Revision of the Quality Regulation

1. MAH's* responsibility for the quality management * Marketing Authorization Holder
2. Approval Matters Requirements Change
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

4. Consolidation of the Legal Positioning of GMP

- **Became a <u>requirement</u> for product approval**
- GMP inspection **<u>prior to approval</u>**, and periodical GMP inspection in post-marketing phase
- GMP inspection **<u>at the time of application</u> for partial change of the approval matters**
- GMP inspection **<u>at foreign sites</u>**

Revision of the Quality Regulation

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5. Revision and Consolidation of GMP Standards

- Revised Pharmaceutical Affairs Law (passed July 2002, Effective April 2005)
- MHLW Ministerial Ordinance No. 179 on GMP (published December 2004)
- Notification on GMP (March 30, 2005) – "Instructions to inspection body RE the Ministerial Ordinance, revision of Validation standards"

Major Changes:

Content of Approval Letters (Manufacturing Processes, Container Closure etc)-define where GMP applies "legally"

Change control and Deviation control

Perceived Problems

- Superficial approaches to GMP -non validated procedures, little connection with QC results, procedures override science
- Regulations might not encourage good practices
- Poor communication between R&D and Manufacturing Plant
- Poor development and or change control of manufacturing
- Detail GMP related guidance and inspection manuals are NOT readily available in Japan

GMP related guidelines

- **Product GMP Guideline**: Level is similar to ICH Q7A, with emphasis of Periodical Quality Review Technology Transfer, Process Validation Strategy, and Site Qualification of Pharmacopoeia Tests
- **Technology Transfer Guideline**: R&D responsibility and on Study Report ←ICH Q8
- **Laboratory Control Guideline**

The guidelines are posted at NIHS web site.

Challenges

- Training for reviewers and inspectors on process/manufacturing sciences

- Industry side

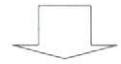
•Reluctant or unable to give a complete story

•Regulatory personnel training

•Superficial development (meeting specs is all)

Establishment of Pharmaceuticals and Medical Devises Agency (PMDA)

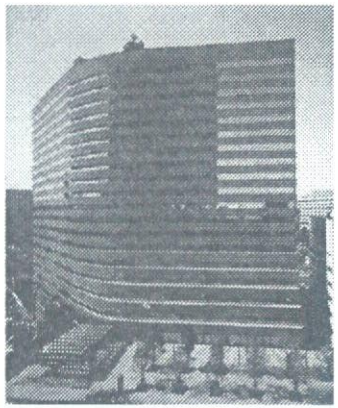
- Integration of review division, safety information management division, and GMP inspection division
- Strengthening resources for review and inspection
- Established in April 2004



✧ Efficient review system

✧ More emphasis on pharmaceuticals with high risks

Introduction of PMDA



- **PMDA**

  New Office:6th-10th FLOOR

The Feature of PMDA

- Effective operation under **"Mid-term Plan"** for 5 years' activities
- Subject to regular evaluation of performance by Independent **" Administrative Agency Evaluation Committee"**
- Financial resources are consist of
  - **User fee** (Review and inspection)
  - **Contribution Funds** (Post-marketing, Relief)
  - **National Budget**

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Establishing the PMDA

OPSR/KIKO
Equivalency Review, Clinical trial consultation, compliance audit, safety information (Drug)

PMDEC
Substantial NDA review (excluding the duties of OPSR/KIKO)

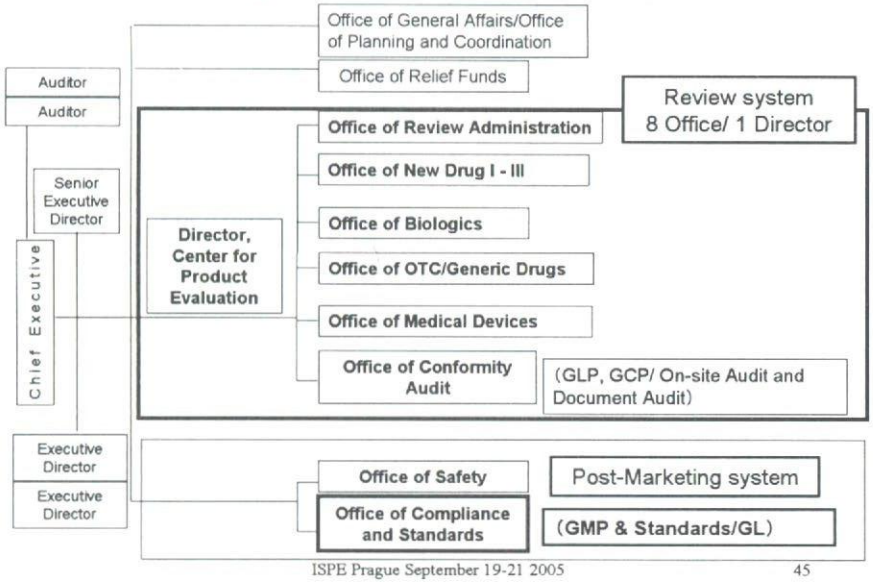
JAAME
Equivalency Review (Device)

Regional Bureau of MHLW
GMP Inspection

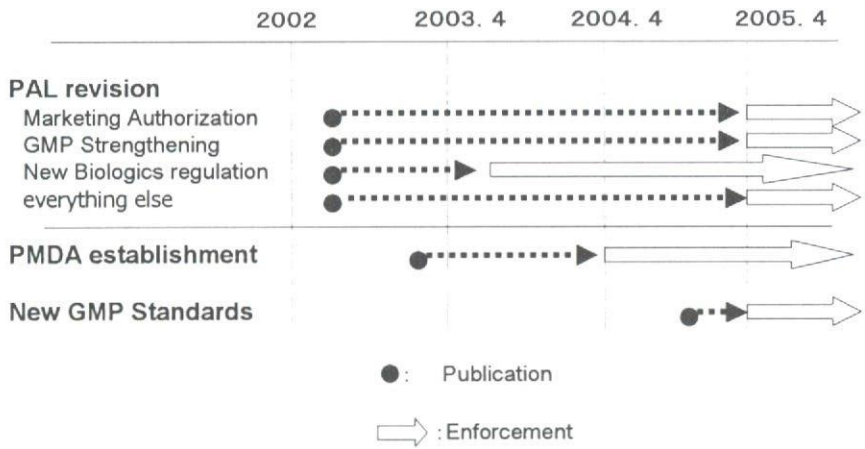
PMDA

Law for the incorporated Administrative agency-Pharmaceuticals and Medical Devices Agency

PMDA Organizational Structure (Outline)



Enforcement of New Regulations

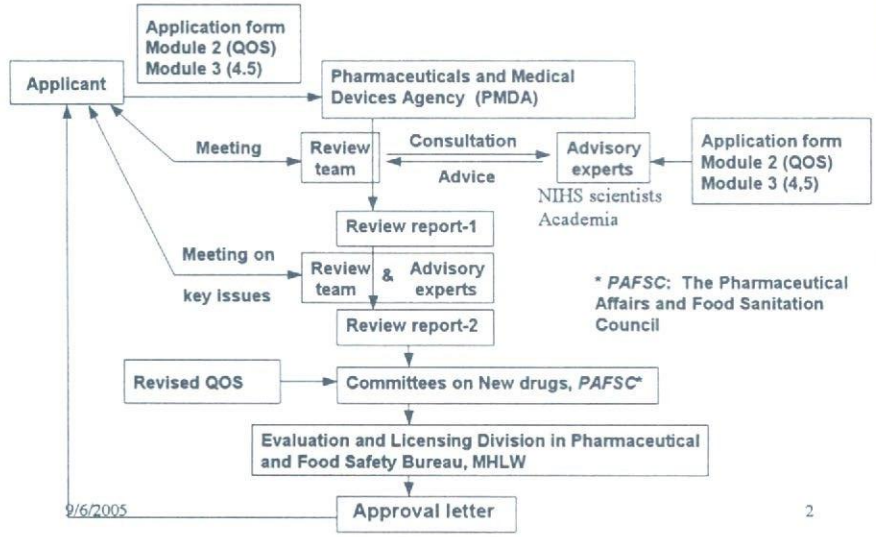


Japanese CMC Review System with the Quality overall Summary

Yukio Hiyama, Ph.D.

Section Chief, Division of Drugs, National Institute of Health Sciences, Ministry of Health, Labour and Welfare, JAPAN

Flowchart of Reviewing Process



Ensure Product Quality and Consistency

- Thorough product characterization during development (*including manufacturing process)
- Appropriate specifications
- Adherence to GMP;

  suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing
  FROM ICH Q6A &B

Quality (CMC) Review Areas

Risk Evaluation Phase:Identify basis for Quality

- Design and establishment of product
- Design and establishment of process and quality control of drug substance and products

Risk Control Phase:

- Commitment of control methods of process and quality control of drug substance and products

(This phase was NOT well reviewed in Japan for system reasons before April 2005)

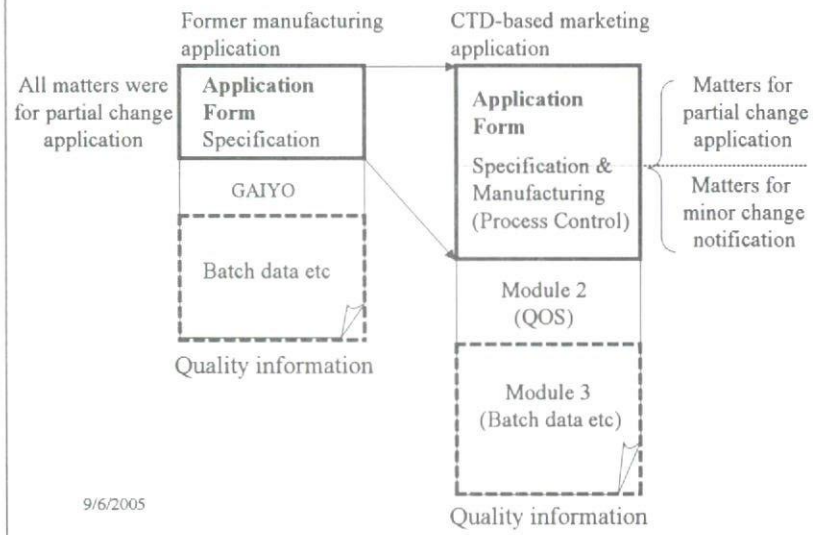
Basis for Quality(CMC) Review

- ICH Guidelines are the basis for NDA review.
  - PMDA has a CTD-based GRP(Good Review Practices).
- There are some domestic guides for those not covered by ICH Guidelines.
- The Japanese Pharmacopoeia (JP) is also the basis for setting specifications and acceptance criteria of drug substances and drug products.
  - "General methods described in the JP, and internationally harmonized methods are considered to be validated."

Basis for Quality Review

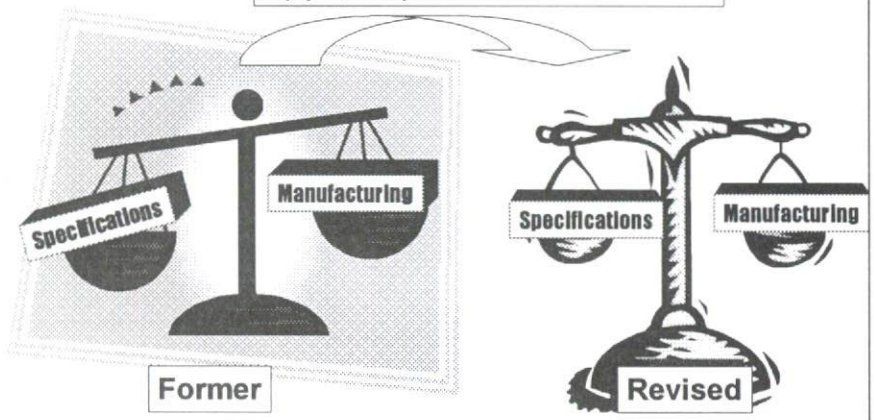
- ICH Q8 concept (minimum; identify risk, additional; Design Space) may be used to classify approval matters in the manufacturing process.

Comparison of Application Forms before and after the Revision



Balance between "Specification" and "Control of Manufacturing"

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



Comparison of Purposes of QOS between EU/USA and Japan

EU/USA	Japan
➢ Considered as a summary; not reviewed; not used as the basis for approval decision • Used as an introduction to Module 3 • Module 3 is reviewed and serves as the basis for assessment report . • EU: can be used as a frame for drafting assessment report.	➢ QOS is main review document. • Applicants are expected to summarize critical data in module 3 into QOS, along with a sufficient discussion on every critical point for ensuring the quality, efficacy and safety of the drug. • QOS makes it possible for reviewers to understand the characteristics of the drug within a short time, and to review the NDA application efficiently.

Characteristics of Japanese QOS

- Within CTD guideline
- Include many figures and tables which summarize critical data
- Include narrative summary and/or discussion on data
- Should be written in Japanese :Tables & Figures may be in English

QOS is main Document for Reviewing NDA in Japan

1. **Expert team in PMDA reviews NDA application using module 2 (QOS) as main review document and referring to module 3, and prepares a review report.**
2. **(Final)QOS and review report are submitted to the Committees on new drugs in the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).**
3. **The committee members discuss quality, efficacy and safety of the drug based on the review report and QOS. (Usually, the committee members do not review module 3.)**
4. **The opinion of the committee is sent to MHLW together with the review report, then the Minister of Health, Labor and Welfare grants the new drug approval to the applicant.**

Requirements for Mockup of QOS

Preparation of Mockup of Module 2 (QOS)

What to describe?
How to describe?

Former NDA Dossier

1) Determination of structure
2) Physicochemical properties
3) Manufacturing process (brief outline)
4) Specifications and test methods
5) Stability: stress test, accelerated test, long-term test

CTD-based NDA Dossier

3.2.S.2 (P.2) Manufacture
3.2.S.6 (P.7) Container closure system
3.2.P.2 Pharmaceutical development
3.2.P.4 Control of excipients

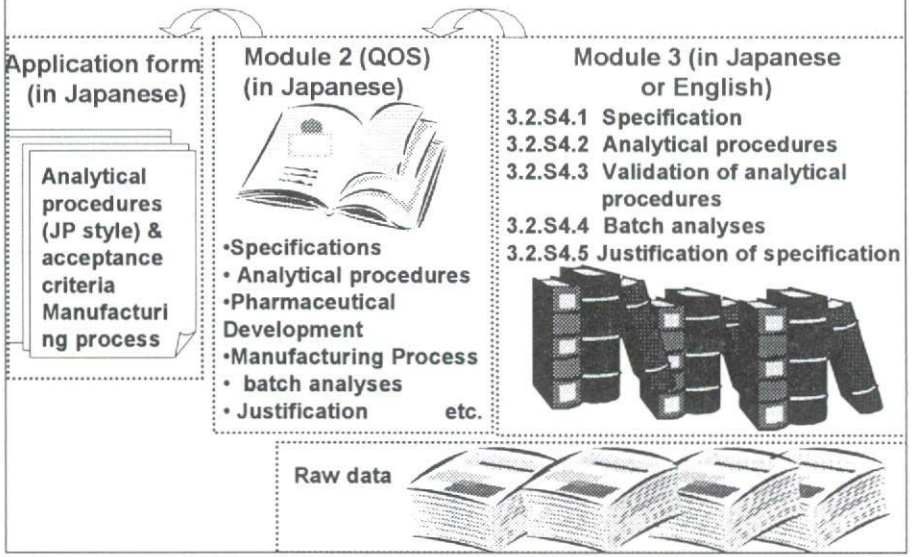
3.2.S.1 General information
3.2.S.3 Characterization
3.2.S.4 (P.5) Control of drug substances (products)
3.2.S.5 (P.6) Reference standards or materials

3.2.S.7 (P.8) Stability

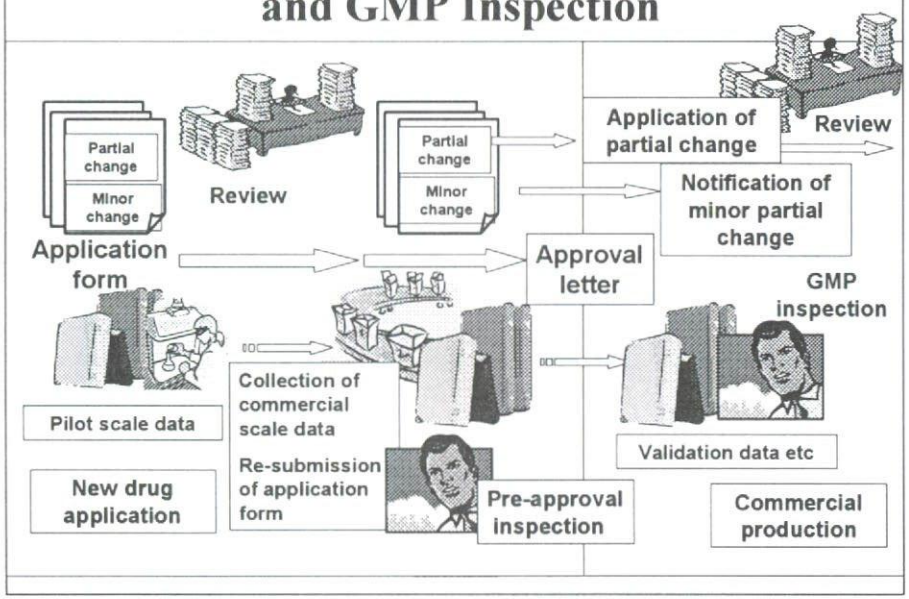
Mockup of Japanese QOS

- 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.

Relationship between Application Form and CTD Documents



Revised Framework for Review and GMP Inspection



Benefits from comprehensive QoS

- Writing Japanese style QoS takes significant time and energy. BUT it helps the applicant organizations to understand own product and process consistently
- QoS can be a vehicle for knowledge management in regulatory authorities and in industry

AAPS Workshop on Pharmaceutical Quality Assessment -
A Science and Risk-Based CMC Approach in the 21st Century

Co-sponsored with ISPE & FDA
October 6, 2005

Breakout Session G: QOS

Can QOS be used as an effective review tool?

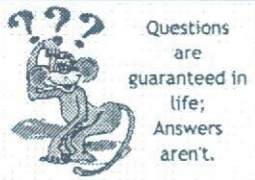
Moderators:

Gary Condran, Health Canada
Yukio Hiyama, MHLW, Japan
Norman Schmuff, US FDA
Richard Poska, Abbott

Breakout Session Outline

- Issues Discussed
- Shared Understanding & Agreements
- Remaining Challenges
- Recommendations
  - Strategies to implement agreed-upon issues
  - Proposals to resolve remaining challenges

Issues Discussed



- What are the pros and cons of the different QOS models? Should QOS be re-examined?
- How could the QOS be repurposed/redefined to be a more useful document for industry and regulatory agencies?
- What are the current challenges in preparing QOSs for global submissions and what challenges can be anticipated in revisiting the document to achieve a better QOS?
- Should a harmonized QOS be an ICH topic?
- Can the QOS be utilized for post-approval changes?

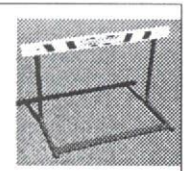
Shared Understanding and Agreements

- QOS should be re-examined
- Industry willing to revisit QOS

Shared Understanding and Agreements

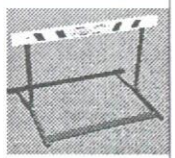
- QOS should be re-examined
  - Regional differences in how QOS is prepared
  - Need for clarification on how QOS will be used
    - Primary Review vs Summary document
    - Current US/EU application of QOS lacks sufficient detail to be primary review document
- Industry willing to revisit QOS
  - Potential benefit is improved CMC review efficiency
  - Prefer single globally accepted QOS model and a single primary review document

Remaining Challenges and Outstanding Issues



- Regional barriers to general submission harmonization
  - E.g. Compendial standards, DMFs, packages
- Clarification of relationship QOS to Module 3
  - Include P2 or not or summarized?
  - How/when/where should design space be captured?
  - QOS should not be a data dump from Module 3
  - Should QOS length be determined by product complexity?

Remaining Challenges and Outstanding Issues

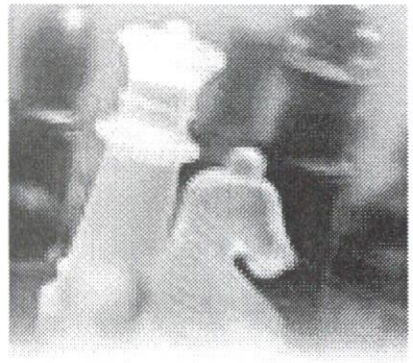


- What constitutes the regulatory agreement and relationship to QOS?
- Is there a potential use of QOS during IND Phases?
- Role in post approval submissions
  - Portions vs. no involvement
  - ICH Q10
- Is QOS a living vs. static document?

Recommendations

Strategies to implement agreed-upon issues

- Further discussion and clarification required for a re-worked QOS
- If there is a decision to revisit QOS, it should be globally harmonized through the ICH process



Recommendations

Proposals to resolve remaining challenges

Work towards
globally harmonized
regulatory review practice &
expectations

Acknowledgement