Current GMP Inspection of PMDA

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Office of Compliance and Standards Pharmaceuticals and Medical Devices Agency (PMDA), JAPAN
GMP Inspection related Organizations in Japan
Organizations

Ministry of Health Labour and Welfare (MHLW)

Prefectural Governments (47 Prefectures)

Pharmaceuticals and Medical Devices Agency (PMDA)
### Inspectors ~ Number ~

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHLW</td>
<td>57</td>
<td>P.I.</td>
</tr>
<tr>
<td>Pref. Gov. (47)</td>
<td>2,723</td>
<td>P.I.</td>
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<td>Designated Cities(60)/Wards(23)</td>
<td>926</td>
<td>P.I.</td>
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<tr>
<td>PMDA (1.Apr.2008)</td>
<td>37</td>
<td>GMP/QMS ( dedicated )</td>
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</tbody>
</table>

**Pharmaceutical Inspection (P.I.):**
Not only GMP Inspection but also Inspection to Supervise or to Guide Poor Quality and/or incorrectly labeled (Advertised) Drugs (illegal drugs, counterfeit drugs, etc.)
<table>
<thead>
<tr>
<th></th>
<th>Domestic Site</th>
<th>Foreign Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Drugs, Biological Products, Radio Pharmaceuticals</td>
<td>PMDA</td>
<td>PMDA</td>
</tr>
<tr>
<td>Other Drugs (General Drugs)</td>
<td>Pref. Gov.</td>
<td>PMDA</td>
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</tbody>
</table>
• Full Name: **Incorporated Administrative Agency – Pharmaceuticals and Medical Devices Agency**
• Abbreviation: **PMDA**
• Establishment: **April 1, 2004**
• Legal classification: **Incorporated administrative agency with non-civil servant status**
Our Mission

To ensure faster accessibility to better and safer drugs/devices for the public

Improving Public Health
Office of Compliance and Standards

Director of Planning and Management Division
Administration and coordination

Director for GMP Inspection
GMP Inspection of drugs

Director for QMS Inspection
QMS Inspection of medical devices and In-vitro diagnostics

Director of Standards Division
Japanese Pharmacopeia and other standards of drugs and medical devices
Japanese GMP legislations
## Enforcement of New Regulations

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003.4</th>
<th>2004.4</th>
<th>2005.4</th>
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<tbody>
<tr>
<td><strong>PAL revision</strong></td>
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<tr>
<td>New Approval System</td>
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<tr>
<td>New Biologics regulation</td>
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<tr>
<td>Other</td>
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<tr>
<td><strong>PMDA establishment</strong></td>
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<tr>
<td><strong>New GMP Standards</strong></td>
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</table>

- ●: Publication
- ➤: Enforcement

### Notes:
- PAL revision and PMDA establishment are key initiatives that mark the implementation of new regulations.
- New GMP Standards are incrementally enforced, starting from 2002.
- Enforcement takes place over the subsequent years, with a notable increase in 2004.
Approval System

Product Approval

Marketing Approval Application

Review & Inspection

Marketing Approval

Release

License for Stakeholder

Drug Marketing License Holder (Product Distributor)

Requirements
- Quality, Efficacy & Safety of Products
- Licensed Stakeholder
- GMP-Compliant Manufacturing Sites

Licensed or Accredited Manufacturer

Requirements
- Human Resources
- GQP/GVP-Compliant

Requirements
- Human Resources
- Building & Facility
Requirement of license for manufacture or accreditation of foreign manufacturers

• Regulation for Buildings and Facilities of Pharmacies, etc
Requirement of product approval

Ministerial Ordinance on Standard for Manufacturing control and Quality Control for Drugs and Quasi-drugs (GMP)
Cherry Blossom at Mishima Shrine
GMP Inspections by PMDA
Types of GMP Inspection

• Compliance Inspection
  – Pre-approval Inspection
  – Inspection conducted at the times of marketing approval renewal
• Inspection for license of minister permitted manufacturers
• Inspection for accreditation of foreign manufacturers
  (For cause inspection, Regular inspection)
• On-site Inspections etc. (article 69-2)
• Cancellation etc. of Accreditation of Foreign Manufacturers (article 75-4)
Subjects of GMP Inspection by PMDA

○ Domestic manufacturing sites which are manufacturing following products;
  – New drugs
  – Biological Products
  – Products derived from human blood and human plasma
  – Vaccines
  – Products derived from cell-tissue etc.
  – Radiopharmaceuticals
  – Biotechnology-applied products

○ Foreign manufacturing sites
Two types of GMP Inspection

- On site Inspection
- Document Inspection

Basically we conduct on site inspection, but select by risk based approach of some reasons for human resources
Risk based approach of the decision

Risk evaluation
- Product
- Process
- Dosage form
- Inspection by foreign authorities
- Past nonconformity
- Past recall
- No history of inspection by PMDA
- Facility information etc

Data base

Document Inspection

On site Inspection

Overall assessment by evaluation of 6 systems*
6 systems: Quality system, Facilities and equipment system, Materials system, Production system, Packaging and labeling system, Laboratory control system
Inspection schedule (standard)

**Day 1: Morning**
1. Opening meeting
2. Company and site overview (presentation by manufacturer)
3. Plant tour (1)
   - Warehouse

**Day 1: Afternoon**
- Manufacturing area, packaging area, in-process laboratory
- Support system
  - Water system
  - Air handling system
  - Waste treatment system
4. Plant tour (2)
   - QC laboratory
     - sample receiving area
     - testing area
     - biological tests
     - stability test area
     - retain sample area
Day 2: Morning

5. Document check (1)
   (1) Quality system
     • GMP organization, job description of key personnel
     • Document control
     • Standard cords, SOPs
       Manufacturing control
       Quality control
       Manufacturing hygiene control
       Product master file

Day 2: Afternoon

• Handling of Information on Quality, etc.
• Recall
• Deviation control
• Change control
• Training
• Release procedure
• Self inspection
• Control of contract manufacture, supplier control
• Written agreement with the Japanese marketing authorization holder
**Day 3: Morning**

6. **Document check (2)**
   (2) Buildings and facilities
      - Daily check of buildings, equipment and utilities
      - Preventative maintenance

(3) Control of raw materials, packaging materials
   - Material receipt, quarantine
   - Sampling procedure, storage of released material, use for manufacture
   - Compliance to the Japanese standard for the raw materials of animal origin

**Day 3: Afternoon**

(4) Manufacture
   - Product standard code (Master formula) manufacturing instruction, batch record
   - Validation
   - Reprocess, rework

(5) Packaging and labeling

(6) Test and inspection

7. Summary by inspectors
8. Closing meeting
   - Comments by inspectors
   - Discussion
Follow up of the inspection

Written observation items (in Japanese) will be sent to the manufacturer (usually via marketing authorization holder) around 3 weeks after completion of inspection.

Written response (in Japanese) is required within 3 weeks.
We request following points to prepare written responses to the observation items.

1. Submit photographs or drawings if it is easy to demonstrate the corrective action.
2. Submit summary report if some tests or validation work are carried out.
3. If SOPs are revised, submit a copy of the revised part.
4. If completion of the corrective action is anticipated to take a time, submit a schedule of the action specifying the actions to be taken and expected time of report.
Requests for document inspection

1. Outline of the manufacturing site
2. Site map, floor plan of the area involved in the manufacture and control of the product.
   (1) floor plan showing materials and personnel flow
   (2) floor plan showing level of environmental control in each area (room)
   (3) floor plan showing pressure difference
Requests for document inspection (cont.)

3. GMP organization chart and the document describing the quality assurance system
4. GMP document system
5. Manufacturing flow chart and detailed description of the actual manufacturing process of the product in the site
6. In-process controls and their limits for the product
   (The documents related to the items 5 and 6 are master batch instruction, master batch record or manufacturing SOPs actually used in the site)
Requests for document inspection (cont.)

7. Documents for specifications and test methods for in-process material and finished product

8. Documents for specifications and test methods applied for the actual acceptance test of the raw materials described in the column of components and composition in the new drug application

(The documents related to the above items 7 and 8 are copies of product master file, master test and inspection record, or test and inspection procedure of the relevant raw materials actually used in the site)
Requests for document inspection (cont.)

9. Report of process validation (report of full scale production batches)
10. Report of cleaning validation
11. Manufacturing history (batch number, date of manufacture and batch size) or intended annual manufacturing schedule
12. Copy of deviation control procedure and summary of actual deviation events (for past two years)
13. Copy of change control procedure and summary of actual changes occurred in the past two years
14. Copy of release procedure
15. Document (s) describing the status for compliance to the Standards for Biologically derived raw materials
16. (Site Master File)

Total number of applications: 2144, Number of domestic applications: 657
## On site inspections for foreign facility

### Areas

<table>
<thead>
<tr>
<th>Area</th>
<th>EU</th>
<th>North America</th>
<th>Central and South America</th>
<th>Asia</th>
<th>Other</th>
<th>Total</th>
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<tbody>
<tr>
<td>Drugs</td>
<td>41</td>
<td>55</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>110</td>
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<tr>
<td>Medical Devices</td>
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<td>48</td>
<td>78</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>140</td>
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April 2005 - March 2008

37 Persons : Number of GMP inspectors in PMDA (1. Apr. 2008)
## On site inspections for foreign facility

<table>
<thead>
<tr>
<th>Category</th>
<th>EU</th>
<th>North America</th>
<th>Central and South America</th>
<th>Asia</th>
<th>Other</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Sterile drugs, Biologics</td>
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<td>30</td>
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<td>2</td>
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<td>API (chemicals)</td>
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<td>8</td>
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<td>0</td>
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<tr>
<td>Total</td>
<td>41</td>
<td>55</td>
<td>1</td>
<td>12</td>
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April.2005-March.2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Area</th>
<th>Number</th>
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<tbody>
<tr>
<td>API</td>
<td>137</td>
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<td>46</td>
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<td>Packaging</td>
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<td>EU</td>
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</tr>
</tbody>
</table>

Total number of approved generic product: 163

About 84% (137) : API

API: Korea, India, Italy, China...
Problems experienced in foreign on site inspection

- Insufficient concern of Japanese marketing approval holder in control of manufacturer
- Nonconformity to the Japanese Standards for Biological ingredients
framework of the Japanese international cooperation
Present framework of the Japanese international cooperation of Japan

- Mutual Recognition Agreement with EC
- Memorandum of Understanding
- Drugs for export (Article 80 of PAL)
Mutual Recognition Agreement with EC

- Come into effect on 29. May. 2004
- Mutual Acceptance of GMP inspection for manufacturing site and certificate of analysis for each batches of products
- Country: Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden, United Kingdom
MoU (Memorandum of Understanding)

• Cooperation for issuance of inspection reports, etc

• Pharmaceuticals: Germany, Sweden, Switzerland, Australia

* Under review of the current status by MHLW
GMP Inspection for Foreign Sites

– MRA*: Document inspection only for pharmaceuticals except sterile products and biologics
– MOU*: Document inspection only for Pharmaceuticals

MRA* Japan-EU Mutual Recognition Agreement (API: out of scope)
MOU* Memorandum of Understanding between Japan and Australia, Germany, Sweden, Switzerland
Quality Control of Drugs for export

- Article 80 of the Pharmaceutical Affairs Law
- Manufacture of drugs for export shall be in compliance with GMP. If a certificate for an exporting drug is required, the certificate will be issued under WHO guideline.
- Renewal every 5 years
Future efforts

Points to consider

1. Developing a scheme on cooperation among stakeholders
2. Understanding of regulations of each country
3. Resource (Increase of number of inspectors, etc)
4. Training of Inspectors
5. Mutual benefit
6. Collaboration with MHLW on expansion of scope of MRA with EU
7. ICH, PIC/S, other activities
Thank you for your attention.

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