Overview of Our Review Practices

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Pharmaceuticals and Medical Devices Agency, Japan

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On Medical Products-Nov. 8, Chinese Taipei
Outline of My Presentation

☑ Functions and Roles of PMDA
☑ Overview of PMDA review process
  overview of orthopedics review
  case introduction
  changing procedures
☑ Action program
Functions and Roles of PMDA

R&D → Non-clinical Study → Clinical Study → Application → Market

- GLP
- GCP
- GMP/QMS/GQP
- GPSP/GVP

Consultation → Approval Review → Post-Marketing Safety → Relief Funds

PMDA:
- Review Report → Approval

MHLW
New Organization To Strengthen MD Review System

Chief Executive

Special Assistant

Executive Director (Review・Research)

Senior Executive Director (Tech. Mng.)

Safety Dept.

Executive Director (Gen. Coordination)

Office of Review Innovation

Director, Center for Product Evaluation

Deputy Center Director for Medical Devices

Deputy Center Director for Cellular- and Tissue-based Products

Relief Dept.

Adm. Dept.

Science Board

Review Department

(as of June 2012)
New Organization To Strengthen MD Review System

Director, Center for Product Evaluation
Dept. Center Directors

Office of Medical Devices  I  II  III

Office of Review Management

Office of International Programs

Sec. of Pharmaceutical Affairs Consultation on R&D Strategy

International Coordination Officer for MDs

Office of Standards and Guidelines Development
### Review Teams of MDs

<table>
<thead>
<tr>
<th>Team 1</th>
<th>Field of ophthalmology, otorhinolaryngology</th>
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<tbody>
<tr>
<td>Team 2</td>
<td>Field of dentistry</td>
</tr>
<tr>
<td>Team 3</td>
<td>Field of neurosurgery, cardiology, vascular surgery, respiratory</td>
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<tr>
<td>Team 4</td>
<td>Field of neurosurgery, cardiology, vascular surgery, respiratory (electronic devices)</td>
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<tr>
<td>Team 5</td>
<td>Field of gastroenterology, urology, gynecology</td>
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<td><strong>Team 6</strong></td>
<td><strong>Field of orthopedics, plastic surgery, dermatology</strong></td>
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<tr>
<td>Team 7</td>
<td>In vitro diagnostic medical devices</td>
</tr>
<tr>
<td>Team 8</td>
<td>Others</td>
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</table>
Outline of My Presentation

✓ Functions and Roles of PMDA
✓ Overview of PMDA review process
  overview of orthopedics review
  case introduction
  changing procedures
✓ Action program
### Overview of Pre-Market Regulation for MDs

<table>
<thead>
<tr>
<th>GHTF Classification</th>
<th>PAL classification</th>
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<tr>
<td>Class A</td>
<td>General MDs (Class I)</td>
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<tr>
<td>extremely low risk</td>
<td>Low risk MRI, digestive catheters</td>
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<tr>
<td>X-Ray film</td>
<td>medium risk artificial bones, dialyzer</td>
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<tr>
<td>Class B</td>
<td>high risk pacemaker, artificial heart valves</td>
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<td>Class C</td>
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<td>Class D</td>
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Prior Assessment Consultation

PMDA evaluates the data set prior to an application
Application Dossier

- Brand-new MDs
  - Application Form
  - Summary of the technical documents (STED)
  - Attachment
    - Evaluation reports
    - Declaration of conformity
    - etc.

- Improved MDs, Generic MDs
  - Application Form
  - Attachment (STED with data set)
Application Form

✓ Identities of the product

“approved product information”

- 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
<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
<td>Outline of the device</td>
</tr>
<tr>
<td>2.</td>
<td>Basic requirements, and compatibility with the basic requirements</td>
</tr>
<tr>
<td>3.</td>
<td>Information on the device</td>
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<td>4.</td>
<td>Summaries of design verification and documents confirming validity</td>
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<td>5.</td>
<td>Labeling</td>
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<td>6.</td>
<td>Risk analysis</td>
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<tr>
<td>7.</td>
<td>Information on manufacturing</td>
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</table>
General Review Points

the purpose of development

Clinical positioning

Non-clinical test

Clinical trial

Appropriate evaluation based on its concept

- Novel materials
  - Efficacy
  - Safety

- Device performance
  - Efficacy
  - Safety

Alternative? Unmet need?
Similar products or innovative?

- Purpose
- Study population
- Control
- Endpoint
- Safety
- Duration

Appropriate study design & evaluation based on its clinical positioning
Overview of review process

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

Applicant

Office of Medical Devices
Application documents

PMDA

Office of Conformity Audit
GLP and GCP Inspection

Office of Compliance and Standards
QMS Inspection

Experts

Manufacturing site

MHLW
SOPs and Templates

- We have developed several standard operating procedures (SOPs) on review process.
- SOPs provide annotated report templates indicating how they should be completed, as well as blank templates.
Review SOP Examples

✓ About the whole process of review
✓ About consultation on clinical evaluation
✓ About review of brand-new devices, improved devices and generic devices
✓ About management of original application dossiers
✓ About review progress meeting
✓ Etc.
Review Points of Orthopedics MDs

✓ Substantial equivalence of shape and construction to the predicted devices

✓ Specification of devices used together

✓ Evaluation of the efficacy and safety of the whole system
Review of Hip Joints

There is a review guideline for hip joints:

- Specification of the indication for use
- A range of materials those have been used
- Requirements of the products: physical and chemical properties, biological safety, mechanical performance,
- Stability
- Validation of sterilization, etc
Review of Hip Joints

mechanical performance

e.g. Strength
-ISO7206-4 for stems
-ISO7206-8 for necks

cement or non-cement, surface coatings, etc
Review of Bone Graft Materials

- Specification of the materials and evaluation of their biological safety
- Specification Final composition
- Pore size, pore percentage, morphology
- Compression strength, bending strength
- In vivo study (animal experimentation) to show decomposition characteristics and bone growth
Examples of Our Questions

✓ About substantial equivalence to predicted devices
✓ About design concepts
✓ About sales performance and safety hazards in other countries and areas
✓ About biological safety
✓ About mechanical performance
Case introduction-The X STOP ®

- relieve symptoms of lumbar spinal stenosis, a narrowing of the passages for the spinal cord and nerves
- a titanium implant that fits between the spinous processes of the lower (lumbar) spine
- made from titanium alloy and consists of two components: a spacer assembly and a wing assembly.

Indications for use:
patients aged 50 or older suffering from pain or cramping in the legs secondary to a confirmed diagnosis of lumbar spinal stenosis.

(Refer to FDA website)
Case introduction - The X STOP ®

Nonclinical evaluation
✓ the change of the construction of the spacer

Before
a single layer with titanium alloy

After
Two layers with a titanium alloy inner hub and a PEEK outer shell.

(Refer to PMDA website)
Case introduction - The X STOP ®

clinical evaluation

✓ the validity of using the clinical data of the products before changing

✓ the benefit and risk of X-STOP among the current treatment options for lumbar spinal stenosis

✓ Conduct a post-approval study to determine whether patient selection criteria are adequate and whether the clinical study results are generalizable to Japanese patient population

(Refer to PMDA website)
Clinical Study Data Carried Out in Foreign Countries

✓ Clinical data acceptable
  – Corresponding country or region has its official legal regulation for performing clinical investigation of medical devices, and
    ① Such regulation is considered to be equivalent to or exceed the Japanese GCP regulation, and the data were obtained according to such regulation, or
    ② The data of investigation considered to be equivalent to the above.
Changing Procedures

• MHLW/PMDA has the responsibility for “approved product information”

• PMDA has the responsibility to review changes of devices related to the quality, efficacy and safety

If approved products change, procedure is required
Changing Procedures

There are three procedures for changing
✓ Partial changes are not required
✓ Minor change notification
✓ Partial change approval application

“Procedures Associated with Partial Change for Medical Devices”
MHLW Notification by Director, OMDE, Yakushokuki-hatsu
No.1023001 dated October 23, 2008 (Japanese)
Changing Procedures

Partial changes are not required

Changes that are not related to the efficacy and the safety, and the equality is maintained

e.g.

☑ Change of indicator from light bulb to LED
☑ Change of length/shape of pumping/suction tube exceed the scope of the access site
Changing Procedures

Minor change notification

Changes except for following:

- Change of manufacturing method related to essence, characteristics, performance and safety
- Deletion/change of properties and specifications
- Change related to quality, efficacy and safety

E.g.

Changes of shape and size within the approved range without change of purpose, affected area, method of operation and specification.
Changing Procedures

Partial change approval application

Changes except for minor change notification/no action required

e.g.

✓ The intended use
✓ Materials of implantable devices
✓ Principle composition adding
A Common Case

Change of materials - Silicon

- **Silicon A**
  - Made by A company
  - Product #1212

- **Silicon A’**
  - Made by A company
  - Product #1312

- **Silicon B**
  - Made by B company
  - Product #B102

If the applicant could not show substantial equivalence between Silicon A to Silicon A’ or Silicon B, a partial change approval application is necessary although they seem familiar commonly.
A Common Case

Change of Materials

- ultra high molecular weight-polyethylene (UHMWPE)

UHMWPE A
Made by A company
Product #1212
ASTM F648

UHMWPE A’
Made by A company
Product #1312
ASTM F648

UHMWPE B
Made by B company
Product #B102
ASTM F648

A partial change approval application is not necessary because all of them conform the same industry standard ASTM F648 which guarantees their substantial equivalence.
Outline of My Presentation

- Functions and Roles of PMDA
- Overview of PMDA review process
  - overview of orthopedics review
  - case introduction
  - changing procedures
- Action program
Action Program for Acceleration of MDs Reviews
(issued in Dec. 2008)

accelerate the Medical Device review processes and
reduce total review time* to 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)
# Performance Goal & Annual Milestone of Action Program

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<tr>
<th>Action</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tbody>
<tr>
<td>Improve quality by increasing the number of staff and enhancing training</td>
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<td></td>
<td></td>
<td>Increase reviewers from 35 to 104 by 2013</td>
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<tr>
<td>Introduce 3-Track system</td>
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<td>Prepare the operation</td>
<td>3-track Review System</td>
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<tr>
<td>Clarify review criteria</td>
<td>Formulate Approval standards/Good Review Guideline</td>
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<tr>
<td>Set review time goals</td>
<td>Brand-New MD : Standard <strong>14 mos.</strong> Priority <strong>10 mos.</strong></td>
<td></td>
<td>Improved MD : w/ clinical data 10 mos. w/o clinical data 6 mos.</td>
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<td></td>
<td>Improved MD : w/ clinical data 10 mos. w/o clinical data 6 mos.</td>
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<tr>
<td></td>
<td>Generic(Me-too) MD 4 mos.</td>
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<tr>
<td>Full transition to Third-party Certificate of Class II MDs</td>
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<td>Transit by FY2011</td>
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</table>
PMDA Staff Size

- Administrative part
- Safety Department
- Review Department
- Planned
Background of MDs Reviewers

90 reviewers
### Performance Goal of the Time Period

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

<table>
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<td><strong>Improved MD (Kairyo)</strong></td>
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# Performance Goal and Results of FY2011

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<tr>
<th>Item Description</th>
<th>FY2011</th>
<th>Performance Goal</th>
<th>Results</th>
<th># of Approval</th>
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<tbody>
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<td>review time (median, unit: months)</td>
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<td><strong>Brand-new MD</strong> <em>(Shin)</em></td>
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<td>Standard items</td>
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Thank you!!

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