Premarket Submission and Approval Requirements in Japan

Madoka Murakami
Office of International Programs
Pharmaceuticals and Medical Devices Agency
Introduction of PMDA

Pharmaceuticals and Medical Devices Agency (PMDA)

- an Incorporated Administrative Agency (IAA)

PMDA’s Safety Triangle

- Review: Reduction in risk
- Securing Safety and Efficacy
- Three-pillar System Unique to Japan
- Safety: Continuous risk mitigation efforts
- Japanese citizens
- Relief: Relief measures for health damage caused by risk factors
What’s PMDA?

MHLW (Ministry of Health and Labour, Welfare)

PMDA (Pharmaceuticals and Medical Device Agency)

Company

Incorporated administrative agency

Scientific review

Application

Regulatory Agency

Approval

report
Shared Responsibilities

[MHLW] (Ministry of Health, Labor and Welfare)

Ultimate Responsibilities in policies & administrative measures
ex.  • Final judgment on approval
• Product withdrawal from market

[PMDA]

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
# Overview of Medical Device Regulation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extremely low risk</td>
<td>Low risk</td>
<td>Medium risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Example</td>
<td>X-Ray film</td>
<td>MRI</td>
<td>Dialyzer, Artificial bone</td>
<td>Pacemaker, Artificial heart valve</td>
</tr>
<tr>
<td>Category</td>
<td>General MDs</td>
<td>Controlled MDs</td>
<td>Specially controlled MDs</td>
<td></td>
</tr>
<tr>
<td>Review regulation</td>
<td>Self-declaration</td>
<td>Third party certification</td>
<td>Minister’s approval (PMDA’s review)</td>
<td></td>
</tr>
<tr>
<td>Post-market safety vigilance/surveillance</td>
<td>PMDA and MHLW</td>
<td>Re-examination for Brand New MDs, Re-evaluation, AE reporting, Researches, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Medical Devices Regulation

<table>
<thead>
<tr>
<th></th>
<th>EU</th>
<th>Japan</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-market review</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notified body certification (requirements depend on device classification)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class III, IV: Minister’s approval</td>
<td>Class II: Notified body certification</td>
<td>Class III: PMA Approval</td>
</tr>
<tr>
<td></td>
<td>Class I: Self-declaration</td>
<td>Class II: 510(k) clearance,</td>
<td>Class I: exemption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Governmental approval/license**:
- **Notified body review/certification**
- **Self declaration/exemption**
Overview of review process

1. Application
2. Review
3. Inspection
4. Site Inspection
5. Approval
6. follow-up Inspection (Post-market)

PMDA
- Office of Medical Devices
  - Application documents

Applicant
- Experts

Manufacturing site
- Office of Conformity Audit
  - GLP and GCP Inspection
- Office of Manufacturing/ Quality and Compliance
  - QMS Inspection

MHLW
Medical Device Marketing Regulation in Japan

**Marketing Regulation**

**License for Manufacturing**
(Accreditation for Foreign Manufacturers)
- Standards of buildings and facilities
- Obligation of QMS regulation compliance

**License for Marketing**
- GQP (Good Quality System)
- GVP (Good Vigilance Practice)

**Marketing Approval**
- Review of quality, efficacy and safety
- Compliance with QMS regulation on each manufacturing site
Application document

- Submission Dossier
- STED (*Summary Technical Documentation, GHTF SG1N11)
- Supporting Data
- Reference Data

Identification of application items

Justifying data
Submission Dossier and Supporting Data

Submission Dossier

- Category
- Designation
- Purpose of use, indication
- Shape, structure and principles
- Raw materials or component parts
- Specification of the device
- Method of operation or usage
- Manufacturing method
- Storage and expiry date
- Manufacturers of items for production and distribution
- Manufacturer of raw materials
- Remarks

Supporting Data

- Efficacy
- Safety
- Quality

Identification of application items

Justifying data
Pre-market review

Risk < Benefit

Then,

On the Market

Essential Principles

Conformity Assessment

• Standards
• Device Specification
• Design Control
• Design verification and validation
• Clinical Evidence
• STED
• Declaration of conformity
# Approval/Certification Standards

<table>
<thead>
<tr>
<th>Class</th>
<th>Japanese Medical Device Nomenclature (JMDN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>1,195</td>
</tr>
<tr>
<td>Class II</td>
<td>1,800</td>
</tr>
<tr>
<td>Class III</td>
<td>756</td>
</tr>
<tr>
<td>Class IV</td>
<td>343</td>
</tr>
<tr>
<td>Total</td>
<td>4,094</td>
</tr>
</tbody>
</table>

Certification Standards: 827 (JMDN: 1369)

Approval Standards: 44 (JMDN: 90)

As of February 21, 2014
### Essential Principle Checklist for Approval/Certification Standards

<table>
<thead>
<tr>
<th>General Requirements</th>
<th>Applicable to the Device?</th>
<th>Method Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential Principle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>第1条 医療機の整備等のための要求に使用されるものでないものとされているもの（以下、整備等を意味）</td>
<td>適用</td>
<td>要件を含む自管者で示す。</td>
<td>JIS I 19971:「医療機器リスクマネジメントの医療機器への適用」</td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>第2条 医療機の整備等に係る製造販売等における製造者（以下、製造販売等を意味）</td>
<td>適用</td>
<td>要件を含む自管者で示す。</td>
<td>JIS I 19971:「医療機器リスクマネジメントの医療機器への適用」</td>
</tr>
</tbody>
</table>

- Clearly showing requirements for the products in individual standards
- JIS standards are referred but most JIS standards are basically harmonized with ISO, IEC etc standards
- Products which doesn’t meet standards can be reviewed via other review process
Acceptance of Foreign Clinical Data

- MHLW/PMDA have accepted foreign clinical data for years if it is good enough to evaluate a device’s clinical safety and efficacy on Japanese population under Japanese medical practice/environment.

Number of devices approved after review with clinical trial data

<table>
<thead>
<tr>
<th></th>
<th>FY2009</th>
<th>FY2010</th>
<th>FY2011</th>
<th>FY2012</th>
<th>FY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign clinical study results</td>
<td>32</td>
<td>29</td>
<td>38</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Domestic and foreign clinical study results</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Domestic clinical study results</td>
<td>14</td>
<td>19</td>
<td>14</td>
<td>23</td>
<td>24</td>
</tr>
</tbody>
</table>

*Source: PMDA annual report FY2013.*
Action Program for Acceleration of Medical Device Reviews (issued in Dec. 2008)

MHLW / PMDA will accelerate the Medical Device review processes and reduce total review time* for approval,

- on the premise of ensuring quality, efficacy, and safety of medical devices
- paying due consideration to minimize burdens to applicants
- under combined efforts by both the regulatory side and the applicants side
- by taking scientific and reasonable measures

(* Total elapsed time from submission to approval)
### Action program for Acceleration of Medical Device Reviews

<table>
<thead>
<tr>
<th></th>
<th>FY2009</th>
<th>FY2010</th>
<th>FY2011</th>
<th>FY2012</th>
<th>FY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve quality by increasing the number of staff and enhancing training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase staff 35 → 104 (FY2013)</td>
</tr>
<tr>
<td>Introduce 3-Track system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-track Review System</td>
</tr>
<tr>
<td>Clarify review criteria</td>
<td>Formulate Approval standards/ Good Review Guideline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Set review time goals                 | • New Medical Devices (Standard 14 mos. Priority 10 mos.)  
• Improved MD with clinical data: 10 mos.  
  w/o clinical data: 6 mos.  
• Generic MD 4 mos. (FY2013) |
| Full transition to Third-party Certificate of class II Medical Devices | Transit by FY2011 |
| Progress management                   | Government & Industry Dialogue 2/year (from FY2009) |
## Performance Goal of the Time Period of Review

With combined efforts by both regulatory & applicants, total review time should be reduced to the below goal:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New MD (Shin) Standard items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total time</td>
<td>~ 21</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>for agency</td>
<td>~ 8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>for applicant</td>
<td>~ 14</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Priority items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total time</td>
<td>~ 16</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>for agency</td>
<td>~ 9</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>for applicant</td>
<td>~ 9</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Improved MD (Kairyo) with clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total time</td>
<td>~ 16</td>
<td>16</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>for agency</td>
<td>~ 9</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>for applicant</td>
<td>~ 7</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>w/o clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total time</td>
<td>~ 11</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>for agency</td>
<td>~ 6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>for applicant</td>
<td>~ 5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Generic MD (Kohatsu) (with specific criteria)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total time</td>
<td>~ 8</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>for agency</td>
<td>~ 5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>for applicant</td>
<td>~ 3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Quantitative Increase and Background of Medical Device Reviewers

- Medical doctor and Dentist
- Veterinarian
- Biochemist and agronomist
- Pharmacist
- Engineer
- Other

AP started
### 90% Tile Review Times for Medical Devices

(Total time in submission cohort)

<table>
<thead>
<tr>
<th>Category</th>
<th>FY</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td></td>
<td>100%</td>
<td>92.0%</td>
<td>95.2%</td>
<td>96.3%</td>
<td>46.9%</td>
</tr>
<tr>
<td>Improved (w clinical data)</td>
<td></td>
<td>100%</td>
<td>96.1%</td>
<td>96.0%</td>
<td>100%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Improved (w/o clinical data)</td>
<td></td>
<td>100%</td>
<td>95.7%</td>
<td>94.2%</td>
<td>88.9%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Generic</td>
<td></td>
<td>98.4%</td>
<td>96.2%</td>
<td>97.2%</td>
<td>95.6%</td>
<td>63.9%</td>
</tr>
</tbody>
</table>
PMDA’s Consultation Menu

Very early stage

Market and Literature Surveys

Pre-development consultation

Non-Clinical

Safety Confirmation Consultation

Stability Test

Biological Safety Test

Electrical Safety Test

Performance Test

CT required?

Consultation on Clinical Evaluation

Consultation on Performance Test

Exploratory Clinical Trial Consultation

Clinical Test for Verification

CT

Clinical Trial Consultation

Application Procedural Consultation

Pre-application Consultation

Development of Application Dossier

Pharmaceutical Affairs Consultation on R&D Strategy

Prior Assessment Consultation
Number of consultations for Medical Devices

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>110</td>
</tr>
<tr>
<td>2010</td>
<td>112</td>
</tr>
<tr>
<td>2011</td>
<td>141</td>
</tr>
<tr>
<td>2012</td>
<td>173</td>
</tr>
<tr>
<td>2013</td>
<td>169</td>
</tr>
</tbody>
</table>
Collaboration Plan for Acceleration of Medical Device Review (FY2014～FY2018)
(issued on Mar. 31, 2014)

Quality concerns in the review process of medical devices need to be improved by both administration and applicants, and both parties should work together towards the following measures to further shorten the period required for approval of medical devices and to promote standardization.

1. **Initiatives for quality enhancement during review process**
2. **Establishment of regular review periods**
3. **Progress management, etc.**
New Performance Goal towards FY2018*

(Total Time)

• New Medical Device
  ➢ Standard items: 12 months
  ➢ Priority items: 9 months

• Improved Medical Device
  ➢ With clinical data: 9 months
  ➢ Without clinical data: 7 months

• Generic Medical Device
  ➢ New application: 5 months
  ➢ Partial change application: 4 months

* In order to set higher target, 80 percentile figures are adopted instead of median

産 Industry

学 Academia

国民 The People

官 Regulatory Authorities
International Medical Device Regulators Forum

Established in October 2011

Management Committee member

Founding member of GHTF

Brazil, China, Russia

World Health Organization

APEC – Asia-Pacific Economic Cooperation

Life Science Innovation Forum

Asian Harmonization Working Party

Pan American Health Organization
2nd PMDA MD training seminar (regulators only)

• Date: February 2 – 6, 2015
• Venue: PMDA (Tokyo, JAPAN)
• Fee: Free
• Topics
  ✓ Pre-market review
  ✓ QMS
  ✓ Clinical trials
  ✓ Case study
  ✓ Post-market surveillance system
  ✓ Facility Tour
Make it GLOBAL
(Win-Win Relationship)
Any questions?

Contact Information
URL: http://www.pmda.go.jp/english/contact/index.html
Thank you!!

http://www.pmda.go.jp/english/