ICH Harmonisation and Japanese Pharmaceutical Regulations

APEC LSIF ICH Quality Guidelines Q8 and Q9
Challenges of Implementations

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Presentation Outline

- Pharmaceutical Affairs Law (PAL) changes, ICH discussion and MHLW studies

- Quality Regulations under the Revised Pharmaceutical Affairs Law

- Commitment of Manufacturing Process as Approval Matters and Role of ICH Q8, Q9 and Q10
The 2003 ICH Quality Vision

Industry parties and regulatory authorities of the ICH Quality met in Brussels in July 2003 and agreed on the ICH Quality vision “A harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science”.

In order to develop a modern pharmaceutical quality system, discussions on two topics, 1) Pharmaceutical Development (Q8) and 2) Quality Risk Management (Q9) started. The guidelines on the two topics were published in 2006 in the three ICH regions.

(Pharmaceutical Quality System (Q10) reached step 2 in May, 2007.)
Expected Outcome

For Industry

- Establishment of quality management system from development to post-marketing

For regulatory authority

- Improvement of the approval review system by integration of the review and the GMP inspection
- To concentrate on higher risk products
- The establishment of effective, efficient, and streamlined quality regulation
MHLW’s Expectation to ICH

Comprehensive approach for quality management

- Throughout the product life cycle
  - From development to post-marketing

- Includes;
  - Risk management
  - Technology transfer
  - Change control, etc.
ICH and Quality regulation in Japan

ICH

2004

Q8 and Q9 step4

2005

Q8 and Q9 step5

2006

Q8 and Q9 step5

2007

JAPAN

• PMDA established

• Revised PAL enforced

• GMP guidance

Approval matters policy

Inspection policy
# Pharmaceutical Affairs Law (PAL), ICH Q8/Q9/Q10 and MHLW Grant Regulatory Science Studies

<table>
<thead>
<tr>
<th>PAL regulation changes</th>
<th>ICH discussion</th>
<th>Regulatory science groups</th>
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<tbody>
<tr>
<td>2002 Revised PAL published</td>
<td>2002 CTD Q&amp;A</td>
<td>2002 QS/GMP guidance</td>
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<tr>
<td><strong>2004</strong> PMDA established</td>
<td><strong>2003</strong> GMP workshop in Brussels</td>
<td><strong>2003</strong> CTD mock Approval matters</td>
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<tr>
<td>New GMP standards</td>
<td><strong>2004</strong> Q8 reached step 2</td>
<td><strong>2004</strong> Approval matters Inspection Policy</td>
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<tr>
<td><strong>2005</strong> Approval matters policy</td>
<td><strong>2005</strong> Q9 reached step 2</td>
<td><strong>2005</strong> GMP guidelines Inspection Policy</td>
</tr>
<tr>
<td>Revised PAL enforced</td>
<td><strong>2006</strong> Q8 and Q9 reached step 4</td>
<td><strong>2005</strong> Skip Test guidance Inspection Checklist</td>
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<tr>
<td>Inspection policy published</td>
<td><strong>2007</strong> Q10 started</td>
<td><strong>2006-2008</strong> P2 /application mock</td>
</tr>
<tr>
<td><strong>2006</strong> Product GMP guidance</td>
<td><strong>2007</strong> Q10 reached step 2</td>
<td><strong>2006-2008</strong> Change management system</td>
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Revision of the Pharmaceutical Affairs Regulation
(effective April 2005)

- Revision of the Approval and Licensing System
  - From Manufacturing (or Importation) Approval/License to Marketing Authorization

- Enhancement of Post-marketing Measures
  - To clarify the Market Authorization Holder’s (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)
Revision of the Quality Regulation

1. MAH’s* responsibility for the Quality management
   *Marketing Authorization Holder

2. Requirement Changes in Approval Matters

3. Drug Master File system to support CTD based application

4. Consolidation of the Legal Positioning of GMP

5. Revision and Consolidation of GMP standards

6. Establishment of Pharmaceuticals and Medical Devices Agency (PMDA)
1. MAH’s responsibility for quality management (GQP)

- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.
Marketing and Manufacturing

Marketing Approval Holder
in M prefecture

- Supervise and manage the manufacture
- Ensure proper release to market

Manufacturers

Manufacturer C
(packaging, label)
In C prefecture

Manufacture B
(bulk product)
In B prefecture

Manufacturer A
(API)
In country X

Market Release

External Testing laboratory

GQP
Good Quality Practice (GQP)

Marketing Approval Holder

Marketing Approval

GQP

Market Release

GMP
Raw Materials
Bulk Products
Final products

Manufacturers

Pre-market

Market
2. Manufacturing Process Commitment
Application Form and Approval Matters-
A Unique System

Contents provided in the NDA application form are dealt with as “matters subject to approval.”

Contents described in approval letter are “legal binding” approval matters.
### Approval Matters

- General name (for drug substance)
- Brand name
- Composition
- Manufacturing process, including control of materials ← NEW under rPAL
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures
Approval Matters Policy
Notification from Director of Review Management, 0210001
February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale will become approval matters. Principle and quality end point for each manufacturing step will be subject to pre-approval review.

- In-process procedure is pre-approval matter if it replaces final specification test.
A pilot scale manufacturing processes may be submitted at Application.

The commercial scale processes will be subject to Pre-approval GMP inspection and the commercial scale must be described in the approval.

Pre-approval vs. notification classification may be determined through the review process
## Distinctions between Partial Change Approval Application and Minor Change Notification

<table>
<thead>
<tr>
<th>Partial Change Approval Application</th>
<th>Minor Partial Change Notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in the principle of unit operation of critical process</td>
<td>Process parameter to control the quality endpoint criteria</td>
</tr>
<tr>
<td>Change in process control criteria as quality endpoint criteria</td>
<td></td>
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</table>
Application Form after the Enforcement of Revised Pharmaceutical Affairs Law

OLD APPLICATION
Manufacturing Application

Approval Matter (Specification)
GAIYO
Batch Data etc
Quality Information

CTD-BASED APPLICATION
Marketing Application

Partial Change (application)
Miner change (notification)
Module 2
Batch Data etc
Quality Information

Module 3

Application form
Specification + Manufacturing (Process Control)

Possibility that changes affect drug quality
High
Low

Affect drug quality
Possibility that changes

Batch Data etc

Quality Information

Module 2
4. Consolidation of the Legal Positioning of GMP

- Became a **requirement** for product approval
- GMP inspection **prior to approval**, and periodical GMP inspection in post-marketing phase
- GMP inspection **at the time of application for partial change** (pre-approval required) of the approval matters
- GMP inspection **at foreign sites**
Comparison Flowcharts of Approval and License

Points: (1) MAH’s requirements for PMS system, (2) Allow complete subcontract manufacturing, (3) Introduce marketing approval system

OLD system

Product
Manufacturing Application (MHLW)

Quality, Safety & Efficacy

Establishment
License application (Prefecture)

inspection (5 yearly renewal)

Establishment License

Start manufacturing

Partial subcontracting

Partial License

REVISED system

Product
Marketing Application (MHLW)

Quality, Safety & Efficacy

Establishment
Marketing Approval

1-Step process

Licensed Marketing Approval Holder

• Companies’ PMS compliance system
• Companies’ Quality Assurance System

Self production OR Subcontracting

Establishment
Licensed Establishment

Start production

• MHLW inspection:
  New drug & biologics
• Prefectural inspection: Others

GMP Requirement

inspection (Renewal) Every 5 years

Start marketing
GMP/QMS Inspection for Foreign Sites

• GMP/QMS* inspection for foreign manufacturing facilities started since April, 2005.
  – MRA*: Document check only for pharmaceuticals except sterile products and biologics
  – MOU*: Document check only for Pharmaceuticals

• Number of facilities inspected (~July. 2007)
  – Pharmaceuticals: 75
  – Medical devices: 24

QMS*: Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents; MRA* Japan-EU Mutual Recognition Agreement (API: out of scope); MOU* Memorandum of Understanding between Japan and Australia, Germany, Sweden, Switzerland)
### Number of Foreign Facilities inspected by PMDA (~July.2007)

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<thead>
<tr>
<th>Category</th>
<th>Europe</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/ Biologics</td>
<td>17</td>
<td>21</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Oral solid etc</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>API (Chemical)</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Packaging, Labelling, Storage and Laboratory</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>40</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>75</td>
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</table>
Role of Module 2

- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
  - Reviewers evaluate Module 2 and then narrow down into Module 3, 4, or 5 when they need more detailed information.
  - Module 1 and 2 together with reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.
Relationship between Application Form and CTD Documents

Application form (in Japanese)

Module 2 (QOS) (in Japanese)

- Specifications
- Analytical procedures
- Pharmaceutical Development
- Manufacturing Process
- batch analyses
- Justification etc.

Module 3 (in Japanese or English)

- 3.2.S4.1 Specification
- 3.2.S4.2 Analytical procedures
- 3.2.S4.3 Validation of analytical procedures
- 3.2.S4.4 Batch analyses
- 3.2.S4.5 Justification of specification

Raw data

Analytical procedures (JP style) & acceptance criteria
Manufacturing process
Framework for Review and Inspection

- Partial Change
- Minor Change

Application form

Review

Collection of production scale data

Re-submission of application form

Pre-approval GMP Inspection

Notification of minor partial change

Approval letter

GMP inspection

Validation Data etc.

Commercial Production
Challenges when implementing rPAL regulations with ICH Q8

- Baseline expectations need to be clarified
  “At minimum (identify risks and risks controlled)” expectations do not seem to be traditionally submitted in Japanese NDA. With “traditionally” submitted contents, it is difficult to sort out pre-approval matters, minor change matters. ← expect Q8(R) address this

- Range for excipients as a design space: scientific basis, description in approval letter ← under consideration with “approval matters” study group

- Design spaces with interacting multi-variables and with interacting unit operations: description in approval letter ← see industry’s creativity

- Real time release: process and facility dependence ← Need final scale data to justify. Specification with test method would not go away because of need for later evaluations including generics
Revision Mockup of Japanese QoS

• Old Version was published by Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation in July 2002

• Merely shows an example of description for each module 2 section and just a reference for an applicant to prepare QoS.

• Not covers all information required for each NDA, nor shows acceptance criteria for each categories.

• NEED more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8 and the revised PAL.←2006-2008 MHLW “Approval matters” study group
Opportunities by Q9

• Integration to Industry’s Pharmaceutical Quality Systems
  (ICH Q10 will address this area)
• Integration to Regulatory Authorities’ work process (e.g. QS for GMP inspectrate)
• Integration to Guidance Development and Pharmacopoeia Policy (Government and Industry joint effort)
A QRM process from Development to Manufacturing

Target Product Profile

Drug substance properties; prior knowledge

Proposed formulation and manufacturing process (Risk Identification)

Cause and effect process (Risk Analysis)

Risk-based classification (Risk Evaluation)

Proposed Parameters to investigate (e.g. by DOE) (Risk Reduction)

FORMULATION DESIGN SPACE

CONTROL STRATEGY (Risk Reduction)

PROCESS DESIGN SPACE BY UNIT OPERATION

(Risk Review)

Modified from EFPIA Mock P2

(Initiating QRM process)
6. Establishment Pharmaceuticals and Medical Devices Agency (PMDA)

• Reviews and Related Operations
  – Approval reviews of pharmaceuticals and medical devices GMP/QMS audits to assess pharmaceutical and medical device facilities, processes, and quality management systems
  – Re-assessment and re-evaluation based on Pharmaceutical Affairs Law etc.

• Post-marketing Safety Operations

• Adverse Health Effect Relief Services
Organization of PMDA

- **Center for Product Evaluation**
  - Review: New Drugs, Medical Devices, Biologics, Generics and OTC
  - Audits: GLP, GCP

- **Office of General Affairs, Planning & Coordination**
  - Audits: GLP, GCP etc.
  - Reviews and Related Operations / Postmarketing Safety

- **Office of Relief Funds**
  - Adverse Health Effect Relief Services

- **Office of Compliance and Standards**
  - Audits: Drug GMP and MD Quality System

- **Office of Safety**
  - Reviews and Related Operations / Postmarketing Safety
Balance between “Specification” and “Control of Manufacturing”

- Implementation of ICH-CTD (July, 2003)
- Revision of Pharmaceutical Affairs Law (April, 2005)

ICH Q8, Q9&Q10 Help us to implement rPAL

Former Revised