APEC Harmonization Center

2011 AHC Workshop on Medical Devices:
"Implementation of GHTF Documents"

Understanding Japanese Medical Device Requirements

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Pharmaceutical Affairs Law (PAL)

- **Pharmaceutical Affairs Law (PAL)** covers regulations on pharmaceuticals, medical devices and cosmetics.

- Under the PAL, the Minister of Health, Labour and Welfare has the authority
  - to give an marketing approval
  - to issue a license for marketing authorization holder
  - to issue a manufacturer license

Key pharmaceutical legislation

Law

- Pharmaceutical Affairs Law (PAL, 1960)

Cabinet Ordinance

- Cabinet Ordinance on PAL, 1961
- Cabinet Ordinance on PAFSC, 2000

Ministerial OrdinanceB

- Ministerial Ordinance on PAL, 1961
- GCP for pharmaceuticals, 1997, for MD, 2005
- Good Vigilance Practice (GVP), 2004
- Good Quality Practice (GQP), 2004 etc.

Ministerial Notification

- Essential Principles
- Certification standards for class II devices
- Classification of medical devices
- List of orphan designation etc.

Notification

- Information on application procedures
- Guidelines for clinical evaluation etc.

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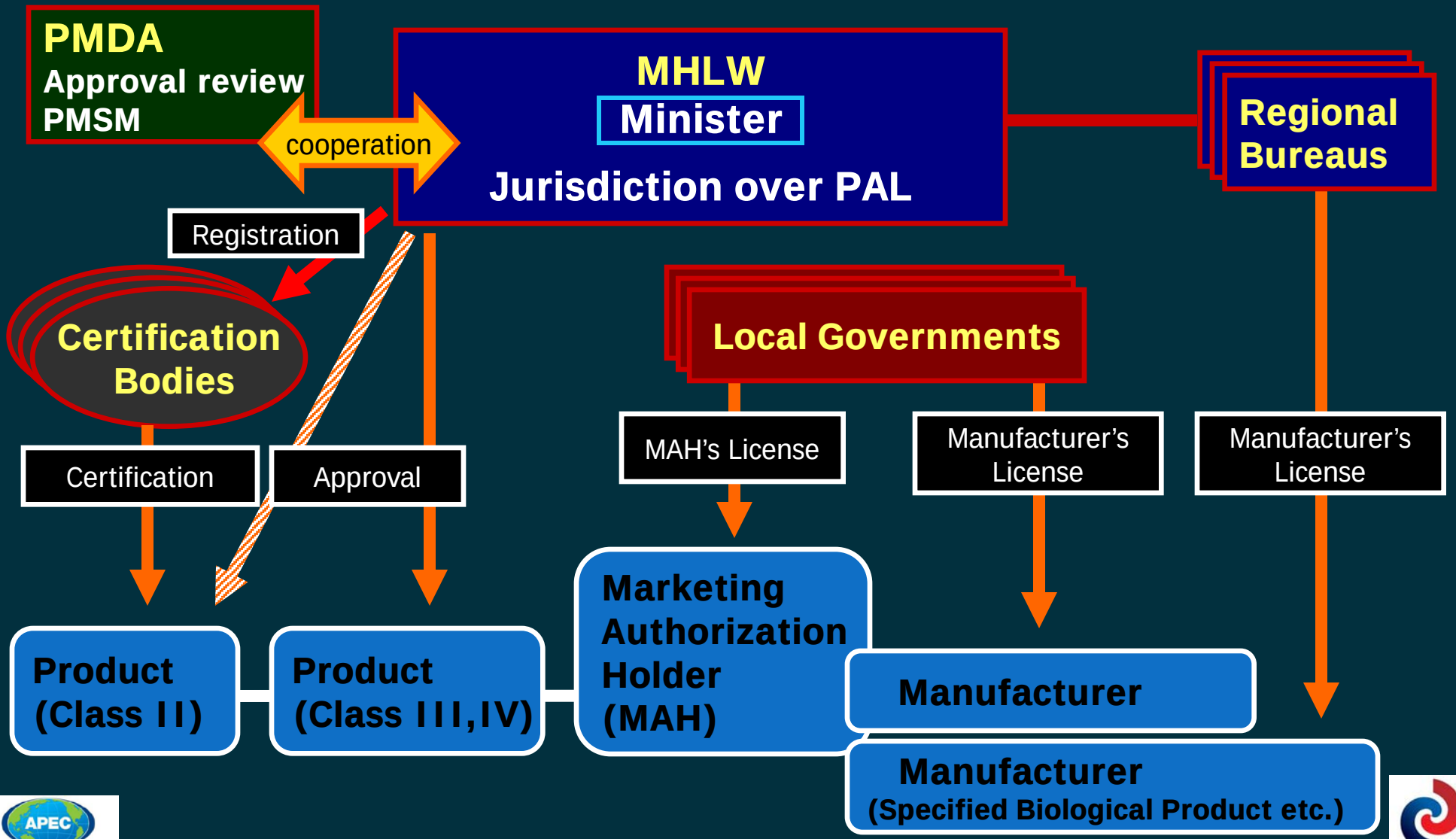
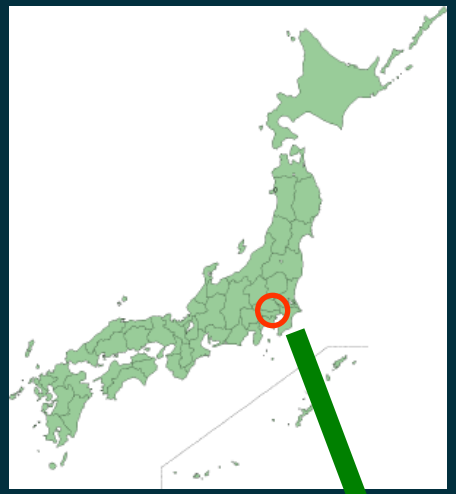
Authorities of MD regulation



Ministry of Health Labor & Welfare (MHLW) & Pharmaceuticals & Medical Devices Agency (PMDA)



Shared Responsibilities

[MHLW]

Ultimate Responsibilities in policies & administrative measures

ex. ・Final judgment on approval
・Product withdrawal from market

[PMDA] "TECHNICAL ARM of MHLW"

Actual review, examination, data analysis, etc. to assist MHLW'S measures

ex. ・Approval Review of MDs
・QMS/GLP/GCP inspection
・Collection and analysis of Adverse Event Reports

Prerequisites to bring MDs into the Japanese Market

Product

- Minister's Approval (*shonin 承認*) (Art.14)
- or 3rd party Certification (*ninsho 認証*) (Art.23-2)
- or Marketing Notification (*todokede 届出*) (Art.14-9)

Company

- License for Marketing Authorization Holder (*Seizohanbai-gyo-kyoka 製造販売業許可*) (Art.12)

Plant

- License for Manufacturer (*seizo-gyo-kyoka 製造業許可*) (Art. 13)
- or Status as Recognized Foreign Manufacturer (*gaikoku seizo-gyosya nintei 外国製造業者認定*) (Art. 13-3)

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Medical Devices Regulation of Japan, EU and US

- EU :Notified Body Certification
  (All Medical Devices)

- Japan :Third Party Certification
  (Low Risk Medical Devices)
  Minister's Approval on basis of PMDA review
  (High Risk Medical Devices)

- US FDA : Approval or Pre-market Clearance

(Note) under pilot study of Third Party review system for some low risk medical devices

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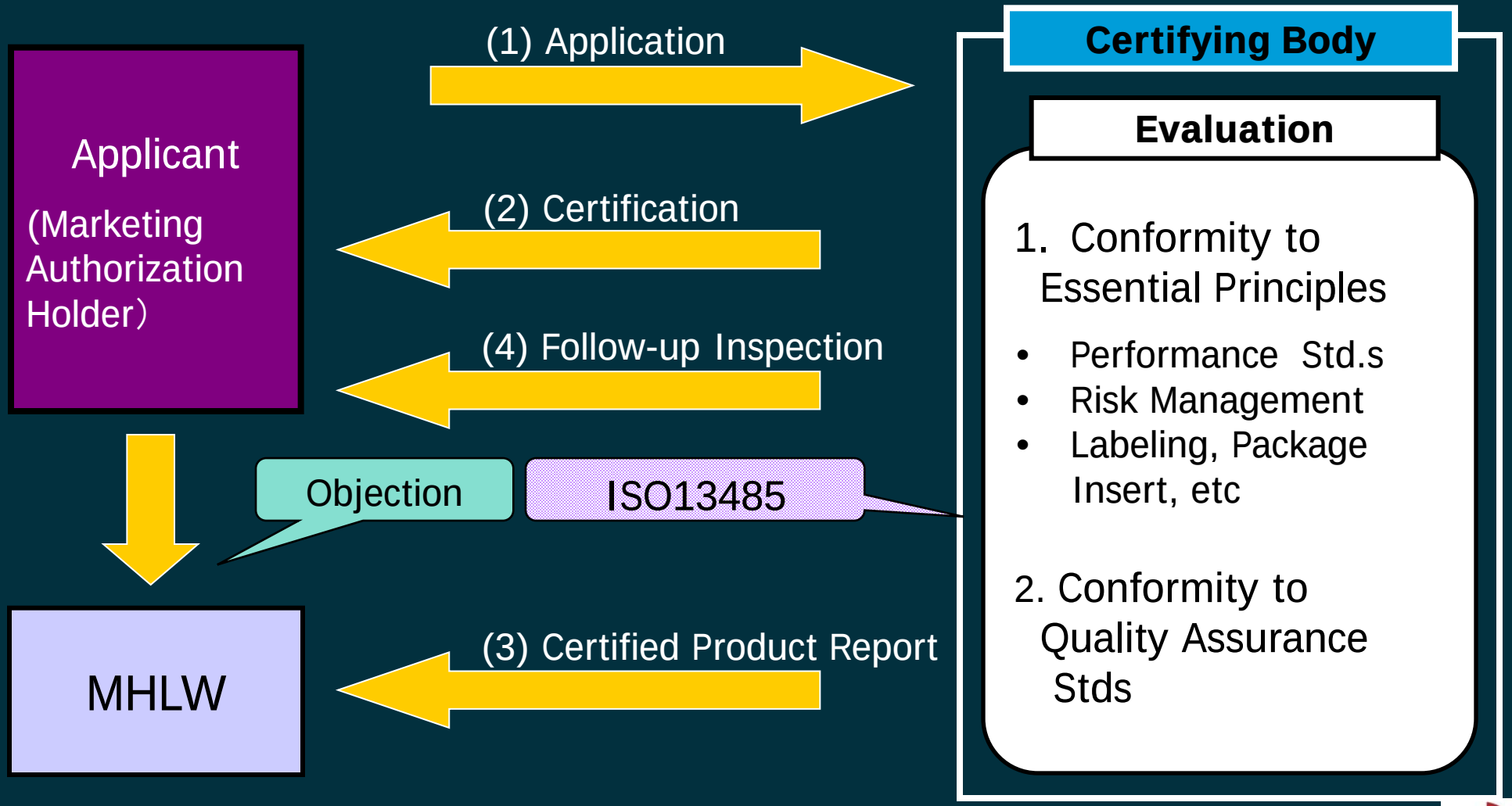
Overview of Classification and Pre-market Regulation for Medical Devices

GHTF Classification	
Class A	extremely low risk X-Ray film
Class B	low risk MRI, digestive catheters
Class C	medium risk artificial bones, dialyzer
Class D	high risk pacemaker, artificial heart valves

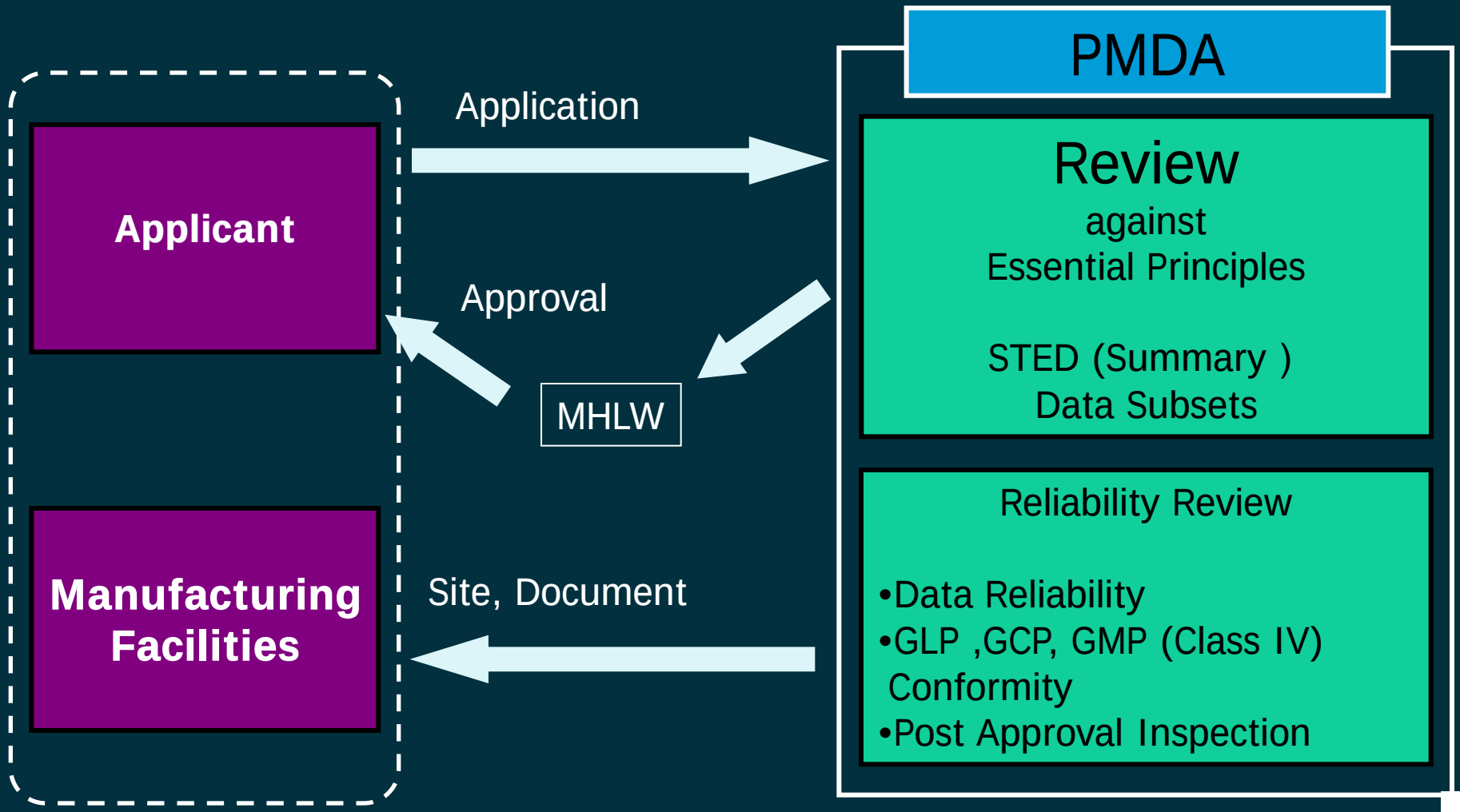
PAL classification		
Category	Pre-market regulation	Japanese MD Nomenclature
General MDs (Class I)	Self declaration	1,195
Controlled MDs (class II)	Third party Certification	1,788 (910 for 3rd Party)
Specially Controlled MDs (class III & IV)	Minister's Approval	748
		331

(MHLW Ministerial Notification No.298, July 20, 2004)

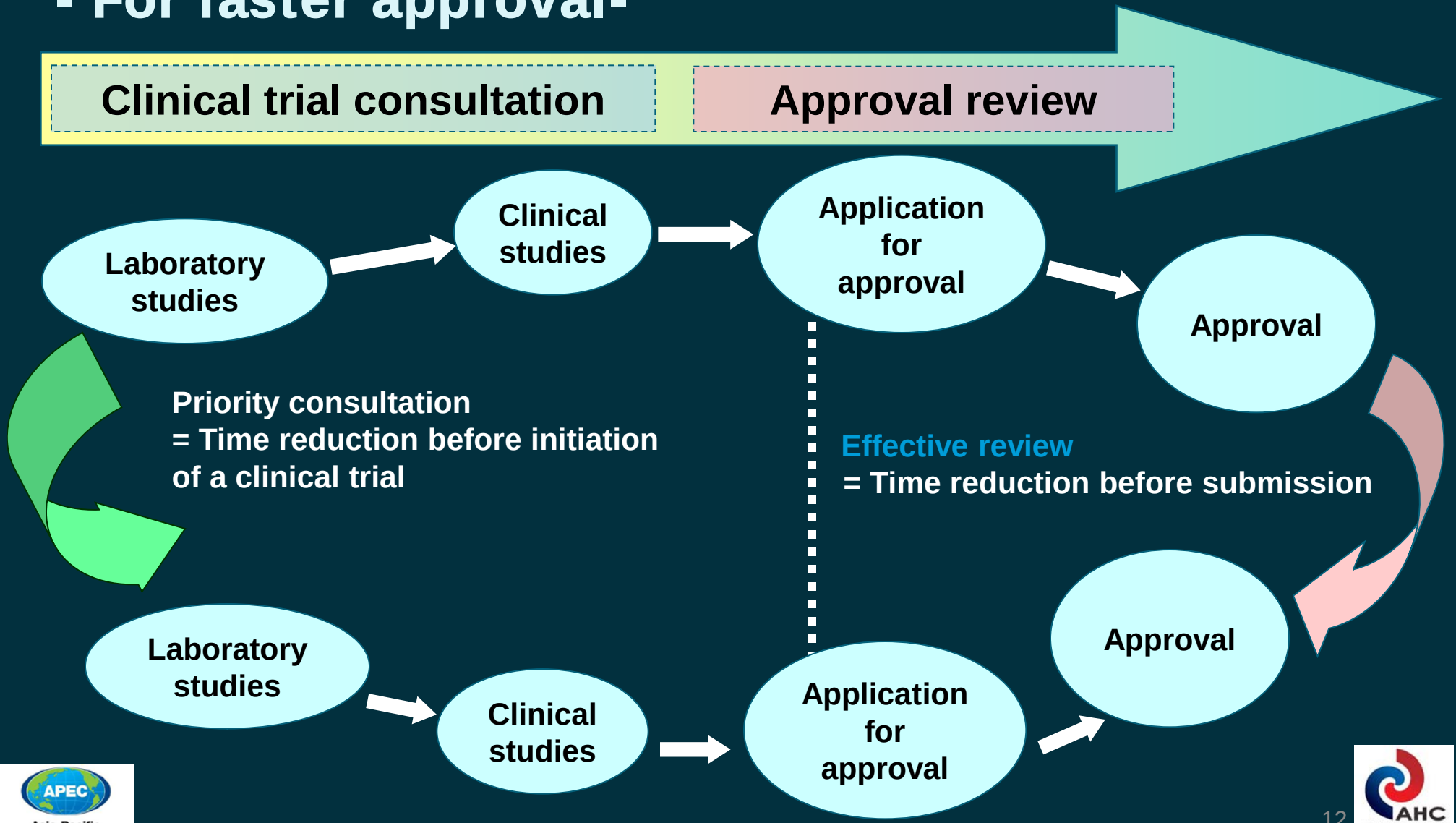
Third Party Notification Process



Medical Device Approval Process



Review System of PMDA
- For faster approval-



What is necessary to be thought when cooking?

- Taste?
- Main Ingredient
- Cuisine?
- Dietary?
- Cooking Type
- Seasonality?
- Special Occasions
- Holidays?
- Cooking Method

What is necessary to be thought when you make medical devices?

To provide a comprehensive list of **design and manufacturing requirements** of safety and performance, some of which are relevant to each medical device.

- Safety
- Performance/Effectiveness
- Quality

Essential Principles

- Six **general requirements** of safety and performance that apply to all medical devices

- A comprehensive list of **design and manufacturing** requirements
  - *Some of which* are relevant to each medical device

General Requirements

1. Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

General Requirements

2. The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed:

- identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse,
- eliminate risks as far as reasonably practicable through inherently safe design and manufacture,
- reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms,
- inform users of any residual risks.

General Requirements

3. Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction.

General Requirements

4. The characteristics and performances referred to in Clauses 5.1, 5.2 and 5.3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.

General Requirements

5. The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.

General Requirements

6. The benefits must be determined to outweigh any undesirable side effects for the performances intended.

These design and manufacturing requirements are grouped as:

- Chemical, physical and biological properties.
- Infection and microbial contamination.
- Manufacturing and environmental properties.
- Devices with a diagnostic or measuring function.
- Protection against radiation.
- Requirements for medical devices connected to or equipped with an energy source.
- Protection against mechanical risks.
- Protection against the risks posed to the patient by supplied energy or substances.
- Protection against the risks posed to the patient for devices for self-testing or selfadministration.
- Information supplied by the manufacturer.
- Performance evaluation including, where appropriate, clinical evaluation.

Application Dossier

Application Form
(Form22-3 of Ministerial Ordinance on PAL)

+

STED

+

Data set

Declaration of Conformity with EP

- GHTF-based STED is required.
- Essential Principles from GHTF was introduced in Japanese regulation (PAL Art.41(3)) and any device shall be in conformity with the EPs.

See
•Notification by DG-PFSB, *Yakusyoku-hatsu* #0216002, February 16, 2005
•Notification by Director, OMDE, *Yakusyokuki-hatsu* #0216001, February 16, 2005
•Notification by Director, OMDE, *Yakusyokuki-hatsu* #0216003, February 16, 2005
→ http://www.pmda.go.jp/operations/shonin/info/iryokiki/iryokiki-list.html (Japanese)

Set of Application Documents (Image)

- In case of High Risk exclude GMP conformity assessment -

Shonin Shinsei Syo

Shonin Documents

①Category
②Name
③Purpose of use, Efficacy/
④Shape, Structure or Principle
⑤Raw materials or components
⑥Specifications
⑦Operation for use/Procedure
⑧Manufacturing Process
⑨Storage or UBD
⑩Site for Manufacturing
⑪manufacturing site for Raw material
⑫Remarks: Package Insert etc

STED(Gaiyo)

- Device Overview
- Essential principle & Evidence of conformity
- Device description
- Summary of pre-clinical design verification and validation
- Labeling (Draft)
- Risk analysis
- Manufacturing info.

Attachments

A. Origin or history until discovery and regulatory status in foreign countries
B. Reason/background for specification
C. Stability & Endurance
D. Document for compatibility with Essential Principle
E. Performance
F. Risk Analysis
G. Manufacturing (Process, QC, Sterilization)
H. Clinical Data

- Request for reliability of GCP/GLP
- Request for compliance to GMP(ISO13485)

Essential Principles (EP) Checklist

The STED should contain an EP checklist that identifies:-

a. the Essential Principles;
b. whether each Essential Principle applies to the device and if not, why not;
c. the method(s) used to demonstrate conformity with each Essential Principle that applies;
d. a reference for the method(s) employed (e.g., standard), and
e. the precise identity of the controlled document(s) that offers evidence of conformity with each method used.

Essential Principles (EP) Checklist

Methods used to demonstrate conformity may include one or more of the following:

a. conformity with recognised or other standards;
b. conformity with a commonly accepted industry test method(s);
c. conformity with an in-house test method(s);
d. the evaluation of pre-clinical and clinical evidence.
e. comparison to a similar device already available on the market.

Essential Principles (EP) Checklist

The EP checklist should incorporate a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the STED (when such documentation is specifically required for inclusion in the Summary Technical Documentation as outlined in this guidance).

See GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices*

See GHTF/SG5 guidance documents

Summary Technical Documentation (STED)

- GHTF STED is mandatory using
- Using GHTF Essential Principles (EPs)
- Conformity assessment providing the Check List for EPs providing the Technical Standard (TS)
- TS required International Standard or well used guidance documents

(Those slides originally made by Hiroshi Ishikawa, JFMDA)

How the STED may differ by classification ?

PMDA

Third Party

Application Form 22-3
“ Shonin Shinsei Syo ”

Application Form 64-1
“ Ninshou Shinsei Syo ”

Binding

+

“ Tenpu-Shiryo “
- STED
- Data Sub Set

No need
If provided TS

Local Government

+

Third Party

Request for GMP Conformity Assessment 25-2
“ Tekigousei Cyousa “ 67-1

What is Technical Standard ?

- JIS: Translated International Standard or other recognized standard, whichever *used as internationally.*
  - Translated in Japanese
  - Such as IEC or ISO: IEC60601, ISO13485, 14971
- If there is no such standard, then alternatively using *Guidance Documents* which NCA issues or Industry Standard such as NEMA Standard etc.

Conformity Assessment Technical Standard

- 382 Standards have been established.
- So far 382 new application for MDs and 18 for IVDs are certified by Third Party.

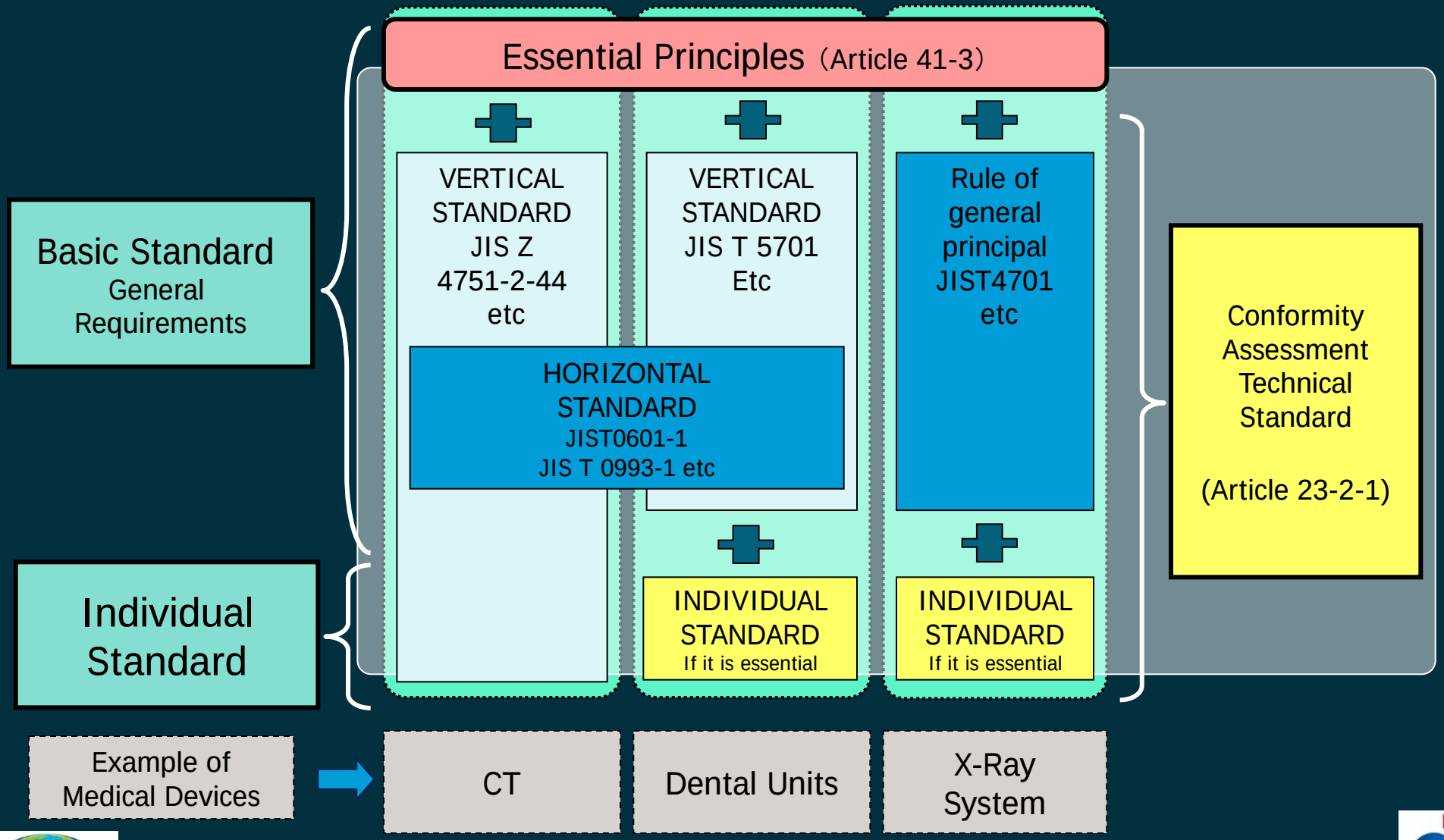
- Technical Standards for conformity assessment handled by Third Party

all of Class II JMDN	1785 items
# of existing MDs	783 items
# of TR for EP	382 items

→44% of Class II JMDN items are covered!

- # of TR for High risk 17 items

Examples for Third Party Certification Using Standards



Summary

- The evidence and procedures the manufacturer may use to demonstrate a medical device is safe and performs as intended.
- The elements that should apply to each class of device such that regulatory demands increase with classification.
- The process that the RA or CAB may confirm elements are correctly applied by the manufacturer.
- The manufacturers written declaration that it has correctly applied the elements relevant to the device.

Future Direction

- MHLW and PMDA will continue to work with industry to deliver innovative medical devices quickly to patients according to the Strategy.
- Good communication and collaboration are key to success!
- Thank you!