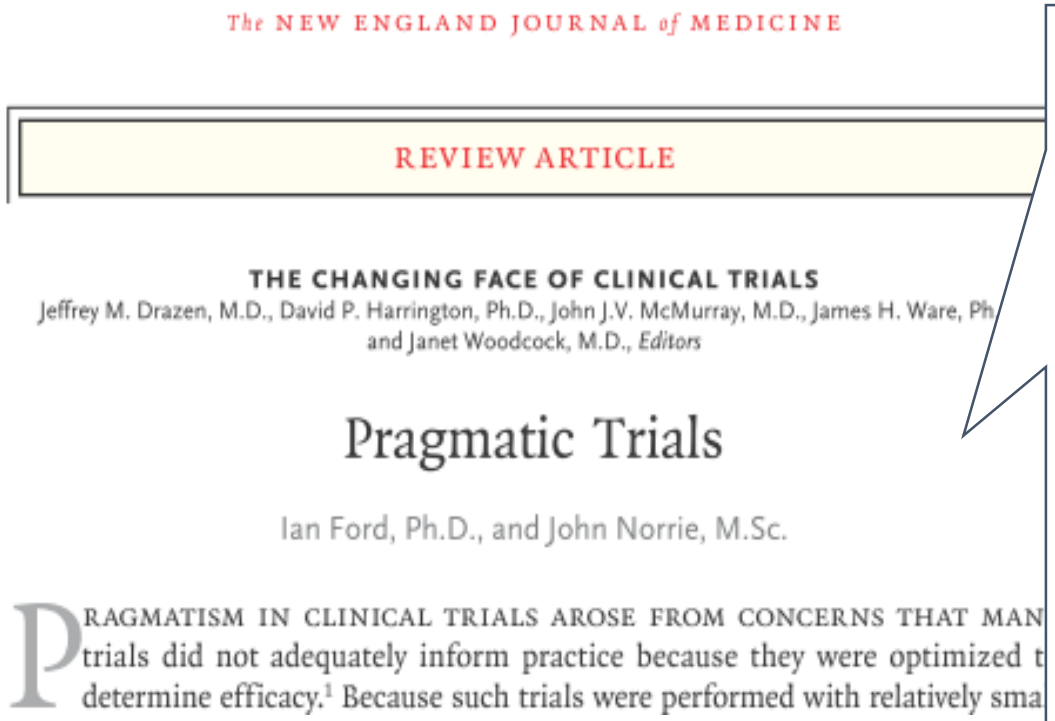
- Algorithm for calculating output is “black box” nature in AI based on deep learning.
- Its performance, especially after post-market training, can only be evaluated by verification of the output.
- How to consider the source or type of the data, authenticity and bias in the learning data?

The 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.

* Referring to MHLW Health Policy Bureau notification that medical doctors are responsible for the final decision in diagnosis and treatment.

# *Use of Real World Data*

- *MHLW is developing regulatory systems supporting pragmatic trials using registries/health records.*



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph
and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MAN
trials did not adequately inform practice because they were optimized t
determine efficacy.[1] Because such trials were performed with relatively sma

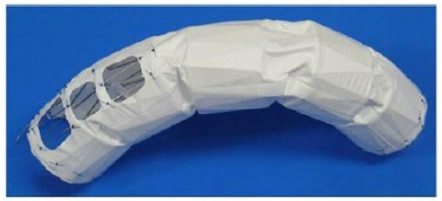
An attractive alternative to trials in which **electronic health records** are used can be found in trials of alternative interventions involving patients who are already enrolled in **disease-specific or intervention-specific registries** that incorporate detailed patient phenotypes and long-term follow-up data. This framework provides **an efficient and low-cost opportunity for conducting pragmatic trials** (e.g. the TASTE trial)

Ford I. et al. NEJM 375;5, 454-463, 2016
http://www.nejm.org/doi/full/10.1056/NEJMra1510059?query=featured_clinical-trials

# Examples of use of Real World Data for pre-market review

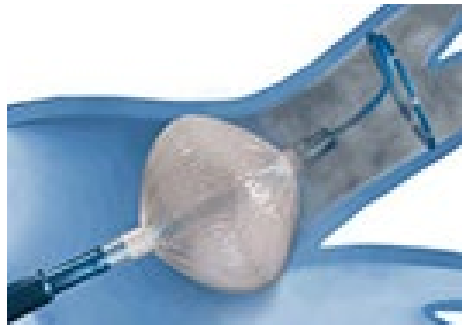
- **Kawasumi Najuta Chest Stent Graft System**
  (Stent graft for prevention of aortic aneurysm rupture)

  Comparison with results from surgery from the historical control group of the Japan Adult Cardiovascular Surgery Database （JACVSD).



- **SATAKE Hot Balloon Catheter**
  (Paroxysmal atrial defibrillation therapy for high-frequency ablation catheters)

  Comparison with results using conventional methods from the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF) of the Japanese Heart Rhythm Society (JHRS).



# Summary

1. Approval system should be established including definition, classification, review process, and MAH/site registration.
2. Risk/Benefit balance should be identified in the approval review process. Use of standards helps efficient process.
3. Application documents should be standardized by incorporating STED and Essential Principles.

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厚生労働省
Ministry of Health, Labour and Welfare

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