Japanese National GLP Monitoring Programme on Medical Products

The Monitoring System of PMDA

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<th>Ministry</th>
<th>Monitoring Authority/Related Organization</th>
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<tr>
<td>1 Pharmaceuticals and Medical Devices</td>
<td>MHLW</td>
<td>Pharmaceuticals and Medical Devices Agency (PMDA)</td>
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<td>2 Workplace Chemicals</td>
<td>MHLW</td>
<td>National Institute of Occupational Safety and Health (JNIOSH)</td>
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<tr>
<td>3 Pesticides</td>
<td>MAFF</td>
<td>Food and Agricultural Materials Inspection Centre (FAMIC)</td>
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<td>4 Veterinary Drugs</td>
<td>MAFF</td>
<td>National Veterinary Assay Laboratory (NVAL)</td>
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<td>5 Feed Additives</td>
<td>MAFF</td>
<td>Food and Agricultural Materials Inspection Centre (FAMIC)</td>
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<td>6 Industrial Chemicals</td>
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<td></td>
</tr>
<tr>
<td>1) Toxicity</td>
<td>MHLW</td>
<td>National Institute of Health Sciences (NIHS)</td>
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<tr>
<td>2) Bioacc./Biodegr.</td>
<td>METI</td>
<td>National Institute of Technology and Evaluation (NITE)</td>
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<tr>
<td>3) Ecotoxicity</td>
<td>ME</td>
<td>National Institute for Environmental Studies (NIES)</td>
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</table>
Relationship

Between Ministry and its related Organization

- Inspection is conducted by ministry with support of organization
  → Workplace chemicals, Industrial chemicals

- Authority of inspection is delegated from ministry to organization
  → Drugs/Medical devices, Pesticides/Vet med/Feed add
Relationship among Ministries (Ministry of Health, Labor and Welfare [MHLW], Ministry of Environment [ME], Ministry of Economy, Trade and Industry [METI], Ministry of Agriculture, Forestry and Fisheries [MAFF])

- Inter-Ministerial GLP Meeting
  (including related Monitoring Authorities/Related Organizations)
Organization of PMDA
Pharmaceuticals and Medical Devices Agency (PMDA)

- Incorporated administrative agency
- Established in 2004
- 648 staff members (April 2011)
- Targets on Pharmaceuticals and Medical Devices
- From development to post-marketing use
- Three key areas: Relief, Review and Safety

Ref: http://www.pmda.go.jp/english/index.html
Our Mission

To Ensure Faster Access to More Effective and Safer Drugs/ Devices for the Public

Improving Public Health
Work Flow of Drug / Device Development

R & D → Non-Clinical Study → Clinical Trial → Application → Post-marketing

- GLP Inspection
- R&D Promotion
- National Institute of Biomedical Innovation (Established in April 2005)
- Health Policy Bureau MHLW
- Pharmaceuticals and Medical Devices Agency (Established in April 2004)
- GCP Inspection
- GMP/QMS Inspection
- GPSP/GVP Inspection
- Clinical Trial Consultation
- Review
- Post-marketing Safety Operations
- Ministry of Health Labour and Welfare (Pharmaceutical and Food Safety Bureau)
- Pharmaceutical Affairs and Food Sanitation Council (PAFSC)
- Review Report Approval
- Relief
Three Major Work Areas of PMDA

**Review and Audit of Efficacy and Safety of Drugs/ Medical Devices**
- Clinical Trial Consultation
- Review of Efficacy and Safety
- Conformity Inspections for Application Materials of GLP, GCP and GMP
- Collection of Safety Information (Database)
- Scientific Review and Research of Safety Information
- Information Provision (via the Internet), Pharmaceutical Consultation for Consumers

**Post-marketing Safety Operations for Drugs/ Medical Devices**
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients

**Relief Services for Adverse Health Effects**
- Relief Service for SMON, HIV-positive and AIDS patients
GLP team
Inspections

GCP team
Inspections

Document Based Conformity Inspection team
Inspections of submitted application dossiers

Office of Conformity Audit

GPSP team
Inspections

Review Departments

Information sharing

Work sharing
Office of Conformity Audit

Office Director

- GCP Inspectors
- GPSP Inspectors
- GLP Inspectors
- Document Based Conformity Inspectors
GLP Inspectors

Number of inspectors: 6 (including two part-time inspectors)

Status: PMDA employees

Education: Veterinary/Pharmaceutical Science
PMDA GLP Monitoring Programme

Legal Bases
The data pursuant to the provisions of the last part of Article 14, Paragraph 3 of the Law shall be collected and complied as specified in the Ordinance on Implementation Standards for Non-Clinical Studies on Safety of Drugs (MHW Ordinance No.21, 1997), ......., the Ordinance on Implementation Standards for Non-Clinical Studies on Safety of Medical Devices (MHLW Ordinance No.37, 2005) .......
GLP Standards for Medical Products

[Pharmaceuticals]
- GLP standard ordinance for non-clinical laboratory studies on safety of drugs  [Ordinance, Ministry of Health and Welfare (Ordinance No.21, 1997, Revision: Ordinance No. 114, 2008)]

[Medical devices]
- GLP standard ordinance for non-clinical laboratory studies on safety of medical devices  [Ordinance, Ministry of Health, Labor and Welfare (Ordinance No.37, 2005 Revision: Ordinance No. 115, 2008)]
Contents of GLP standards (1)

Chapter 1: General Provision

  Article 1: Aim
  Article 2: Definition
  Article 3: Conduct of study
  Article 4: Responsibilities of sponsor

Chapter 2: Personnel and Organization

  Article 5: Personnel
  Article 6: Management
  Article 7: Study director
  Article 8: Quality Assurance Unit
Contents of GLP standards (2)

Chapter 3: Testing facilities and equipment
   Article 9: Testing facilities
   Article 10: Equipment

Chapter 4: Operating at testing facilities
   Article 11: Standard Operating Procedures
   Article 12: Animal care

Chapter 5: Handling of test article
   Article 13: Handling of test and control articles
   Article 14: Reagents and solutions
Contents of GLP standards (3)

Chapter 6: Protocol and conduct of study

Article 15: Protocol
Article 16: Conduct of study

Chapter 7: Report and storing

Article 17: Final report
Article 18: Storage of study related materials

Chapter 8: Conducting multi-site study

Article 19: Obedience items
Guidelines for GLP Inspection for Medical Products

Establishment of Guidelines for On-Site Pharmaceutical GLP or Medical Devices GLP Inspections (Notification from PMDA No. 0620058, No. 0620059 dated June 20, 2008, Revision: Notification No. 0815008 dated August 15, 2008)

Annex 1: Routine inspection (Facility based inspection)

Annex 2: For case inspection (Product based inspection)

- The mechanism whereby test facility enter the program
- The test facility inspection and study audit procedures
- Inspection report
- Others
Test Types covered (Pharmaceuticals) (stipulated by Notification)

- Single dose toxicity study
- Repeated dose toxicity study (sub-acute toxicity)
- Repeated dose toxicity study (chronic toxicity)
- Mutagenicity study
- Carcinogenicity study
- Reproductive & developmental toxicity study
- Local irritation study
- Dependence study
- Antigenicity study
- Skin (light) sensitization study
- Immunotoxicity study
- Safety pharmacology core battery test
- Partially entrusted study
Test Types covered (Medical Devices) (stipulated by Notification)

Cytotoxicity study
Sensitization study
Irritation/intracutaneous reactivity study
Acute systemic toxicity study
Subacute toxicity study
Mutagenicity study
Pyrogen study
Implantation study
Blood compatibility study
Chronic toxicity study
Carcinogenicity study
Reproductive & developmental toxicity study
Biodegradation study
Immunotoxicity study
Partially entrusted study
GLP Inspections
Conducted by PMDA
Conducting Facility based Inspections

- Generally once/three years/test facility
- An Inspection team consists of two-four inspectors
- Both laboratory inspection and study audit are included
- Generally five days for an inspection
  - Opening Meeting
  - Laboratory inspection
  - Study Audit (3-6 studies conducted in the latest three years)
  - Closing Meeting
Reporting Inspection Results

Inspectors’ findings
Agreed by both the inspection team and the test facility at the closing meeting

Inspection Report

The GLP Evaluating Committee
(Consisted of External Experts)

Inspection result Notification to the test facility
(by PMDA Chief Executive)
Number of test facilities inspected

Approximately 30 facilities per year

<table>
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<tr>
<th>Fiscal year</th>
<th>2002</th>
<th>2003</th>
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<td>8</td>
<td>4</td>
<td>11</td>
<td>6</td>
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Domestic Inspections
International Harmonization
Relationship between Japan and Other Countries

- **OECD (34 Countries)**
  - MRA with EC, MOU with Switzerland and USA*

- **Non-members**
  - South Africa, Singapore, India, Brazil, Argentina

- **Malaysia, Thailand (Provisional)**

*M Only pesticides program
Thank you for your attention!