GMP Inspection System and Activities of Japan

PMDA
OFFICE OF MANUFACTURING/QUALITY AND COMPLIANCE
RYOKO NARUSE
# History of GMP

<table>
<thead>
<tr>
<th>Era</th>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1960’s</td>
<td>1960</td>
<td>Existing PAL</td>
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<td>1970’s</td>
<td>1974</td>
<td>Notification of GMP</td>
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<td>1980’s</td>
<td>1980</td>
<td>Legitimization of GMP （Compliance rules）</td>
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<td>1990’s</td>
<td>1994</td>
<td>GMP Licensing system</td>
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<td>1995</td>
<td>Validation standards</td>
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<td>2000’s</td>
<td>2003</td>
<td>Standard on Biologically-derived Raw Material</td>
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<td></td>
<td>2004</td>
<td>Amendment of PAL</td>
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<tr>
<td></td>
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<td>- Addition of GMP to Marketing authorization</td>
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<td></td>
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<td>- Application of GMP to overseas Mfg. sites</td>
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<td>2010’s</td>
<td>2014</td>
<td>Amendment of PAL （PMD Act）</td>
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<td>- Newly Insertion of Regenerative Medicine／GCTP</td>
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MAH shall have the marketing license and GQP (Good Quality Practice) is prerequisite for the license. And also MAH shall have product approval and GMP compliance at each manufacturing site is prerequisite for the approval.

- Supervise and manage the manufacturers
- Ensure proper release to market
Review & Inspection

Application of New Drug
- Submission
- Pilot scale Data
- Production scale Data
- Pre-Approval Inspection
- Approval
- Re-submission

Application of Partial Change (PC) of Approval
- Pre-Approval Inspection
- Application of PC
- Production Based on Approval

5-yearly Inspection
GMP Inspection Authorities

MHLW
(manufacturing license, marketing license, marketing authorization, administrative order, pharmacovigilance, license withdrawal, seizure, penalty, etc.)

PMDA
Prefectures

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

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

In general, only inspection that MHLW conducts with its 8 regional branches is a for-cause inspection.
GMP Inspection Authorities

GMP inspections for pharmaceutical products are conducted by PMDA and prefectural governments as below.

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<tr>
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<th>Domestic</th>
<th>Overseas</th>
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<tr>
<td>New drugs, Biological products, Radio pharmaceuticals</td>
<td>PMDA</td>
<td>PMDA</td>
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<td>Other drugs</td>
<td>Prefectural</td>
<td>PMDA</td>
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<td>governments</td>
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The following 6 items were included on 30 Aug 2013 (legal binding power):
1. Quality Risk Management
2. Product quality review (Annual Review)
3. Supplier Control
4. Stability monitoring
5. Reference - Retention sample
6. More detailed requirement on Validation
GMP Inspectorate Committee

Networking & coordination are basically made within each block. Support from PMDA, e.g. dispatching GMP experts, is available

7 Blocks of Prefectural Govs.

- Hokkaido-Tohoku block
- Kanto-Koshin’etsu block
- Tokai-Hokuriku block
- Kinki block
- Chugoku block
- Shikoku block
- Kyushu-Okinawa block
Location of the 7 blocks

- Hokkaido-Tohoku block (7)
- Kanto-Ko-shin’etsu block (10)
- Tokai-Hokuriku block (6)
- Kinki block (7)
- Chugoku block (5)
- Shikoku block (4)
- Kyushu-Okinawa block (8)

( ): Number of Pref. Govs
Japan and South Korea to Join PIC/S

The Committee invited the competent authorities of Japan and South Korea to join PIC/S as of 1 July 2014. Japan will become the 45th PIC/S Participating Authority and will be represented by the Pharmaceutical & Food Safety Bureau of the Ministry of Health, Labour & Welfare (MHLW), the Pharmaceutical and Medical Devices Agency (PMDA) and the GMP Inspectorates of Japan’s Prefectures. South Korea’s Ministry of Food and Drug Safety (MFDS) will become the 46th PIC/S Participating Authority.
Big Picture of Administrative Efforts based on Globalization

- MHLW-PMDA - 47 Prefectures, OMCL
- Review meeting for enhancement of inspection system
- GMP Inspectorates Community

- Improvement of Mock inspections
- National Institute of Public Health
- Training at PMDA, each block

- Amendment of Procedure for conducting GMP inspection
- Audit of Quality system of each prefecture by PMDA

- Introduction of PIC/S Guide
- Amendment of GMP Notification etc.

Network-ing among Inspectorates

Establishment & Maintenance the Quality Management-System

Continuous training

Global Harmonization of GMP Guideline
Activities of GMP inspectorate Committee

- Holding the Committee meeting
  - Holding 2-3 times a year
  - Discussing inspectorates’ QMS improvement etc.
  - Sharing global information on GMP including PIC/S

- Sharing information thru on-line network/servers
  - Training tools, SOPs etc.

- Training of the inspectors
  - Planning programs for training “leader-class” inspectors
  - Implementing mock inspections among each prefectural block at twice or three times per year
  - Implementing trainings at every meeting

- Planning of activities improving QMS of the inspectorates
  - Allocation of dispatching PMDA GMP experts to observed inspections
  - Planning of auditing QMS of the inspectorates and OMCLs
International Cooperation in GMP

PIC/S

ICH Q7 Q12

MRA

Eudra
Inspection system of Office of Mfg/Quality Compliance, PMDA

Safety Officer

Office Director

Quality Assurance (1)
Reception of complaints for inspections, Internal Audit

Planning & Management for Inspection (2)
Risk evaluation of each application (on-site inspection or desktop inspection)

GMP/GCTP Inspection (22)
GMP inspection of Mfg. sites for drugs, biologics, regenerative medicines etc.

QMS Inspection (17)
QMS inspection of Mfg. sites for medical devices etc.

RCB supervision (4)
Audit of RCB etc.

Kansai Branch (5)
GMP inspection, QMS inspection

( ): the number of inspectors

(As of July 1, 2015)
PMDA’s Contribution to PIC/S (Profile)

- Hosting the Training Seminar on Quality Risk management (QRM) at PMDA (Dec., 2014)
- Entry of Sub-Committee (Communication)
- Participation of Revision of PIC/S Guide
  1) Annex1 (Manufacture of sterile medicinal products)
  2) Classification of Findings
  3) Aide Memoire of Advanced Therapy Medicinal Product (ATMP)
  4) Data Integrity
First QRM Training Course

Advanced Training Course on QRM (Quality Risk Management)

Date: 8-10 December 2014
Place: PMDA
Participant: About 50 Inspectors of PIC/S member and PIC/S applicant

The overall goal is the development and provision of an advanced QRM training course for GMP Inspectors.

This will enable Inspectors to effectively inspect Quality Risk Management activities and decisions on site at an advanced level and to also effectively use the 2012 PIC/S Recommendation in relation to risk-based GMP inspection planning (PI 037/1).
History of International Cooperation of GMP

- MOUs on GMP certificates and mutual recognition of QC data
  - 1986 September with Western German authority
  - 1987 July with Swedish authority
  - 1988 June with Swiss authority

- EOLs on cooperation for exchanging GMP inspection reports
  - 1993 April with Australian authority (TGA)
  - 2000 December with U.S. authority (FDA)

- May 2004 Japan-EC (EU) MRA, GMP Sectoral Annex was enacted after both parties confirmed equivalence of their GMP implementation. (15 countries, solid dosage form)

- July 2014 GMP authorities of Japan, i.e. MHLW, PMDA and 47 prefectural governments became the official member of PIC/S.

MOU: Memorandum of Understanding
EOL: Exchange of Letter
Since 1 Oct. 2013, MHLW and PMDA have started entering GMP-compliance information on Japanese manufacturers, upon their requests, into EMA’s “EudraGMDP” DB.

According to EMA’s website, this is the first time that information from non-EEA regulatory authorities is added to the DB.
Thank you for your kind attention.