Annex 1

Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches *

*Note: This annex reflects potential opportunities to enhance regulatory approaches. The actual 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.

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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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

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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"

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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

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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
   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

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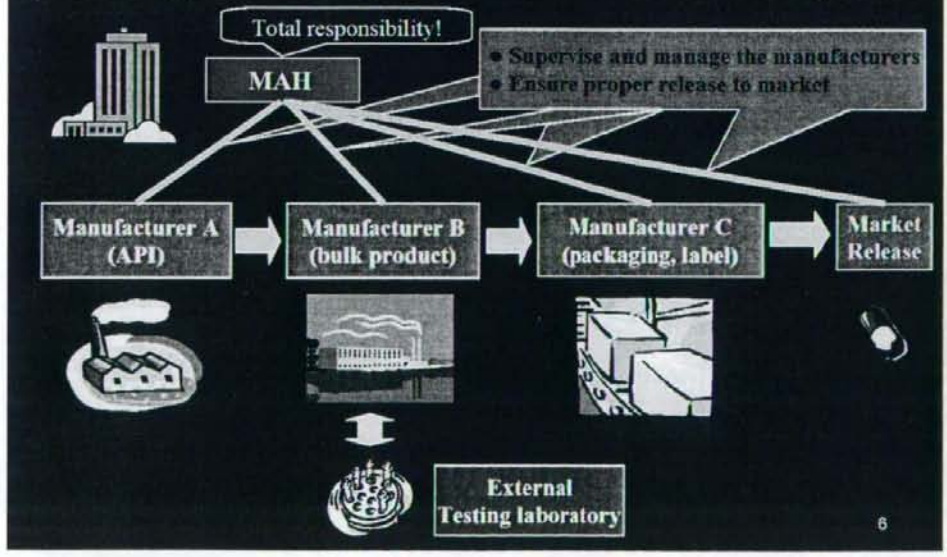
Responsibility of MAH based on GQP



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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.

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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

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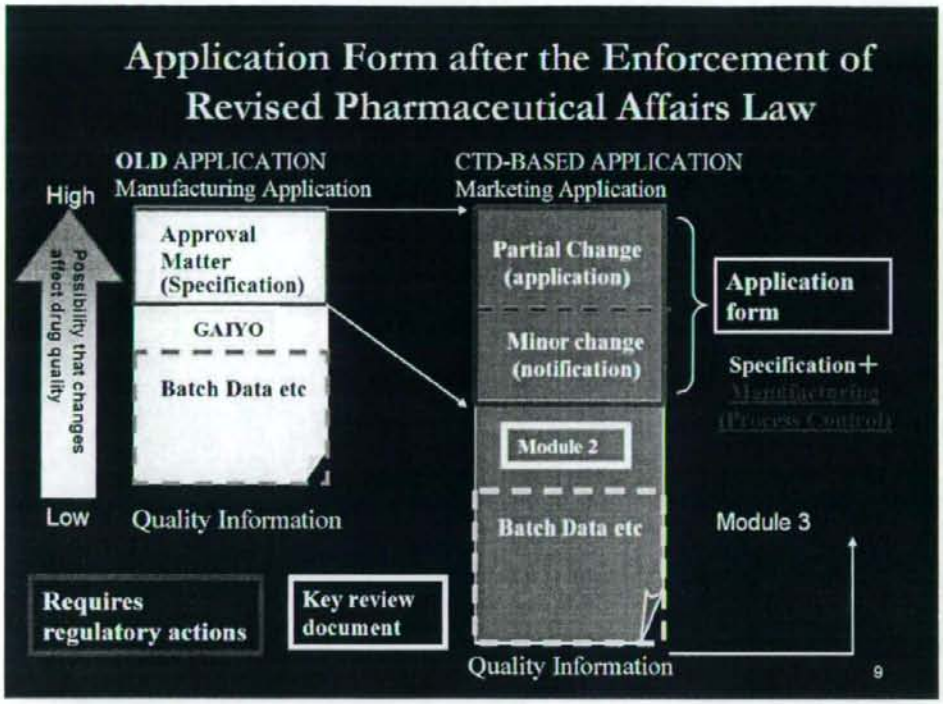
Application Form after the Enforcement of Revised Pharmaceutical Affairs Law
OLD APPLICATION
Manufacturing Application
CTD-BASED APPLICATION
Marketing Application
High
Low
Possibility that changes affect drug quality
Approval Matter (Specification)
GAIYO
Batch Data etc
Quality Information
Partial Change (application)
Minor change (notification)
Application form
Specification+
Module 2
Batch Data etc
Module 3
Quality Information
Requires regulatory actions
Key review document
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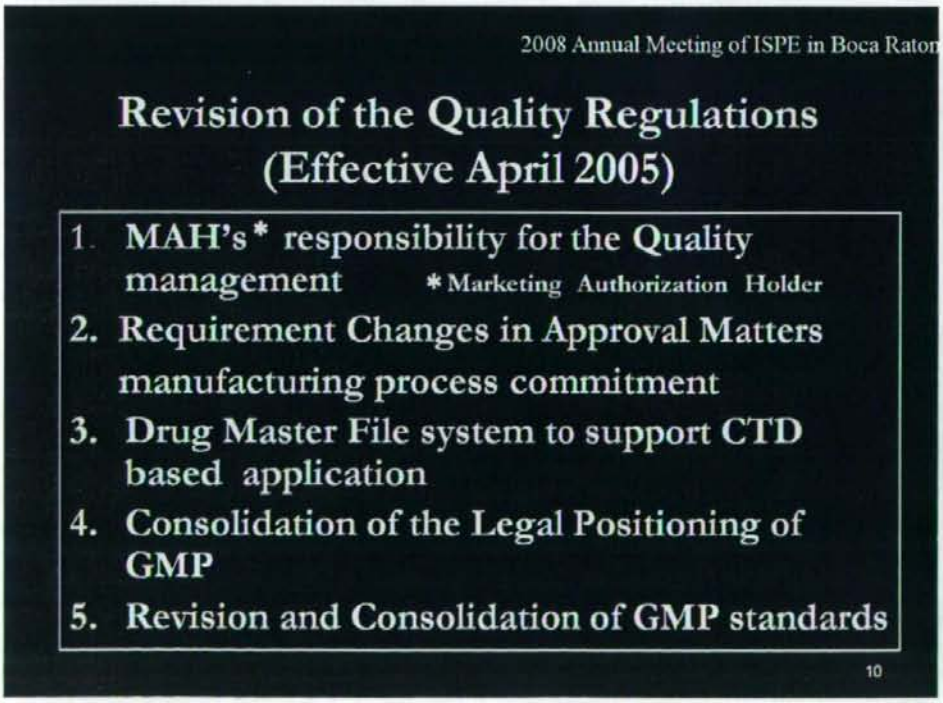
2008 Annual Meeting of ISPE in Boca Raton
Revision of the Quality Regulations (Effective April 2005)
1. MAH's* responsibility for the Quality management
*Marketing Authorization Holder
2. Requirement Changes in Approval Matters
manufacturing process commitment
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards
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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

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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
   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

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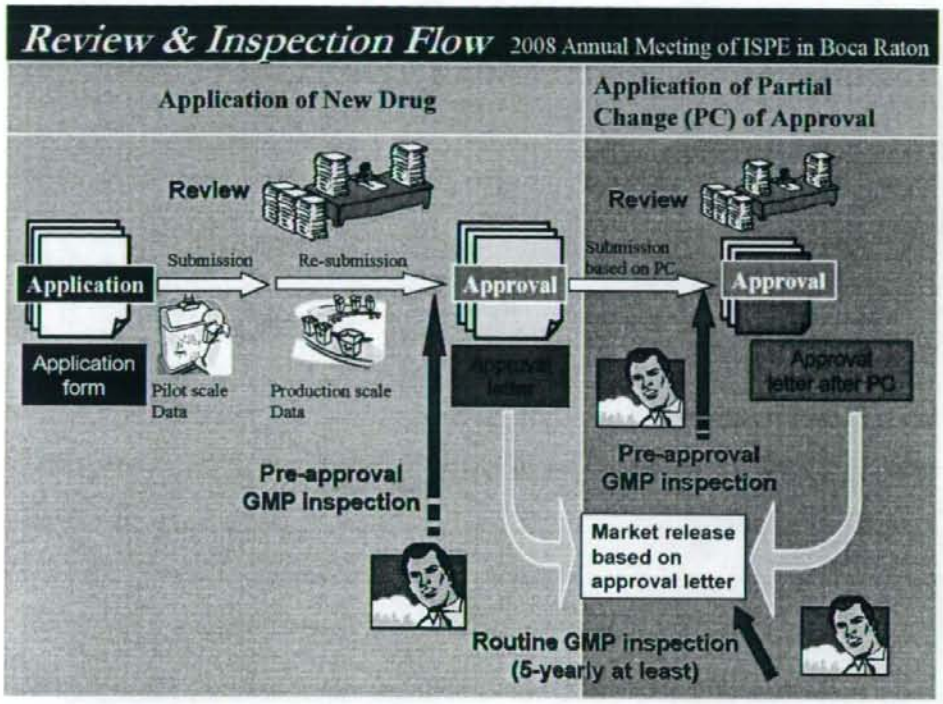

Challenges under the 2005 PAL

- 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.)

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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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2008 Annual Meeting of ISPE in Boca Raton

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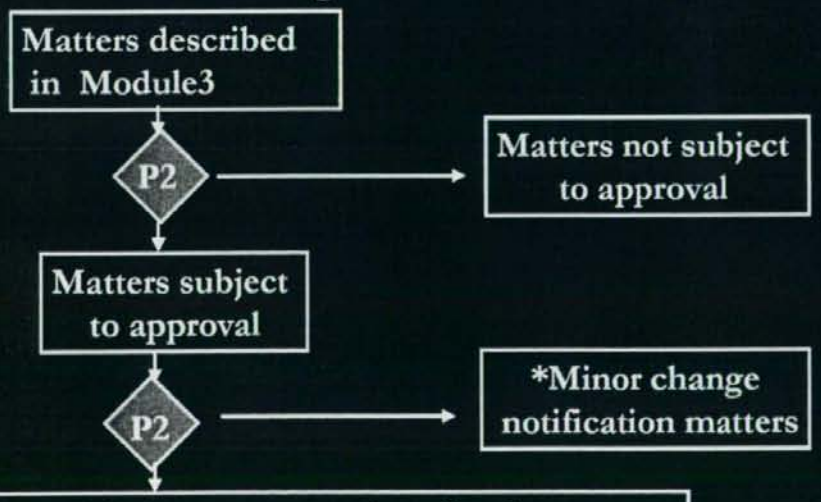
The Role of Pharmaceutical Development(P2) section
-Science and Risk based-
in reviewing NDA under revised PAL



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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

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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."

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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

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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

GMP/QMS Inspection for Foreign Sites

- GMP/QMS* inspection for foreign manufacturing facilities started since April, 2005.
  - MRA*: Document based for pharmaceuticals except sterile products and biologics
  - MOU*: Document based for Pharmaceuticals
- Number of facilities inspected (~September, 2008)
  - Pharmaceuticals: 144
  - Medical devices: 39

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)

On site GMP inspections for foreign facilities

By Category

Apr.2005-Sep.2008

Category	EU	North America	Central and South America	Asia	Others	Total
Sterile drugs, Biologics	30	33	0	3	0	66
Solid products	1	10	0	3	0	14
API (chemicals)	23	10	3	15	1	52
Packaging site, testing labs	1	11	0	0	0	12
Total	55	64	3	21	1	144

Problems experienced in foreign on site inspection

- Discrepancy between Japanese Application file and actual operations in the manufacturing site
- Nonconformity to the Japanese Standards for Biological ingredients

→Insufficient concern of Japanese marketing approval holder in control of manufacturer on foreign site

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Summary and Conclusions

- Overview of the 2005 PAL regulation changes presented.
- Challenges for implementation of the PAL with ICH guideline presented
- Challenges we face are mostly common in all regions. Hope to solve the problems with more work and international collaboration.

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ICH Draft
Supporting documentation

Topic Reference: **Q-IWG on ICH Q8/Q9/Q10**
Subject: **Questions and Answers - Vol 1**

Draft **Step 1, Version 3**
Date: **13.11.08 / after Brussels meeting**

Rapporteur: **Dr. Jean-Louis Robert**

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Table of Contents

1 Introduction

This Questions and Answers document (Q&A) refers to the current working procedure of the ICH Q-IWG on implementing the guidelines of Q8, Q9 and Q10 which have been approved by the ICH Steering committee.

References

ICH Q8	Pharmaceutical Development	approved Nov. 10 2006
ICH Q8(R1)	Pharmaceutical Development – Annex	approved Nov. 13 2008
ICH Q9	Quality Risk Management	approved Nov. 09 2006
ICH Q10	Pharmaceutical Quality Systems	approved Jun. 04 2008

2 Knowledge Management

Q01: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?

Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'.

Knowledge Management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information (e.g. QbD, real time data generation and monitoring systems) will need to be better captured, managed and shared.

In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge, development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.

Q02: Does Q10 suggest an ideal way to manage knowledge?

No. Q10 does not explain how to implement knowledge management. Each company decides how to implement knowledge management, including the depth and extent of information assessment.

Q03: What are potential sources of information for Knowledge Management?

Q10 includes some examples of knowledge sources [see ICH Q10, section 1.6.1]:

- Prior knowledge
- Pharmaceutical development studies
- Technology transfer activities
- Process validation studies
- Manufacturing experience
- Innovation
- Continual improvement
- Change management activities.

Additional examples of potential sources of knowledge are

- Stability reports
- Product Quality Reviews/Annual Product Reviews
- Complaint Reports
- Adverse event reports (Patient safety)
- Deviation Reports, Recall Information
- CAPA reports
- Suppliers and Contractors
- Product history of manufacturing history
- Ongoing manufacturing processes information (e.g. trends)

Information from the above can be shared across a site or company, between companies and suppliers /contractors, products and across different disciplines (e.g. development, manufacturing, engineering, quality units).