PMDA GMP Inspection

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Incorporated Administrative Agency –
The Pharmaceuticals and Medical Devices Agency (PMDA).

Second “India/Japan Pharmaceutical Seminar in Osaka”
Today’s Content

- Outline of Overseas On-Site inspections
- Procedure for Decision of an On-site inspection
- Discrepancy/Inconsistency in Desktop/Questionnaires inspection
- Cases of GMP Non-compliance
- (Reference)
  - Cases indicated when on-site inspections were made at Indian manufacturing sites
Outline of Overseas On-Site inspections
Number of Manufacturing Sites, which are subject to PMDA’s inspection

As of March 2012

- **Overseas Manufacturing Sites**
  - Accreditation-obtained sites: 2385
    - Asia/Middle East: 941 (Drugs: 801, Quasi-drugs: 140)
    - Europe: 983 (Drugs: 914, Quasi-drugs: 69)
    - North-America, Central/South America, Africa and Oceania: 461
      (Drugs: 398, Quasi-drugs: 63)
  - Manufacturing sites with no accreditation required
    (Bulk drug intermediates, (Rx-to-) OTC switched bulk drugs, etc.): about 300 (appropriate figure)

- **Domestic Manufacturing Sites**
  - PMDA is an inspection Authority (Minister-designated facilities): 135
    - Biological Products, etc.: 116
    - Radioactive Products: 19
  - New drugs-related Products
    (Governor-approved sterile, general drugs, etc.): about 350 (appropriate figure)

Overseas mfg. sites: about 2,700

Domestic mfg. sites: about 500
Number of Overseas inspections on a country-by-country basis

Performed from April 2005 though March 2012
(No. of Manufacturing Sites: 438 in 32 countries)
### Outline of GMP inspections by Region and by Field Pertaining to Ethical Generic Drug Products (From April 2006 through March 2012)

<table>
<thead>
<tr>
<th>分野</th>
<th>EU</th>
<th>North America</th>
<th>Central/South America</th>
<th>Asia</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Products, Bio-Pharmaceuticals</td>
<td>70</td>
<td>8</td>
<td>4</td>
<td>38</td>
<td>8</td>
<td>128</td>
</tr>
<tr>
<td>Solid Drug Products</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>59</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>APIs</td>
<td>213</td>
<td>25</td>
<td>3</td>
<td>462</td>
<td>1</td>
<td>704</td>
</tr>
<tr>
<td>Packaging &amp; Test laboratory</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td>37</td>
<td>10</td>
<td>566</td>
<td>14</td>
<td>948</td>
</tr>
</tbody>
</table>

- **APIs**: 74%

Bulk pharmaceutical chemicals/APIs account for 74% of the total, and among them Asia accounts for more than 60% of the BPCs.
Number of Domestic and Overseas On-Site inspections/Annual Transition of inspections by Region over the years
(from April 2006 through March 2012)
GMP inspection (By Country) for Ethical Generic Drugs
(From April 2006 through March 2012)

Bulk Pharmaceutical Chemicals (BPCs): India, Korea, China, Italy, …
Grading of Manufacturing Sites

Based on-site inspection results (assessment), manufacturing sites are graded as S, A, B, C, and D (Degrees and numbers of defects, and assessment by subsystem are totaled for the final grading).

**D : Manufacturers in non-compliance with GMP**

**C: Manufacturers in compliance with GMP but need to be given continuous instructions**

<table>
<thead>
<tr>
<th>Main region</th>
<th>Number of on-site inspection (2007.12 – 2012.10)</th>
<th>Mfg. site classification</th>
<th>Total</th>
<th>(C+ D) ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia (except Japan)</td>
<td>181</td>
<td>50(12)</td>
<td>5(3)</td>
<td>55</td>
</tr>
<tr>
<td>EU</td>
<td>102</td>
<td>4(2)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>North America</td>
<td>66</td>
<td>5(1)</td>
<td>1(1)</td>
<td>6</td>
</tr>
<tr>
<td>Central/South America</td>
<td>13</td>
<td>2(1)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Japan</td>
<td>348</td>
<td>58(19)</td>
<td>5(5*)</td>
<td>63</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate inspections for renewal, and asterisks indicate on the spot inspection.

- The proportion of sites rated C and D remain high in Asia (excluding Japan).
- D in inspections for renewal (periodic inspections) are problematic.

**Strengthen the surveillance system**
【Details of manufactured items】

Others (consistent, etc.): 20%,
New drugs: 10%,
Testing: 4%,
Drug products: 7%
APIs intermediates: 20%,
APIs: 65%,
Generic drugs: 70%
Indian Manufacturing Sites where PMDA conducted the inspections

- APIs
- Intermediate APIs
- Drug Products
- Testing Institution
- N/A

Number of sites: 120

- Desktop Inspection
- Onsite Inspection
Grading Assessment of Manufacturing Sites by On-site inspection
(Collected by the number of manufacturing sites but not by the number of application)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
</tr>
</tbody>
</table>
Procedure for Determining an On-Site inspection
From inspection Application to inspection Initiation

- Outline of inspection-subject product item in the manufacturing site: Form1
- Outline of Drug Product Manufacturing Site (for Foreign Manufacturing Site): Form3

- Risk Assessment
- Determination of inspection procedure

- On-site inspection: Adjustment of schedule → Documents submitted in advance
  - Desktop inspection: inspection data

- Whether some discrepancies exist or not
  - Verification of GMP conformity

- On-site inspection: Indicated matters and the grading of the manufacturing site
  - Desktop inspection: Confirmation by written inquiry
  - Existence/non-existence of Discrepancies
Selection of inspection sites according to risks

Prior information
- Attached documents at the time of application, etc.
  (1) Information about the drug (Attachment 1)
  (2) Information on manufacturing site and history of inspection (Attachment 2 [domestic], Attachment 3 [foreign])
- Results of previous on-site inspections (Profile of manufacturing site)
  (1) Grade of the manufacturing site
  (2) Checking each subsystem

Risk assessment
- Risk assessment items
  - Classification of the product (the drug)
  - Manufacturing process
  - Dosage form
  - History of inspections by foreign regulatory authorities
  - Previous GMP non-compliance
  - Previous recalls
  - Previous inspection by PMDA
  - Information about the manufacturing site (results of the last inspection)
  - Others

Accumulation of data
Preparation of selection sheet
Implementation of inspection

On-site inspection
Desk-top inspection

Note: For attached documents, see Administrative notice dated October 27, 2010.
Decision-making cycle for inspection policy

1. **Determination of on-site inspection plan**
   - Risk assessment
   - Preparation of selection sheet

2. **On-site inspection**
   - Checking documents submitted in advance and SOPs, and meeting with Office of Review Administration for arrangement, etc.
   - Preparation of check list of important inspection points
   - Preparation of internal reports
     - Categorize into 6 subsystems
   - Post-inspection meeting
     - Classify the subsystems and rank manufacturing site
   - Draw up manufacturing site profile
   - Database management

3. **Operating procedures by inspectors**
   - Office of Review Administration is informed of inconsistencies between the actual situation and the application dossier.
   - Participation in PIC/S will (hopefully) increase information about each manufacturing site.
   - Assessment of subsystems, ranking the manufacturing site, etc.
   - Observations are sent

- Attached documents submitted at the time of application for inspection
- Results of previous on-site inspections (profile of manufacturing site)
- Information from Office of Review Administration
- Information from foreign regulatory authorities, etc.
Outline of Drug Manufacturing Sites
(Notice dated October 27, 2010)

<table>
<thead>
<tr>
<th>Name of manufacturing Site</th>
<th>Address</th>
<th>Name of the company</th>
<th>Contact person</th>
<th>Phone</th>
<th>FAX</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Accreditation No.</th>
<th>Date of initial accreditation</th>
<th>Accreditation category</th>
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<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Numbers of employees (including part time employees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
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<tr>
<th></th>
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</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Job title</th>
<th>Phone</th>
<th>FAX</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Responsible person of the Site (Qualified person in the EU, or head of quality unit in other countries)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Job title</th>
<th>Phone</th>
<th>FAX</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>製造品目数 (日本への輸出品目数は ( ) で記載)</td>
<td>原薬・中間体 Manufacturing of APIs/Intermediates</td>
<td>製剤化工程 Manufacturing of drug Products</td>
<td>一次包装工程 After primary packaging</td>
<td>二次包装工程 Secondary packaging のみ</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>製造品目数 Number of products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>高生理活性物質 High pharmacological active substances</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ペニシリン系 抗生物質 Penicillin antibiotics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>βラクタム系 抗生物質 β-lactam antibiotics</td>
<td></td>
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</tbody>
</table>

注 1. 高生理活性物質とは、ある種のステロイド類、細胞毒性のように強い薬理作用又は毒性を有する物質等をいう。 2. 原薬の小分けは、原薬・中間体の欄に記載。 Note 1. High Pharmacological active substances (e.g., certain steroids or cytotoxic substances) 2. In cases of subdividing manufacture of APIs, please fill in the Manufacturing of API/Intermediate column.
Outline of Drug Manufacturing Sites (Continues)

<table>
<thead>
<tr>
<th>Information of the manufacturing site I</th>
</tr>
</thead>
<tbody>
<tr>
<td>製造所敷地面積</td>
</tr>
<tr>
<td>Area of the site</td>
</tr>
<tr>
<td>製造施設面積</td>
</tr>
<tr>
<td>Area of the manufacturing facilities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Information of the manufacturing site II</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Overall function of major computer system adopted in the manufacturing site)</td>
</tr>
<tr>
<td>重要なコンピュータ化システムの名称</td>
</tr>
<tr>
<td>Name of major computer system</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of GMP inspections by regulatory authorities over the past 5 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>行政機関名</td>
</tr>
<tr>
<td>Name of regulatory authorities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of product recall or GMP non-compliance over the past 5 years (Please specify details.)</th>
</tr>
</thead>
</table>
Agreement on GQP and Quality

Marketing Authorization Holders

(Quality Control Work based on GQP)

Involvement of MF domestic care-taker

Agreement, Manufacturing surveillance

Manufacturer (APIs) → Manufacturer (Drug products) → Manufacturer (Packaging and labeling: Testing) → Market

Results/Records → Market Distribution Judgment

GMP Compliance

(Flow of a Product)
From the Preliminary inspection of Marketing Authorization Holders

- There were no records on the manufacturing control and quality control.
- There was no manufacturing facility necessary for the inspection-subject product item.
- No manufacturing activity was done at the inspection-subject manufacturing site.
- GMP control was non-conforming.
Discrepancy/Inconsistency in Desktop inspection
Major Deficiency for Descriptions in Master File (MF)

- Discrepancy in actual manufacturing method/Specification, etc.
- Omission of description of manufacturing facilities, etc.
  - API intermediate and crude API were manufactured in another manufacturing site.
  - Outside contract testing institutions, and a facility with only pulverization process.
- The manufacturing method has been changed.
  - Change registration/minor change notification were not made.
The Causes (1) for Deficiency in Descriptions in MF

- The MF in-country caretaker responded to written inquiries on his/her own judgment without communicating to the manufacturing site.
- Since there were multiple overseas agents who had a connection between the MF in-country caretaker and the manufacturing site, the MF in-country caretaker was unable to communicate directly to the manufacturing site.
- The MF in-country caretaker has made the maintenance of the MF (Description arrangement/Change registration/Minor change notification) based on the old information he/she obtained in the past.
The Causes (2) for Deficiency in Descriptions in MF

- The MF number, which was quoted to the application document for market authorization of a drug (product), was wrong or inappropriate.
- The inquiry content from the PMDA was not correctly conveyed to the MF Registrant (the manufacturing site).
- The MF in-country caretaker could not deal with the Conformity inspection, and thus he was replaced with another MF in-country caretaker in a hurry.
- The descriptions in the MF were inappropriate, such as too simplified content.
MF Registrant (Manufacturing Site) and MF In-Country Caretaker

Article 72, Second Clause of Enforcement Regulations of the Pharmaceutical Affairs Law

A person manufacturing APIs, etc. in a foreign country intends to make application of the registration specified in the preceding clause shall appoint at the time of the application a person who is engaged in deskwork services of the registration, etc. in Japan (hereinafter referred to as “DMF registered in-country caretaker, etc.”) from among the persons who reside in Japan (including a representative in case of a foreign corporation with office in Japan).

- The MF registrant shall appropriately disclose information to the MF in-country caretaker.
  - According to the agreement with the marketing authorization holder, necessary information (Quality information, change, deviation).
  - Via the MF in-country caretaker, disclose minimum necessary information to the marketing authorization holder.
- The MF in-country caretaker shall deal with the pharmaceutical affairs on behalf of the MF registrant.
  - A relationship with the MF registrant to exchange information periodically.
  - Based on the information from the MF registrant, deal with the pharmaceutical affairs.
Cases of non-compliance in recent GMP compliance reviews
Non-Compliance Case (No. 1)

1. Inspection target
   The inspection was carried out on a foreign sterile product manufacturing site (freeze-dried preparations), and it was a periodic inspection.

2. Articles violated: Article 23 Section 1 and Article 24 Section 1 of the Ministerial ordinance
   Lack of sterility assurance due to defects in manufacturing conditions in the aseptic area (grade A)
   (1) After sterilization, vials and rubber stoppers were stored insufficiently protected in a grade B area, and were brought to a grade A area and used. All freeze-dried preparations were capped but there was no proper confirmation of whether they were well sealed, so they were insufficiently protected, and transported through a corridor in a grade B area to the clamping room.
   (2) Workers could freely enter the area, which was required to be grade A, at anytime (frequently during manufacturing) to carry out sterile filling operations and carry vials to freeze dryers, etc.
   (3) In the above formulation process, products were being produced without one-way air flow in the grade A area. The defect was known but was not improved.

* Serious defects other than with the sterile product were not noted in the manufacturing control. However, in terms of the quality system (management/control system) for the manufacturing site as a whole, the defect may have some impact on the manufacturing control of other than the sterile product.
Non-Compliant Case (No. 2)

1. Inspection target
   The inspection was carried out on a foreign manufacturing site (API), and it was a periodic inspection.

2. Articles violated
   Article 6, Article 10 Section 1 items 3 and 5, Article 11 Section 1 items 1 and 2, Article 14 Section 1 items 1 and 2, Article 15, Article 16 Section 1 items 2 and 3, and Article 19 Section 1 item 3 of the Ministerial ordinance
   Most of the records required have not been kept.

   (1) Management/control systems were not implemented.
   There were SOPs for deviation control, complaint handling (quality information management). However, there were no records of them.
   The workers did not understand what a “deviation” is (lack of capabilities and training).

   (2) Reliability of the test data could not be ensured.
   Only test results were kept, and there was no evidence of the test records kept.
   Therefore, it was not certain whether the tests were actually carried out.

   (3) There were no records of actual production quantities.
   Data on the yield and yield rate were missing. How surpluses were handled was not traceable.
Non-Compliant Case (No. 3)

1. Inspection target
   The inspection was carried out on a domestic manufacturing site (biological products), and it was a for-cause inspection.

2. Articles violated
   Article 6 Section 1, Article 10 Section 1 item 9, Article 12 Section 1, and Article 15 Section 1 item 1 of the Ministerial ordinance
   (1) Packaging activities including opening and resealing were routinely conducted when deviations occurred in the products released at the manufacturing site. These deviations were recorded in an “operation memorandum”, not in any GMP documents; no records were kept in the GMP manufacturing documents.
   (2) The above deviations were not known by the quality unit, and the products were distributed without reassessment for release.
   (3) The above handling was conducted under the direction of a manager. The necessity of documenting these deviations in the GMP documents was not understood by the person in charge.
Non-Compliant Case (No. 4)

1. Inspection target
   The inspection was carried out on a foreign manufacturing site (sterile API), and it was a periodic inspection.
   → There were products formulated (filled) and released to the market without sterilization process in Japan.

2. Articles violated
   Article 23 Section 1 item 1 and Article 24 Section 1 items 1, 3 and 7 (a) of the Ministerial ordinance
   There was a lack of sterility assurances with respect to both the facility and operation. The risk of microbial contamination was very high.
   (1) Handling of primary containers after sterilization
       The sterilized containers were handled under class 10,000 conditions, and the conditions were improved. However, the installed clean booth could not be qualified.
   (2) Defects in the condition of charging raw material, which should be charged under the aseptic conditions
       The charging operation was performed under class 10,000 conditions, and it should have been done in an aseptic area. A clean booth was installed to improve the situation. However, the design was not appropriate for ensuring aseptic conditions.
   (3) Aseptic handling was not conducted by workers engaged in a series of operations.
       ⇒ They were not appropriately trained to conduct the aseptic processing.
Thank you very much for your attention!