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 on PAL, 1961
  - Cabinet Ordinance on PAFSC, 2000

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

- **Ministerial Ordinance**
  - 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.
Authorities of MD regulation

- **PMDA**: Approval review
  - PMSM

- **MHLW**: Minister
  - Jurisdiction over PAL

- **Certification Bodies**
  - Certification
  - Approval

- **Regional Bureaus**
  - Local Governments
    - MAH’s License
    - Manufacturer’s License
  - Manufacturer
    - (Specified Biological Product etc.)

- **Product (Class II)**
- **Product (Class III, IV)**

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

10 min. walk
Shared Responsibilities

[MHLW]
Ultimate Responsibilities in policies & administrative measures
- Final judgment on approval
- Product withdrawal from market

[PMDA] “TECHNICAL ARM of MHLW”
Actual review, examination, data analysis, etc. to assist MHLW’S measures
- 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)
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
### Overview of Classification and Pre-market Regulation for Medical Devices

<table>
<thead>
<tr>
<th>GHTF Classification</th>
<th>PAL classification</th>
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<tbody>
<tr>
<td><strong>Class A</strong></td>
<td><strong>Category</strong> &lt;br&gt;extremely low risk &lt;br&gt;X-Ray film</td>
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<tr>
<td><strong>Class B</strong></td>
<td><strong>Pre-market regulation</strong> &lt;br&gt;Self declaration &lt;br&gt;Japanese MD Nomenclature</td>
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<tr>
<td><strong>Class C</strong></td>
<td><strong>General MDs (Class I)</strong></td>
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<tr>
<td><strong>Class D</strong></td>
<td><strong>Controlled MDs (class II)</strong> &lt;br&gt;Third party Certification &lt;br&gt;1,788 (910 for 3rd Party)</td>
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<tr>
<td></td>
<td><strong>Specially Controlled MDs (class III &amp; IV)</strong> &lt;br&gt;Minister’s Approval &lt;br&gt;748</td>
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<td><strong>Minister’s Approval</strong> &lt;br&gt;748</td>
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(MHLW Ministerial Notification No.298, July 20, 2004)
Third Party Notification Process

1. Conformity to Essential Principles
   - Performance Std.s
   - Risk Management
   - Labeling, Package Insert, etc

2. Conformity to Quality Assurance Stds
   - ISO13485

(1) Application
(2) Certification
(4) Follow-up Inspection
(3) Certified Product Report

Certifying Body

Evaluation

1. Conformity to Essential Principles
   - Performance Std.s
   - Risk Management
   - Labeling, Package Insert, etc

2. Conformity to Quality Assurance Stds

Applicant
(Marketing Authorization Holder)

MHLW

Objection

APEC Asia-Pacific Economic Cooperation
Medical Device Approval Process

申请人（Applicant）

- 申请 (Application)
- 审批 (Approval)

MHLW (卫生劳动福利省)

- 生产设施 (Manufacturing Facilities)
- 检查地点，文件 (Site, Document)

PMDA (产品门类监管厅)

- 审查 (Review)
  - 根据基本原理
  - STED (摘要)
  - 数据子集

- 可靠性审查 (Reliability Review)
  - 数据可靠性
  - GLP, GCP, GMP (Class IV) 符合性
  - 事后批准检查
Review System of PMDA
- For faster approval -

Clinical trial consultation → Approval review

Laboratory studies → Clinical studies → Application for approval → Approval

Priority consultation = Time reduction before initiation of a clinical trial

Effective review = Time reduction before submission of an application for approval
What is necessary to be thought when cooking?

- Taste
- Ingredient
- Cuisine?
- Calorie Type
- Specialty Collections
- Holidays & Occasions
- Cooking Method
What is necessary to be thought when you make medical devices?

- Safety
- Performance/Effectiveness
- Quality

To provide a comprehensive list of design and manufacturing requirements of safety and performance, some of which are relevant to each medical device.
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.
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 self-administration.
- Information supplied by the manufacturer.
- Performance evaluation including, where appropriate, clinical evaluation.
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**

1. Category
2. Name
3. Purpose of use, Efficacy/
4. Shape, Structure or Principle
5. Raw materials or components
6. Specifications
7. Operation for use/Procedure
8. Manufacturing Process
9. Storage or UBD
10. Site for Manufacturing
11. Manufacturing site for Raw materials
12. Remarks: 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.
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.
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, J FMDA)
How the STED may differ by classification?

**PMDA**

- Application Form 22-3
  "Shonin Shinsei Syo"

- "Tenpu-Shiryo"
  - STED
  - Data Sub Set

**Third Party**

- Application Form 64-1
  "Ninshou Shinsei Syo"

- No need if provided TS

**Local Government**

- 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 J MDN: 1785 items
- # of existing MDs: 783 items
- # of TR for EP: 382 items
  → 44% of Class II J MDN items are covered!

- # of TR for High risk: 17 items
Examples for Third Party Certification Using Standards

- **Essential Principles (Article 41-3)**
  - **Vertical Standard**
    - JIS Z 4751-2-44, etc.
  - **Vertical Standard**
    - JIS T 5701, Etc.
  - **Rule of general principal**
    - JIST4701, etc.

- **Basic Standard**
  - General Requirements
  - Example of Medical Devices

- **Individual Standard**
  - CT
  - Dental Units
  - X-Ray System

- **Conformity Assessment**
  - Technical Standard
    - (Article 23-2-1)
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!