Current Status of Desk-top GMP inspection in Japan

April 5th, 2017

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Today’s Topics

1. Japanese Regulation
2. Method of GMP Inspection: On-site or Desk-top
3. Submission documents for Desk-top inspection for NDA
4. Key Performance Indicator
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PMDA Philosophy

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

• We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.

• We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.

• We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.

• We play an active role within the international community by promoting international harmonization.

• We conduct services in a way that is trusted by the public based on our experiences from the past.
Responsibilities of MHLW and PMDA

[MHLW: Ministry of Health, Labour and Welfare]
Planning basic policy, enforcement of administrative measures, such as approval, administrative order, etc which are based on the law

- Final judgment on marketing authorisation
- Withdrawal of the product from the market
- Withdrawal of authorisation and license
- Safety measures for emergent and significant cases

[PMDA]
Implementation of work, such as review, examination, data analysis, etc before administrative measures

- Scientific review of Pharmaceuticals and Medical Devices
- GLP/GCP/GMP/QMS/GCTP inspections, Clinical trial consultation
- Collection, examination, analysis, assessment and provision of ADR information
GMP Inspection System

Pharmaceutical Safety and Environmental Health Bureau, MHLW
(manufacturing license, marketing license, marketing authorization, administrative order, pharmacovigilance, license withdrawal, seizure, penalty, etc.)

PMDA is partially vested authority from MHLW (assessment, GMP inspection, information gathering)

Prefectures are vested part of MHLW’s authority to have local autonomy.

Inspectorate

47 Inspectorates
Delegation of MHLW’s authority of GMP inspection to PMDA and prefectural government

<table>
<thead>
<tr>
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<th>Domestic Site</th>
<th>Foreign Site</th>
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<tbody>
<tr>
<td>New Drugs, Biological Products, Radio Pharmaceuticals</td>
<td>MHLW Delegated to PMDA</td>
<td>MHLW Delegated to PMDA</td>
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<tr>
<td>Other Drugs</td>
<td>Pref. Gov.</td>
<td>MHLW Delegated to PMDA</td>
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GMP inspection and product marketing authorization

- GMP requirement is realigned to be product authorization requirement (Art.14.6 of PMD Act.)

- GMP inspection before product authorization (Art.14.6 of PMD Act.)

PMD Act. : Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics
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**On-site inspection or desk-top inspection**

- Article 14.6 of PMD Act. provide that GMP inspection is to be done either by on-site inspection or desk-top inspection

*Article 14-6.*

A person intending to obtain the approval specified in Paragraph 1 or a person obtaining the approval specified the same paragraph, with respect to the drugs, quasi-drugs (abbreviated) specified by Cabinet Order, shall be subjected to a desktop inspection or an on-site inspection performed by the Minister as to whether a method of manufacturing control or quality control of it in the manufacturing establishment complies with the standards specified by MHLW Ministerial Ordinance specified by Paragraph 2, Item 4, when intending to obtain the approval concerned, and at an interval of not less than 3 years as specified by Cabinet Order after obtaining the approval concerned.
On-site inspection or desk-top inspection

• The competent inspectorate has responsibility to select on-site or desk-top inspection at each inspection, based on risk based assessment. This is regulated in the “Procedure for conducting GMP inspection (February 16, 2014, Yakushokukanmahatsu 0216-7)” and is unifying Procedure thorough out Japan.

Section 2.4. Selection of onsite inspection or desk top inspection

Upon receipt of application for GMP inspection, each inspectorate should decide which of the inspection method, onsite inspection or desktop inspection, is employed taking the items in the above Table 1 into consideration, and inform it to the applicant. Onsite inspection should be selected in principle, if the site does not receive on site inspection in the previous 2 years. Onsite inspection may be selected even the site is inspected within 2 years, taking the compliance status or GMP control status into consideration.

• Section 2.2 of the Procedure for conducting GMP inspection provides procedure for both onsite and desk-top inspection.

* SOPs for risk based selection of onsite or desk-top inspection are to be in place at each inspectorate
Selection of inspection sites according to risks

Prior information

Risk assessment

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

Internal database

Preparation of selection sheet

Implementation of inspection

On-site inspection

Desk-top inspection

Attached documents at application, etc.
(1) Information about the drug
   (Form 1)
(2) Information on manufacturing site and history of inspection
   (Form 2 [domestic], Form 3 [foreign])

Previous on-site inspections
(Profile of manufacturing site)
(1) Grade of the manufacturing site
(2) Checking each subsystem
   S, A, B, C or D ranking based upon assessment of 6 subsystems:
   1) Quality systems; 2) facilities & equipment;
   3) materials control; 4) production control, 5) packaging & labelling; and
   6) quality control.
Method of GMP Inspection (PMDA): On-site or Desk-top

On-site:
- Submission Documents prior to On-site Inspection
- On-site Inspection

Desk-top:
- Submission Documents for Desk-top Inspection
- Desk-top Inspection

General information of site eg. SMF
Product specific info.
QMS
Product Specific (PV, MBR etc.)
Japan specific (Standards for Biological Ingredients: Art. 42 PMD Act.)

SMF: Site Master File
QMS: Quality Management System
PV: Process Validation (report)
MBR: Master Batch Records

Pharmaceuticals and Medical Devices Agency
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Flow of Desk-top inspection for NDA

- **Application**
  - Outline of Product(s) Subject to Inspection: Form 1
  - Outline of Drug Manufacturing Site (Domestic or Foreign): Form 2 or 3

- **On-site/Desk-top**
  - Risk Analysis
  - Finalize method of inspection (On-site, Desk-top)

- **Inquiry**
  - Desk-top inspection: Send inquiry to receive desk-top inspection documents

- **Conduct Inspection**
  - Desk-top inspection: Check received documents, additional inquiry if necessary
  - Check discrepancy between the manufacturing method and the content of the marketing approval document
Submission documents (NDA)

- Outline of Product(s) Subject to Inspection: Form 1
- Outline of Drug Manufacturing Site (Domestic or Foreign): Form 2 or 3
- Copy of Marketing approval document
- Copy of results or reports of GMP inspection which conducted past 2 years

Those information will be used for risk assessment to decide method of inspection either on-site or desk-top.
To confirm function of quality management system

- Documents for quality assurance system
- SOP of deviation and record for past 2 years
- SOP of change control and record for past 2 years
- Usage of CSV

To confirm compliance of the regulations

- GMP documentation
- GMP organization chart
To confirm the consistency between practical operations at the site and the marketing authorization application

- Documents relates to the manufacturing process (e.g. Master Batch records)
- Specification and SOP for analytical tests
- Documents on the management status of Standards for Biological Ingredients
- Documents on the status of validation
  - Process validation reports

Other

- Site map
- Floor map
- A list of the number of manufactured batches per year and the amount manufactured per year
- Documents on the status of validations
  - Process simulation tests reports for sterile products
  - Cleaning validation reports for shared equipments
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Timeline for NDA

Submission of NDA

1 year for Total

Review of marketing authorization application by reviewers

Approval

On-site/Desk-top Inspection by GMP inspectors

Submission of GMP Inspection Application (6 month prior to Approval)

Result of GMP inspection

6 month for GMP
Cooperation within PMDA

Office of Review

- Reviewing marketing authorization
- MHLW

Office of Manufacturing/Quality and Compliance

- Adverse Drug Reaction Relief System
- Collect the information relating to safety and efficacy of Drugs and medical devices
- MHLW

Office of Safety

- MHLW

Office of International

- Tie up the international activities relating to drugs and medical devices
- MHLW

Office of Regulatory Sciences Operations

- “Human Resource Development Division”
- General training to entire PMDA employees
New active substance median approval time for six regulatory authorities in 2006-2015

“In 2015, PMDA was the agency with the shortest median approval time (284 days), followed by FDA (351), Health Canada (355), TGA (373), EMA (417), and Swissmedic (464).

The Center for Innovation in Regulatory Science 2016
PMDA’s Achievements

Time Clock at PMDA for Desk-top GMP Inspections

For Desk-top inspection, our KPI is 180 days. Counts start from submission of GMP inspection application until issues of GMP inspection results.

Time clock at PMDA
Average: 79~90 days
PMDA put our much effort to resolve drug lag such as make a clear time line until approval for new drugs.

eg. Total 1 year from submission of NDA to approval. GMP for 6 month)

• For GMP group, we set KPI and every year we are reviewing our performance.

• Need to explain more clearly to the applicants what we are requesting to shorten more inspection period.

Summary