3.2.4 Management Review of Process Performance and Product Quality

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

(a) The management review system should include:

(1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
(2) Periodic quality reviews, that can include:
(i) Measures of customer satisfaction such as product quality complaints and recalls;
(ii) Conclusions of process performance and product quality monitoring;
(iii) The effectiveness of process and product changes including those arising from corrective action and preventive actions.
(3) Any follow-up actions from previous management reviews.

(b) The management review system should identify appropriate actions, such as:

(1) Improvements to manufacturing processes and products;
(2) Provision, training and/or realignment of resources;
(3) Capture and dissemination of knowledge.

Table IV: Application of Management Review of Process Performance and Product Quality throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

4. CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

4.1 Management Review of the Pharmaceutical Quality System

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include:

(a) Measurement of achievement of pharmaceutical quality system objectives;

(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:

(1) Complaint, deviation, CAPA and change management processes;
(2) Feedback on outsourced activities;
(3) Self-assessment processes including risk assessments, trending, and audits;
(4) External assessments such as regulatory inspections and findings and customer audits.

4.2 Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System

Factors monitored by management can include:

(a) Emerging regulations, guidance and quality issues that can impact the Pharmaceutical Quality System;

(b) Innovations that might enhance the pharmaceutical quality system;

(c) Changes in business environment and objectives;

(d) Changes in product ownership.

4.3 Outcomes of Management Review and Monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include:

(a) Improvements to the pharmaceutical quality system and related processes;

(b) Allocation or reallocation of resources and/or personnel training;

(c) Revisions to quality policy and quality objectives;

(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

5. GLOSSARY

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words "requirement", "requirements" or "necessary" appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a Process:

Ability of a process to realise a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change Management:

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Continual Improvement:

Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

Control Strategy:

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective Action:

Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler:

A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback / Feedforward:

Feedback: The modification or control of a process or system by its results or effects.

Feedforward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English by Oxford University Press, 2003)

Feedback/ feedforward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation:

The introduction of new technologies or methodologies. (ICH Q10)

Knowledge Management:

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Outsourced Activities:

Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance Indicators:

Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS):

Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Preventive Action:

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product Realisation:

Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers requirements. (ICH Q10)

Quality:

The degree to which a set of inherent properties of a product, system or process fulfils requirements. (ICH Q9)

Quality Manual:

Document specifying the quality management system of an organisation. (ISO 9000:2005)

Quality Objectives:

A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality Planning:

Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. (ISO 9000:2005)

Quality Policy:

Overall intentions and direction of an organisation related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior Management:

Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilise resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of Control:

A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

526 **Annex 1**

527 **Potential Opportunities to Enhance Science and Risk Based Regulatory**
528 **Approaches ***

529 *Note: This annex reflects potential opportunities to enhance regulatory approaches. The actual
530 regulatory process will be determined by region.

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

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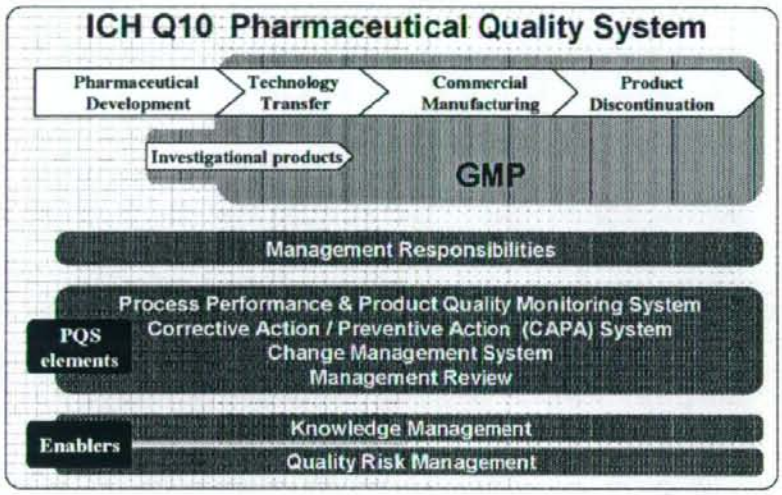
Annex 2

Diagram of the ICH Q10 Pharmaceutical Quality System Model



This diagram illustrates the major features of the ICH Q10 Pharmaceutical Quality System (PQS) model. The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational products.

The next horizontal bar illustrates the importance of management responsibilities explained in Section 2 to all stages of the product lifecycle. The following horizontal bar lists the PQS elements which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each lifecycle stage recognising opportunities to identify areas for continual improvement.

The bottom set of horizontal bars illustrates the enablers: knowledge management and quality risk management, which are applicable throughout the lifecycle stages. These enablers support the PQS goals of achieving product realisation, establishing and maintaining a state of control, and facilitating continual improvement.

Implementation of 2005 Pharmaceutical Affairs Law and ICH Q8-Q10 in Japan

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1

Presentation Outline

- 2005 Pharmaceutical Affairs Law (PAL)
- Approval and Licensing system under PAL
- Review and Inspection
- Regulations under the 2005 PAL

Commitment of Manufacturing Process as Approval Matters, Drug master file

- Challenges under the 2005 PAL
- Implementation of ICH Q8-Q10

2

Pharmaceutical Affairs Law (PAL)

Points on 2002 revision of the PAL (effective 2005)

- Post-marketing safety measures
  Concept of Marketing Approval Holder (MAH)
- Revision of the approval and licensing system
  "Marketing Approval" rather than
  "Manufacturing/Importing Approval"

Responsibility of MAH under PAL
- as prerequisites for license of MAH -

- MAH must comply with GQP for its License.

*GQP: Good Quality Practice
Rules for quality assurance operations

- MAH must comply with GVP for its License.

*GVP: Good Vigilance Practice
Rules for post-marketing safety management

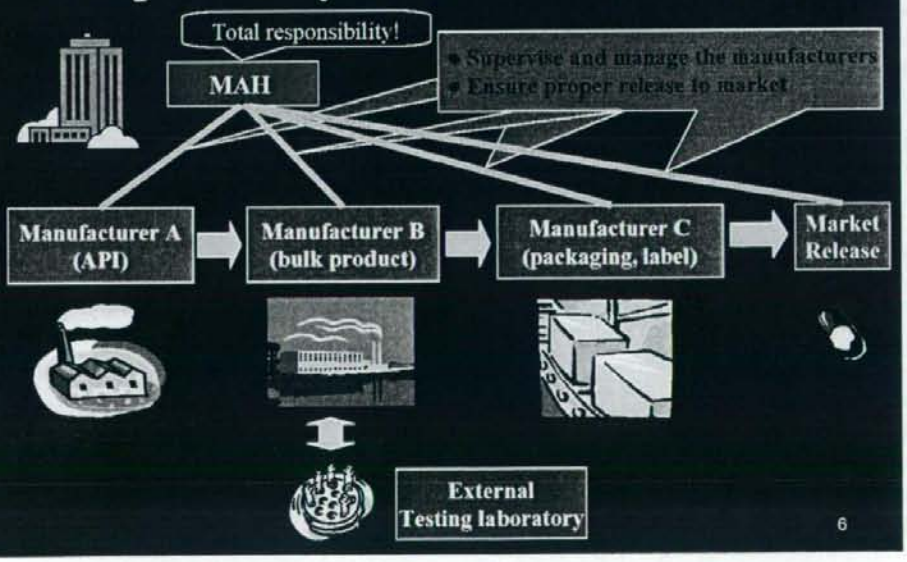
Tentative English translation of GQP, GMP ordinances are posted at
http://www.pmda.go.jp/english/services/reviews/ordinance.html

Revision of the Quality Regulations (Effective April 2005)

1. MAH's* responsibility for the Quality management *Marketing Authorization Holder
2. Requirement Changes in Approval Matters manufacturing process commitment
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

5

Responsibility of MAH based on GQP



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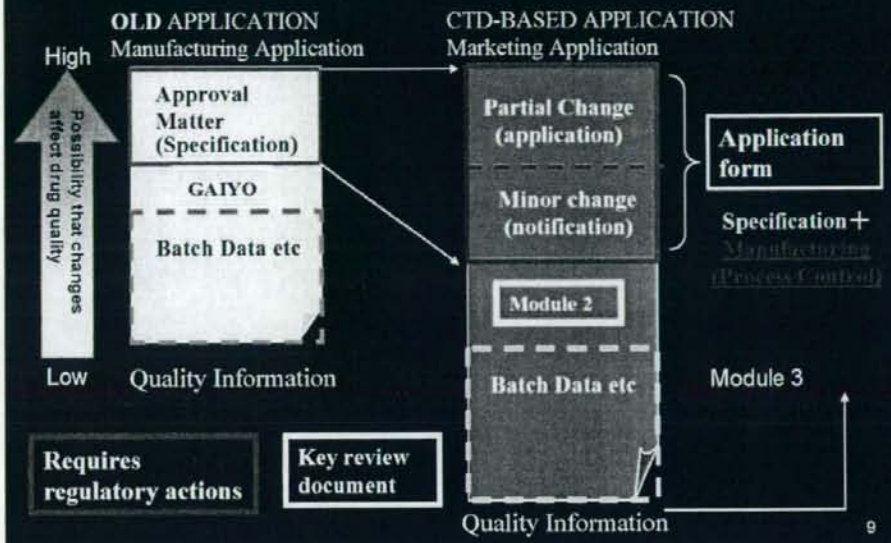
2. Manufacturing Process Commitment Application Form and Approval Matters- A Unique System

- 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

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



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Revision of the Quality Regulations (Effective April 2005)

1. MAH's* responsibility for the Quality management
   * Marketing Authorization Holder
2. Requirement Changes in Approval Matters
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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

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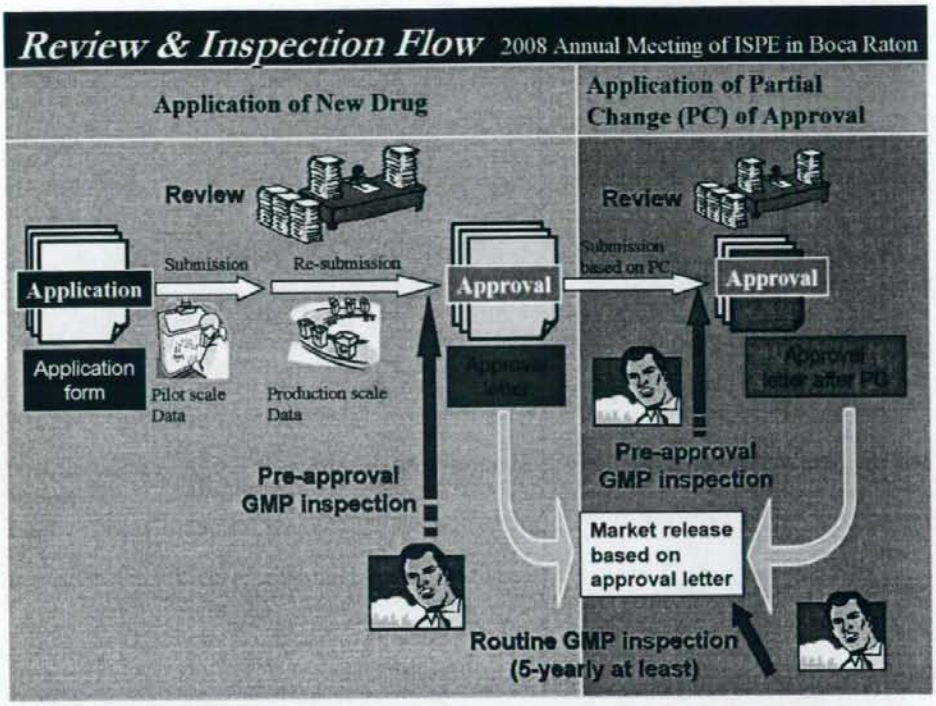
4. Consolidation of the Legal Positioning of GMP

- Became a requirement for product approval
- GMP inspection prior to approval (new product application and partial change (pre-approval) of the approval matters, and periodical GMP inspection in post-marketing phase
- GMP inspection at foreign sites

Revision of the Quality Regulations (Effective April 2005)

1. MAH's* responsibility for the Quality management
   * Marketing Authorization Holder
2. Requirement Changes in Approval Matters
   manufacturing process commitment
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**
   Product Release by Quality Control Department
   Change Control and Deviation Control



Challenges under the 2005 PAL

- Understanding of the new regulations
- Meeting GQP expectations varies

Missing Quality agreements, Periodical quality assurance

- Manufacturing process description
- Drug Master File
- Foreign GMP inspections

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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 step4 and Q8R reached step 2.)

15

MHLW slide at 2003 workshop 14/15

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

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

PAL regulation changes	ICH discussion	Regulatory science groups
2002	2002	2002
Revised PAL published	CTD Q&A	QS/GMP guidance
2004	2003	2003 CTD mock
PMDA established	GMP workshop in Brussels	Approval matters
New GMP standards	Q8 and Q9 started	Inspection Policy
2005	2004	2004 Approval matters
Approval matters policy	Q8 reached step 2	GMP guidelines
Revised PAL enforced	2005	2005 Inspection Policy
Inspection policy published	Q9 reached step 2	Skip Test guidance
2006	Q8 and Q9 reached step4	Inspection Checklist
Product GMP guidance	2007	2006-2008 P2 /application mock
2008	Q10 reached step 2	Change management system
GMP for IP (clinical supply)	Q8R reached step 2	GMP for IP
	2008	
	Q10 reached step4	

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Approval Matters Policy

Notification from Director of Evaluation and licensing division, 0210001 February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale are approval matters. Principle and quality end point for each manufacturing step are subject to pre-approval review.
- In-process procedure is pre-approval matter if it replaces final specification test.

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Approval Matters Policy (continued)

- 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

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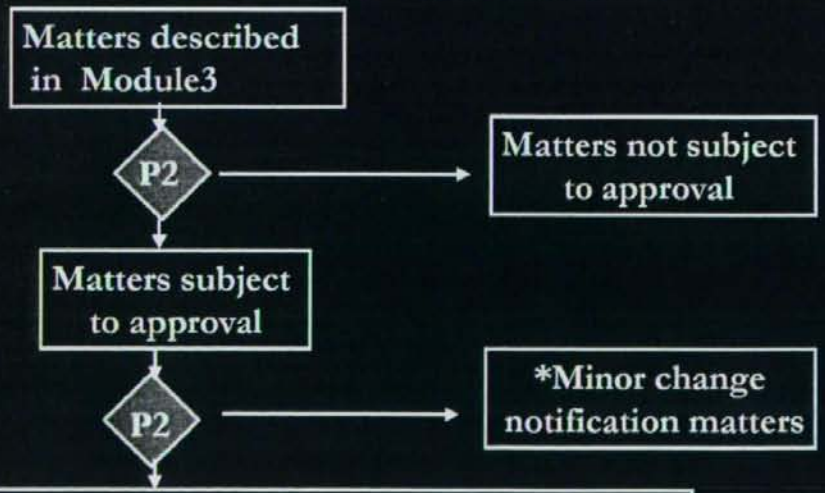
The Role of Pharmaceutical Development(P2) section
-Science and Risk based-
in reviewing NDA under revised PAL



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Health and Labour Sciences Research Grant

- 2006-2008 MHLW "Approval matters" study group began to discuss new QoS
  - Encourage more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8 and the revised PAL

Three sub-themes (according to Q8)

- Enhanced approach
  - 1) Design space team 2) RTR team
- Minimum (Baseline or Traditional) approach
- Design space in formulation

21

P2 mock for enhanced approach

- Risk Assessment before Development, after Process Development and after Risk Control
- Design Space and Real Time Release

The mock is posted at

http://www.nihs.go.jp/drug/DrugDiv-E.html

- More work planned

DS and RTR into Approval Letter

-Decision tree for RTR

-Description of in-process NIR into a test method

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Implementation issues of Q10 in Japan

- Very important ICH guidance for PQS for every pharmaceutical industry- Is this recognized well?
- Q10 says "ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional." Under the Japanese environment, it should read "ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to GMP and pharmaceutical GQP requirements is optional."

23

Implementation issues of Q10 in Japan- continued

- Is that optional? Much of ICH Q10 expectations are covered by GMP and by GQP. All the four elements in Q10 are requirements based on PAL, GMP and GQP (while continual improvement is not required by the regulations.) Understood well?
- Variety of MA holders under GQP

  Self contained,

  Large international companies

  Previously importation licensees
- Is more rigorous GQP inspection needed?

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Ministerial Ordinace on Standards for Quality Assurance for Drugs, Quasi-Drugs, Cosmetics and Medical Devices No136, 2004 (GQP)

Self inspections)

Article 13 The marketing authorisation holder of drugs shall, in accordance with the quality assurance duty procedure documents, etc., have the person designated beforehand conduct the following duties.

(1) To conduct the self-inspections periodically on the quality assurance duties and to establish records of the results, and

(2) .....

2. The marketing authorisation holder of drugs, in case where important improvements are necessary based on the results of the self-inspections, shall have the quality assurance manager take necessary actions, establish records of the actions and report in writing the results of the actions to the general marketing manager.

- (contract with Manufacturers, etc)

Article 7 The marketing authorisation holder of drugs shall conclude a contract for the following items with manufacturers, etc. of the products and describe the details of the agreement in the quality assurance duty procedure documents, etc. to ensure that the manufacturing control and quality control are conducted properly and efficiently by the manufacturers, etc.

(3) The nature and extent of the periodical verification, by the marketing authorisation holder, of the the manufacturing duties that they are conducted under the proper and efficient manufacturing control and quality control

25

Working relation with foreign manufacturing site GQP·GMP

Inadequate or no contract between MAH and site

- Large international companies are NOT willing to write Supply/Quality Agreement between its manufacturing site and MAH(??)
- If size of purchase/supply is small, vendors are unwilling to write contract(??)

Importers keep information from MAH

- In the case of Heparin, most of MAHs did not have information required by the PAL and GQP.

The regulation requires **a contract with manufacturers of the products and describe the details of the agreement in the quality assurance duty procedure documents the periodical verification, by the marketing authorisation holder.**

With or without contract manufacturing, proper control must be in place.

- "Because we use foreign manufacturers, it is difficult to obtain necessary information"---This is Serious PAL violation