Global GMP Harmonisation – A Japanese Perspective

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Presentation Key Points

- Changes in Pharmaceutical Affairs Law
- Quality Regulations under the Revised Pharmaceutical Affairs Law
- Commitment of Manufacturing Process as Approval Matters
- Role of ICH Pharmaceutical Development
- Role of the Quality Overall Summary
- GMP Regulations and related Guidelines

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***

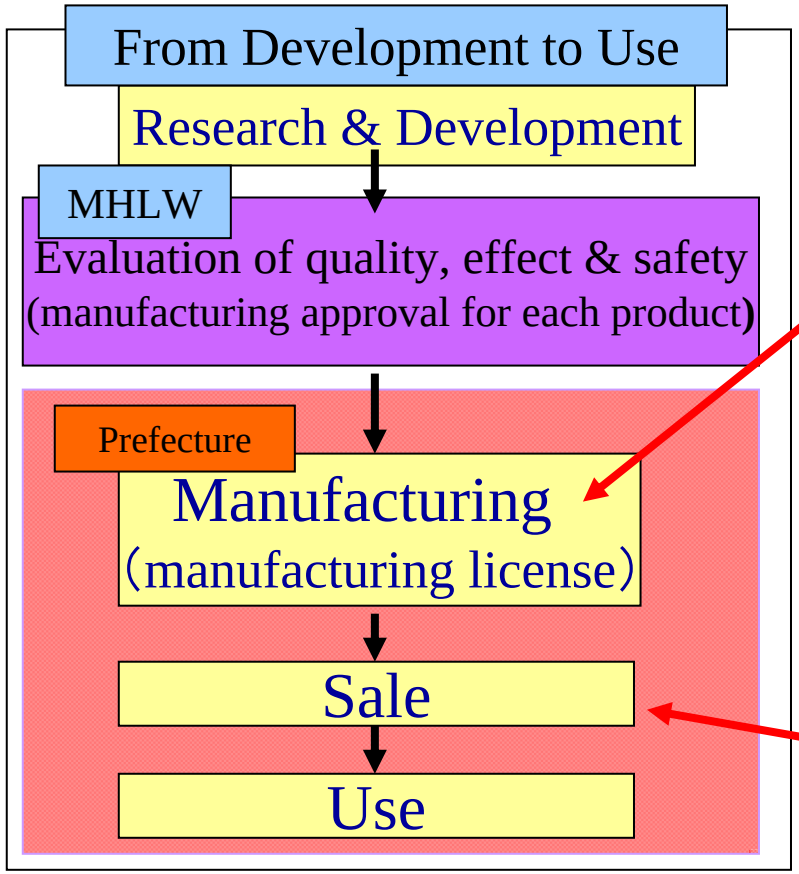
  = To clarify the Market Authorization Holder's (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)

Revision of the Quality Regulation

1. MAH's* responsibility for the Quality management
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

* Marketing Authorization Holder

Revision of approval and license system for pharmaceuticals and medical devices



Attention to manufacturing

Old system

1. Companies are supposed to have their own manufacturing establishment
2. "Approval" is for "manufacturing", not for "marketing" (**Minister manufacturing approval**)
3. Final manufacturing "license" is issued, based on approval. (Mainly **prefectural manufacturing licensing**)

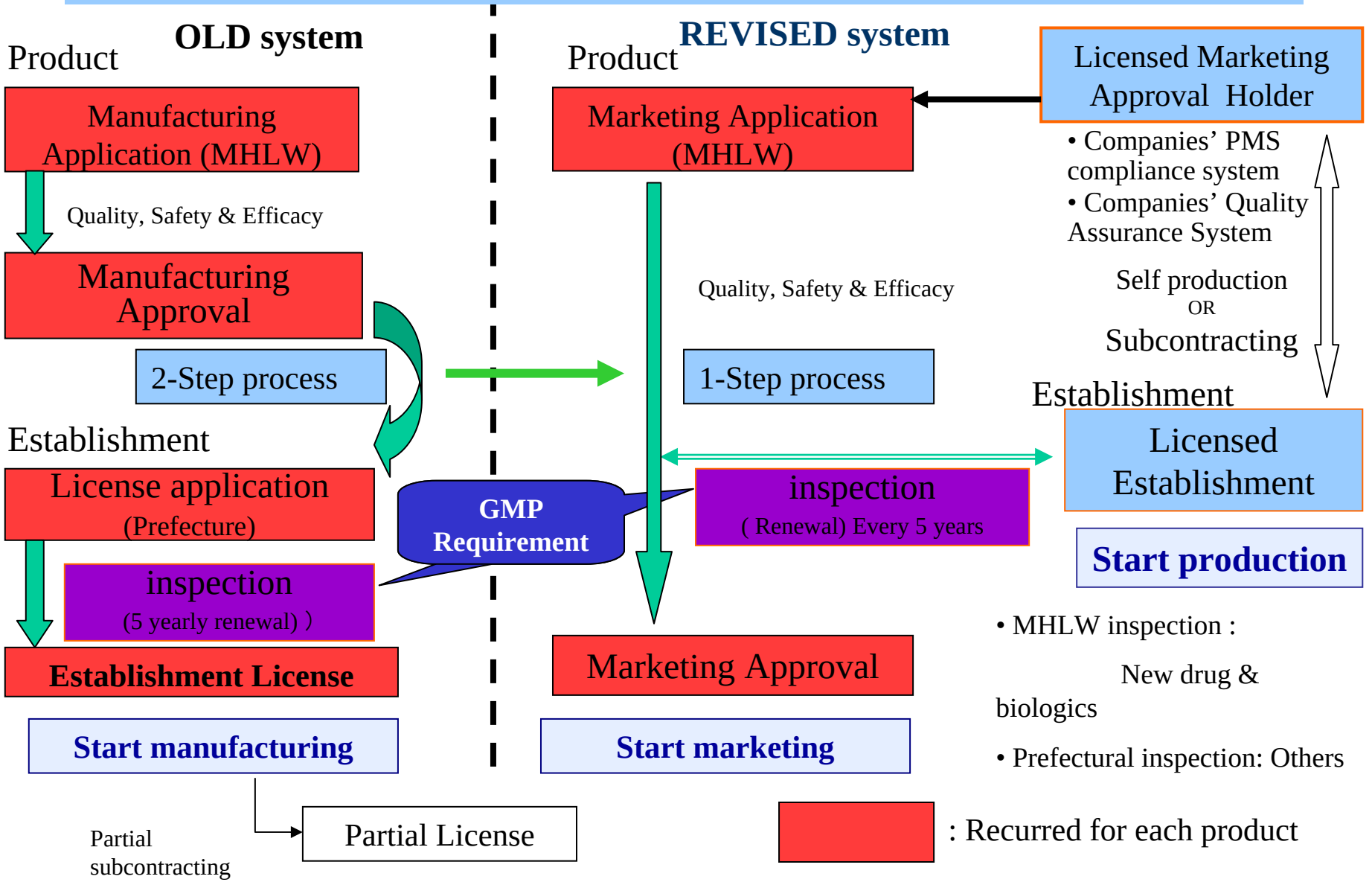
Attention to whole process (from manufacturing to PMS)

New System

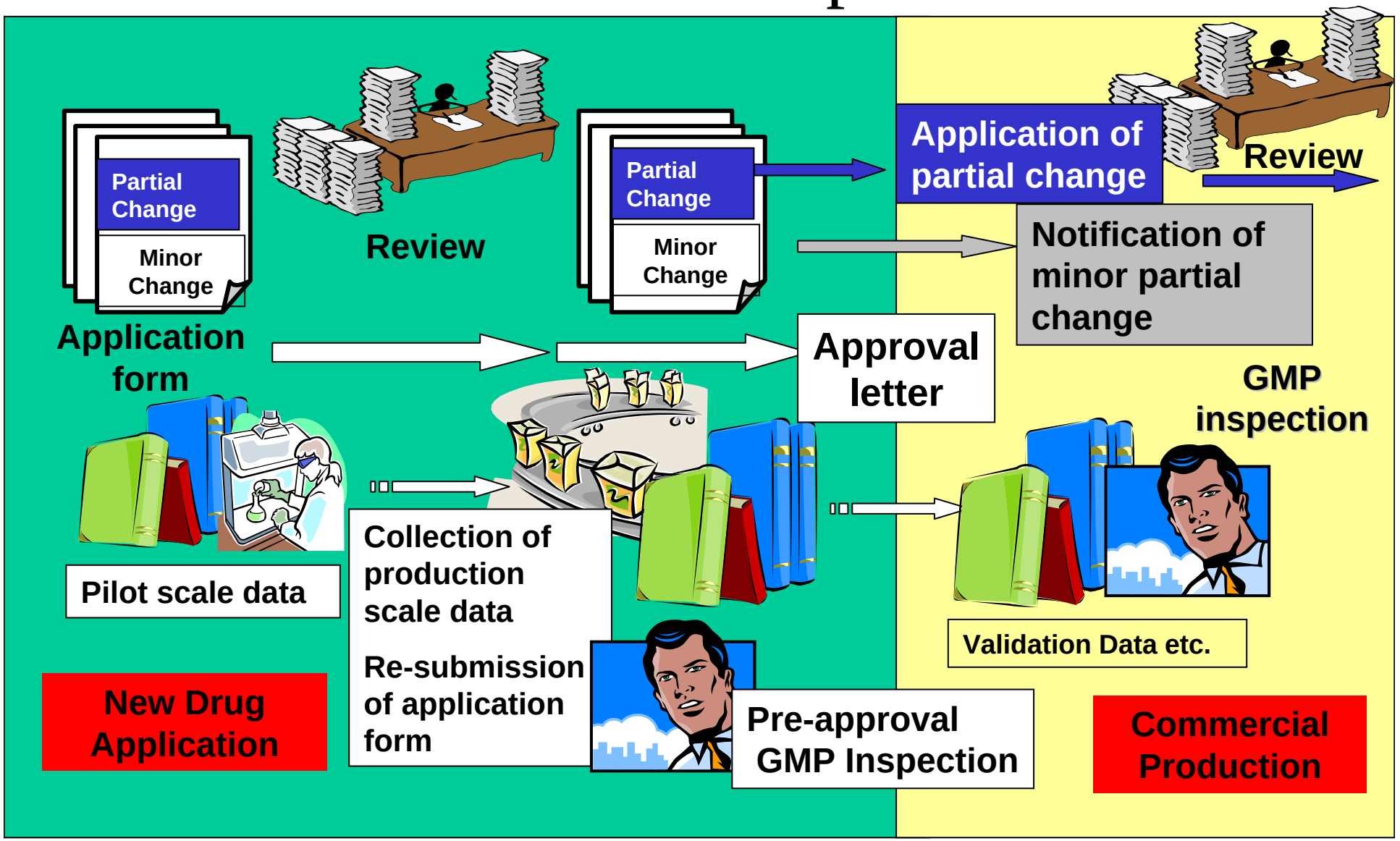
1. Introduction of **"Marketing Approval"** for overall evaluating quality, safety & efficacy and manufacturing for marketing
2. Manufacturing establishment license is separated from product authorisation process, which allows companies to subcontract whole manufacturing process
3. Instead, company's ability of pharmacovigilance is subject to review for Marketing Approval Holder (MAH)

Comparison Flowcharts of Approval and License

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



Framework for Review and Inspection



From Multi sets to One set of regulations

- Previously: No inspections at foreign GMP sites/Under GMPI →Foreign inspections by PMDA
- Previously: Approvals given to API and Product. Only specs are set for API of imported products →Approvals only to products including API specs and manufacturing process
- Previously: Whole Manufacture contracts NOT allowed for domestic industry→ Contracts allowed everyone

Revision of the Quality Regulation

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   *** Marketing Authorization Holder**
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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.

Revision of the Quality Regulation

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2. Application Form and Approval Matters

- 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
- Dosage and administration
- Manufacturing process, including control of materials
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

Approval Letter

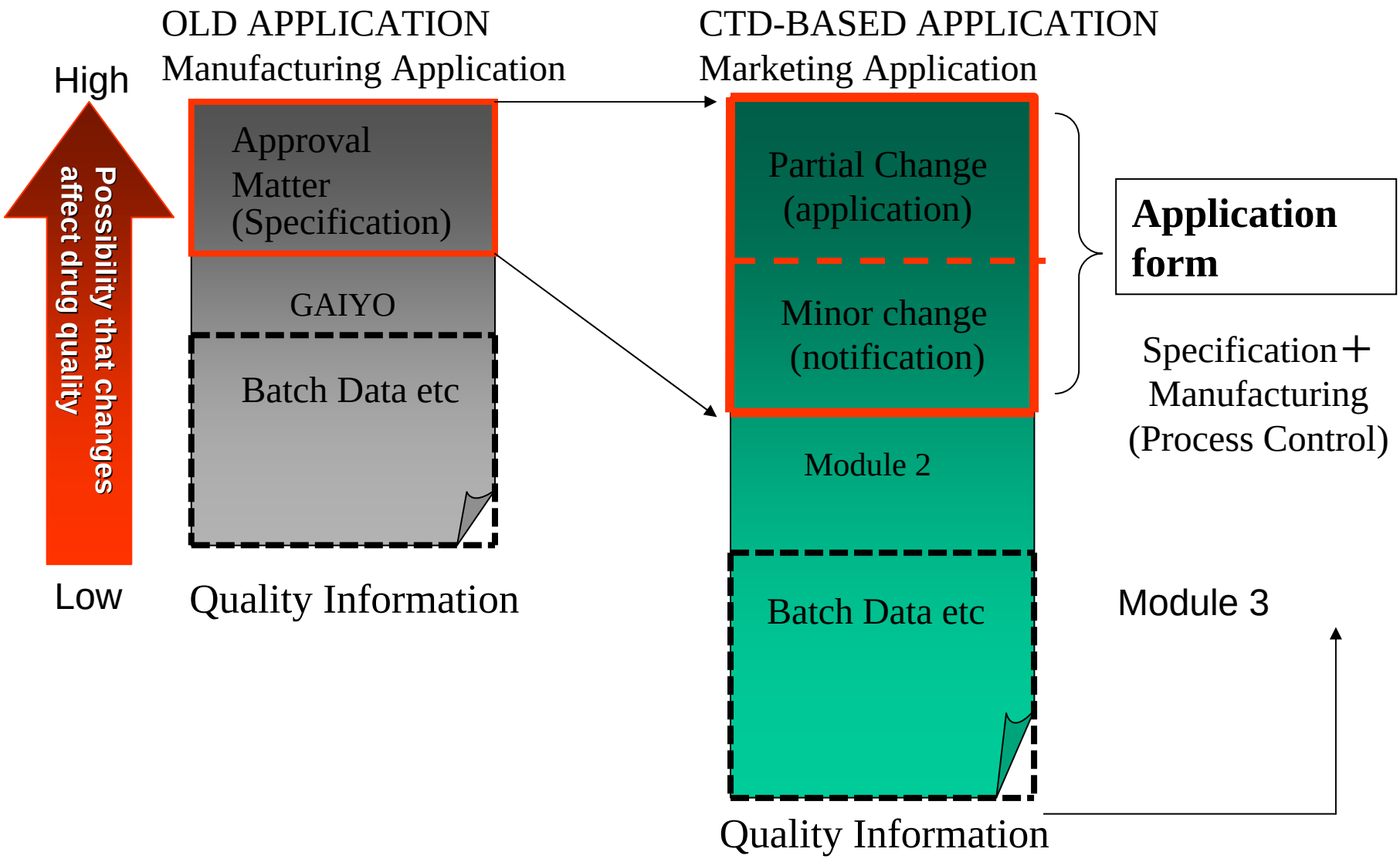
- **No change:**
  - **Approval letter system**
- **Changes:**
  - **From manufacturing approval to marketing approval**
  - **Requirement of detailed description in application form regarding manufacturing process and control**

    Encourage industry to better control quality of products

    Link assessment and inspection
  - **Introduction of a notification system pertaining to minor change**

    Effective regulatory system

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



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.

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

Matter Subject to Approval under Revised Pharmaceutical Affairs Law

(Chemical drug substance and drug product)

- Manufacturing site
- Manufacturing method

  Detailed information about:

  - Manufacturing process and process control
  - Control of material
  - Container-closure system

Matter to Be Described in Application Form -Drug Products-

- **All processes from raw material(s) to packaging process**
  - **A flow diagram of manufacturing process including:**
    - **Raw materials**
    - **Charge-in amount**
    - **Yield**
    - **Solvent**
    - **Intermediate materials**
    - **Process parameter (e.g. Target Value and Set Value)**
  - **A narrative description of manufacturing process**

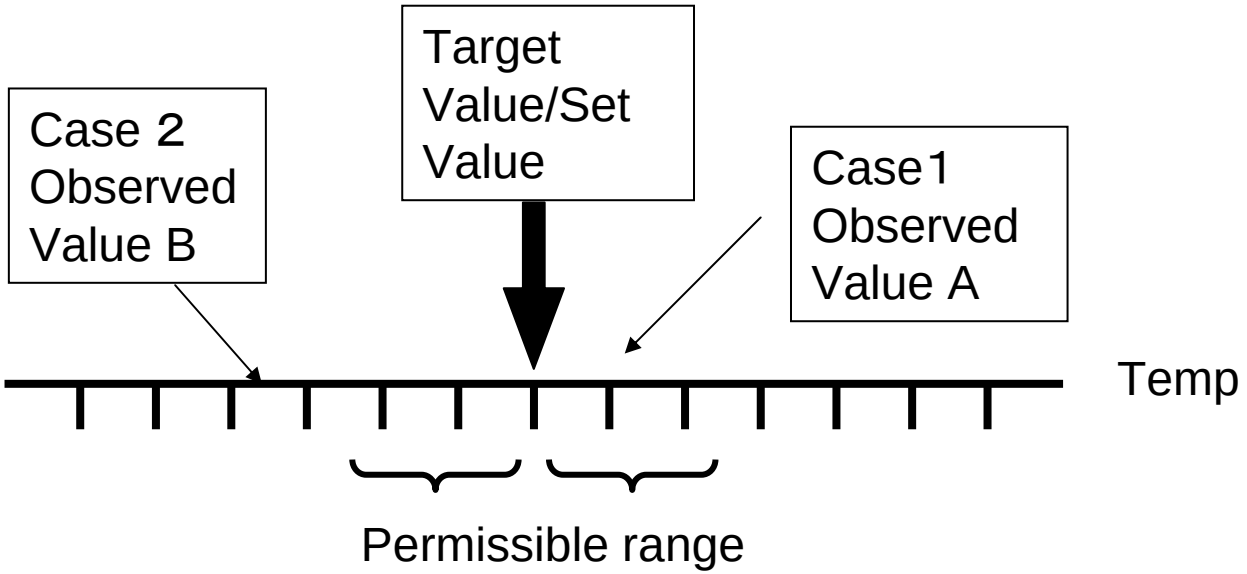
Narrative Description of Manufacturing Process

- Matters needed for assuring the quality consistency should be selected

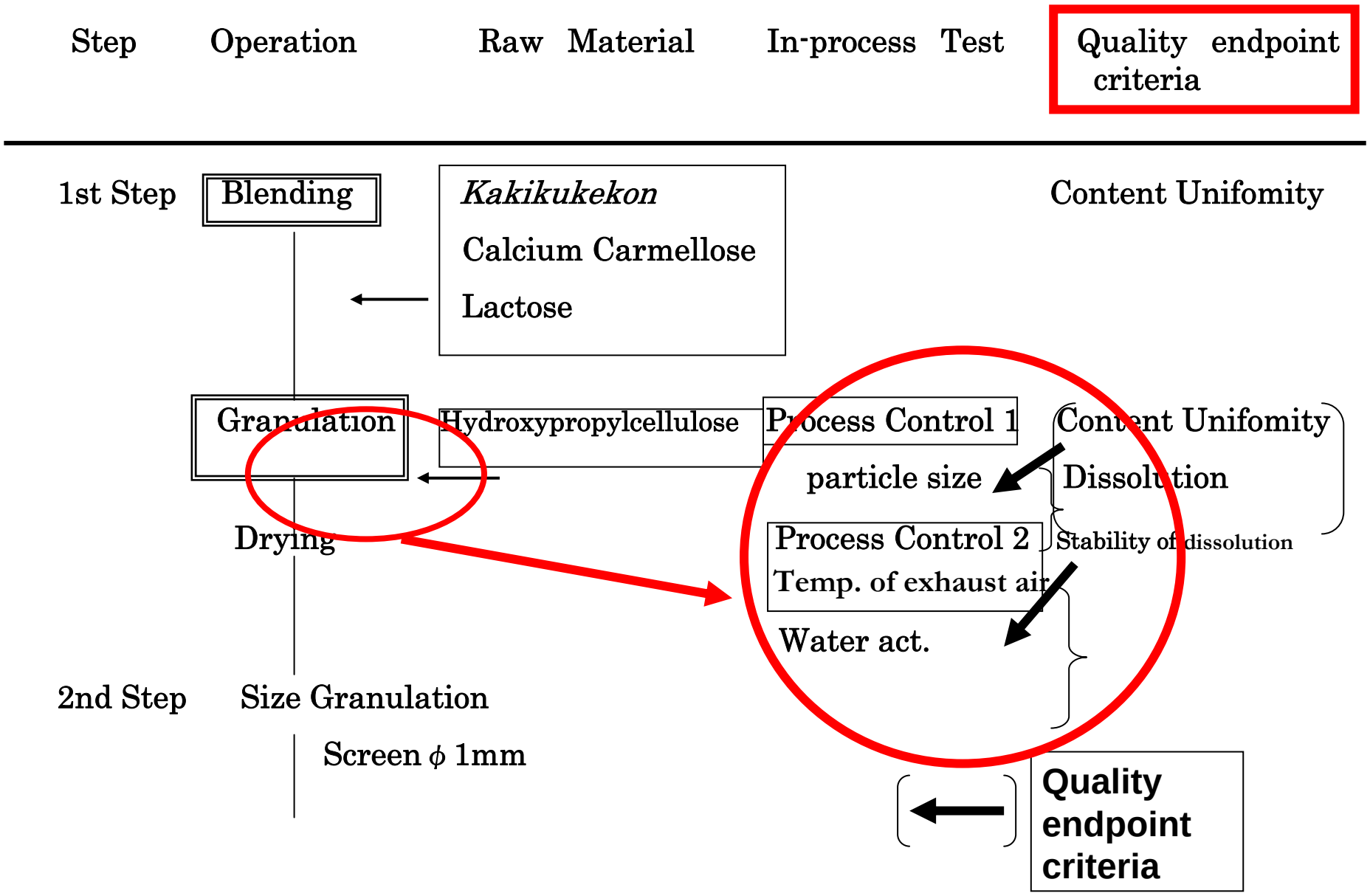
- Quantities of raw materials, critical processes, process control, equipment, process parameter (speed, time, temp., pressure, pH, etc)
- Test and acceptance criteria of critical step and intermediate
- Identity and specification of primary packaging material (or manufacturer and type number of the packaging material)

Target Value and Set Value

- **In cases where target value/set value are set:**
  - **Permissible range of target value/set value must be described on the master production documents or SOPs.**
- **Case 2:**
  - **The suitability of product should be judged based on GMP.**



Flow Diagram of Manufacturing process (Tablet)



Distinctions between Partial Change Approval Application and Minor Change Notification

Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

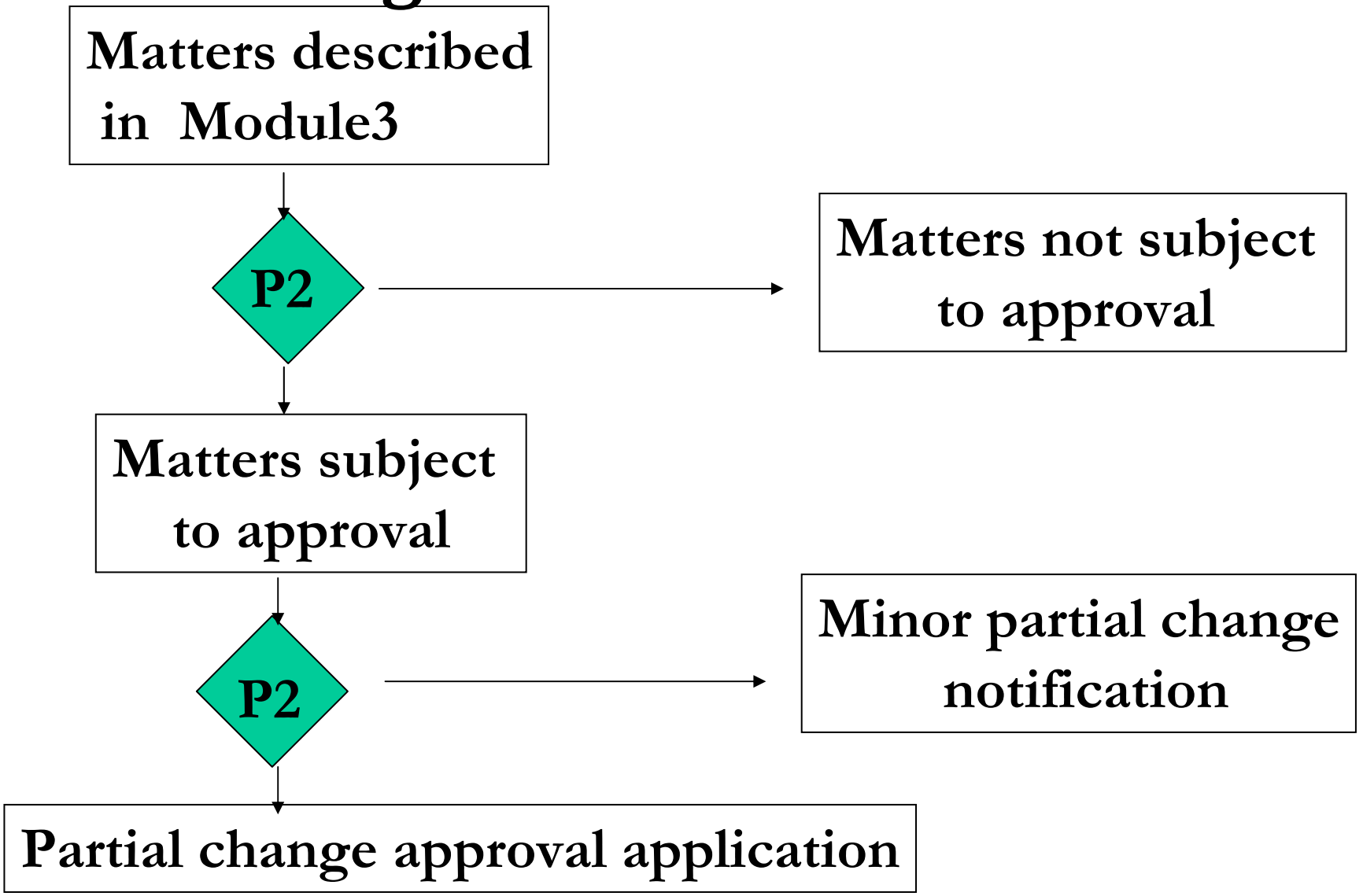
Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - In that case, the evaluation methods which was approved at the time of previous submission might be invalidated.
- Change in materials of primary packaging component
- Change in matters for aseptic manufacturing
- Change in specification of intermediate product in case that the test is performed instead of release test of final drug product

The Role of P2 Document in Reviewing New Drug Application (NDA) under Revised Pharmaceutical Affairs Law (PAL)

Some matters are subject to application of partial change, based on the information described in P2.

The Role of P2 document in reviewing NDA under revised PAL



The new requirement regarding the approval letter is applicable to:

1. market applications after April 2005
2. renewals of existing licenses, which may occur by 2010

for case 2, the manufacturing section of approval letter may be rewritten without review/assessment.

For most of those approvals, CTD information was NOT submitted (did not exist).

Opportunities by ICH CTD based application

- Complete description of product specific quality system
- Better knowledge transfer tool within the sponsor organization, between industry and regulator, and within the regulator organizations---QoS:Module 2 plays important roles
- ICH Pharmaceutical Development Q 8 (step 2 in Yokohama)

Role of Module 2 in Japan

- Module 2 bridges NDA Application Form 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 format

Application form

Approval Matters

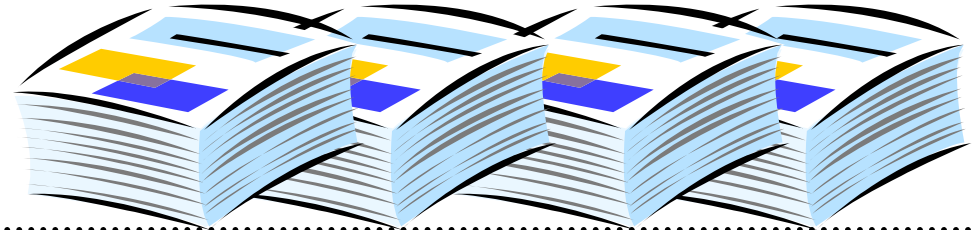
Module 2

- Tabulated summary of specifications
- Analytical procedures
- Tabulated summary of batch analyses
- Justification etc.

Module 3

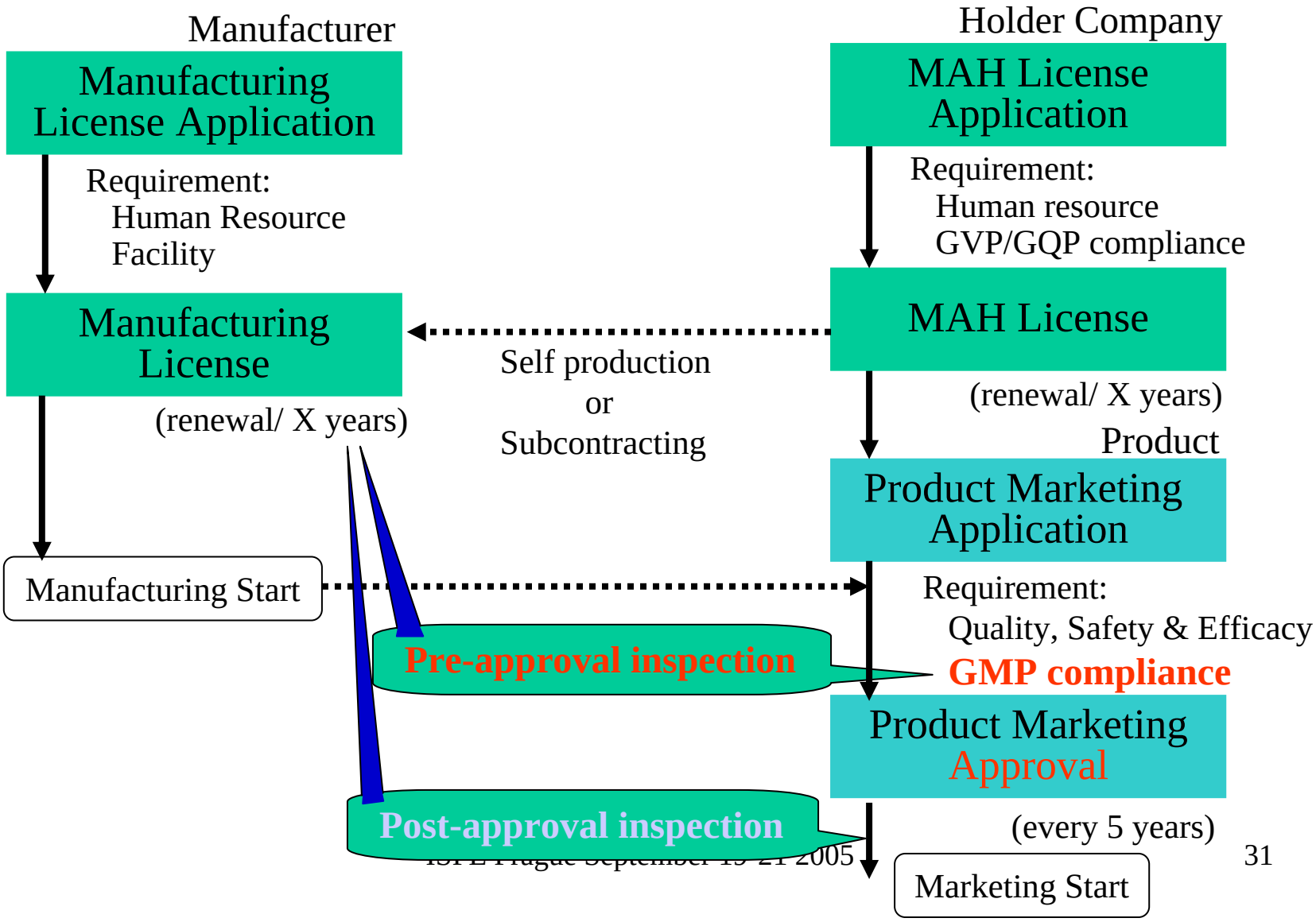
3.2.S4.1 Specification
3.2.S4.2 Analytical Procedures (SOP)
3.2.S4.3 Validation of Analytical Procedures
3.2.S4.4 Batch Analyses
3.2.S4.5 Justification of Specification

Raw data

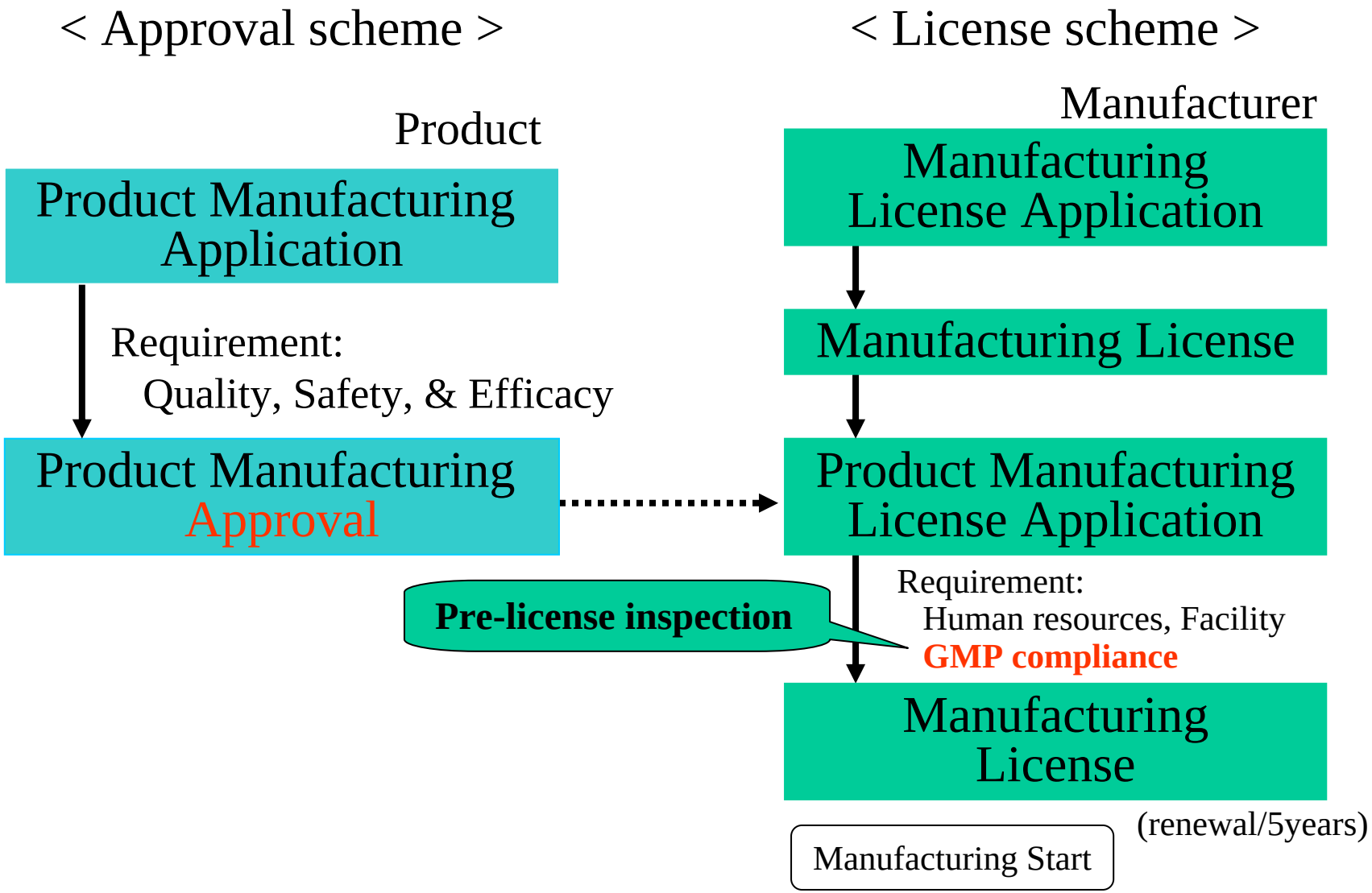


4. Legal position of GMP

Flowchart of Approval and License



Flowchart of Approval and License
(old system)



Revision of the Quality Regulation

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5. Revision and Consolidation of GMP standards

* Marketing Authorization Holder

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 of the approval matters**
- GMP inspection **at foreign sites**

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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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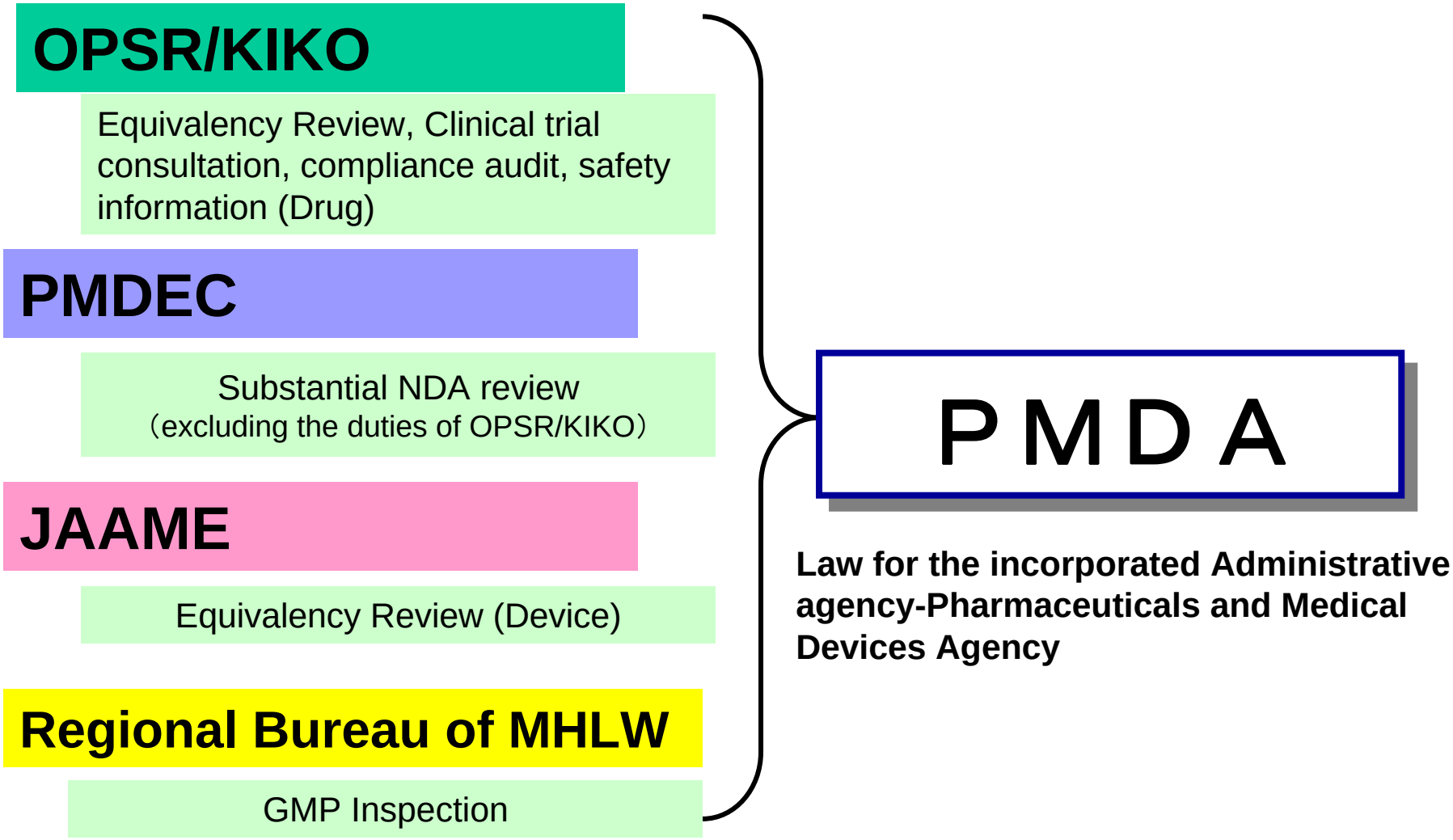
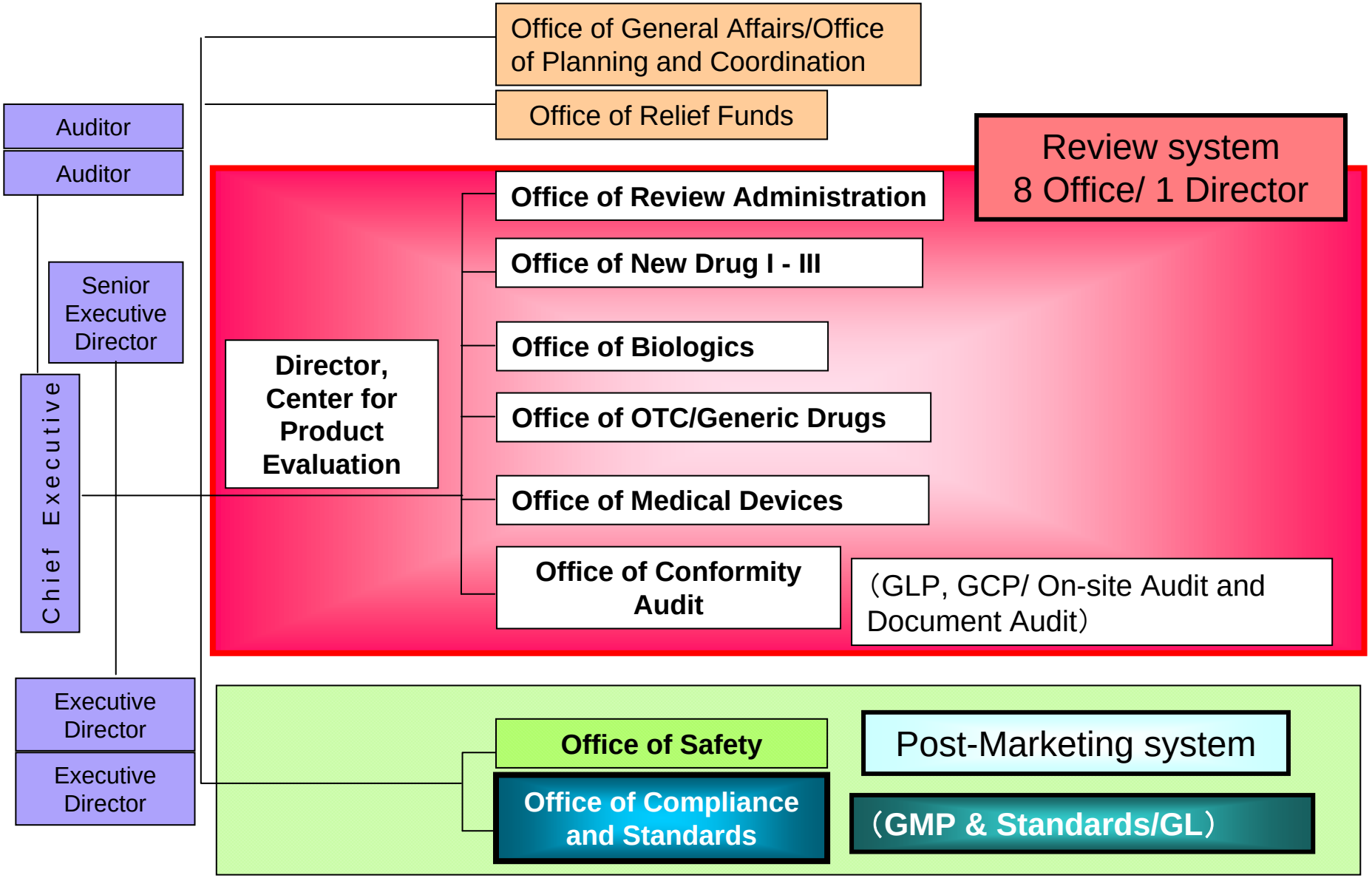
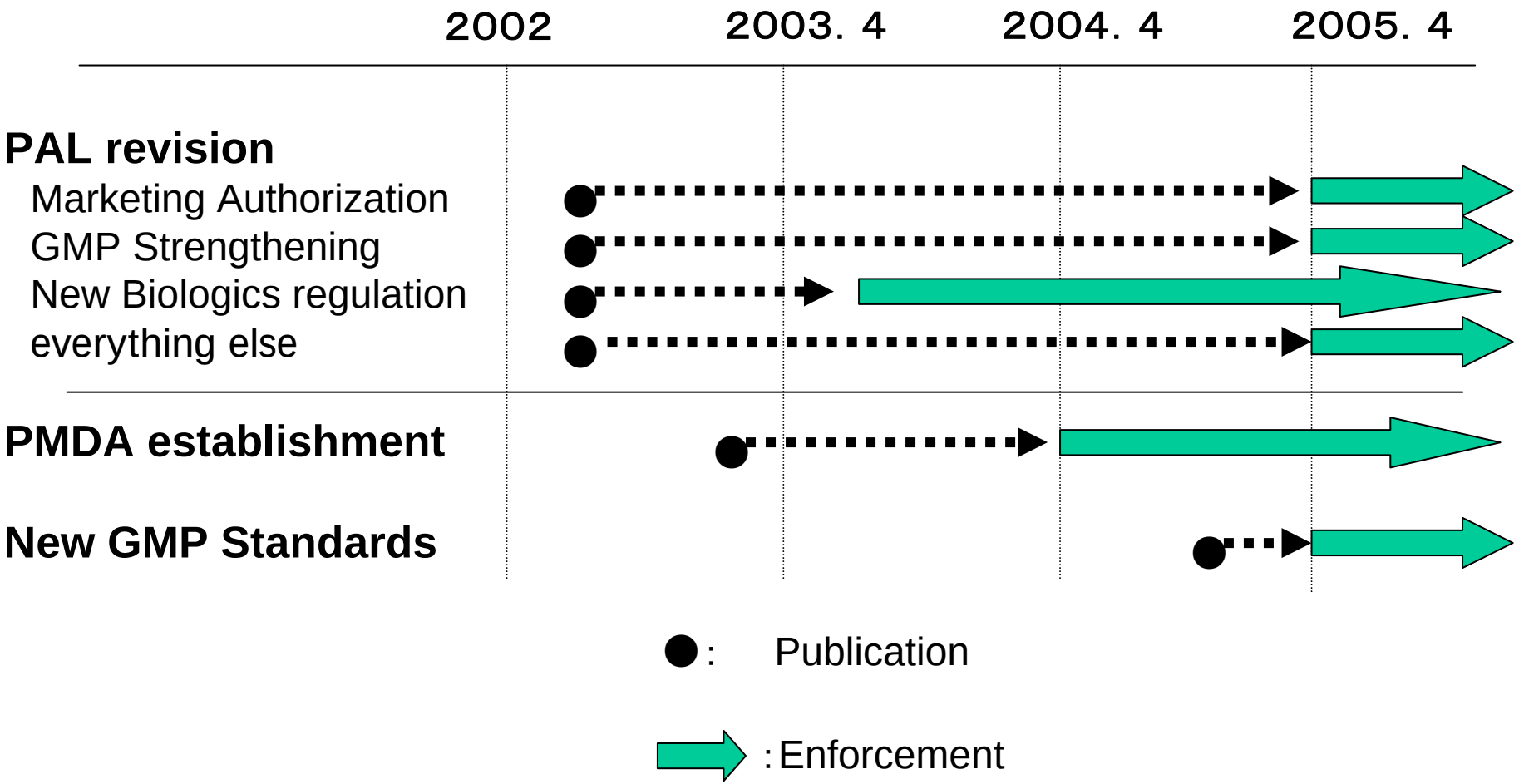
Establishing the PMDA



PMDA Organizational Structure（Outline）



Enforcement of New Regulations



Japanese CMC Review System with the Quality overall Summary

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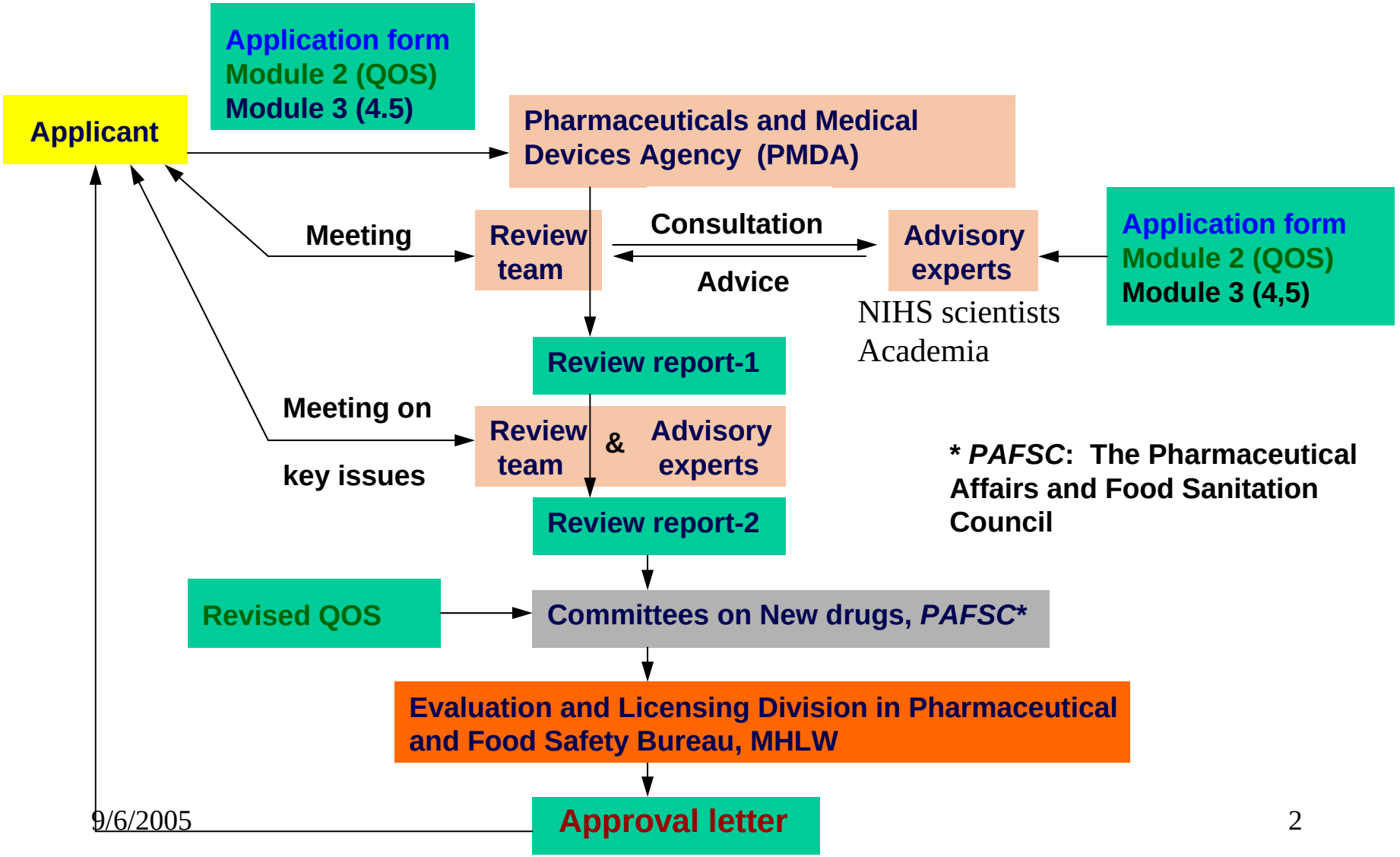
Flowchart of Reviewing Process



* *PAFSC*: The Pharmaceutical Affairs and Food Sanitation Council

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)

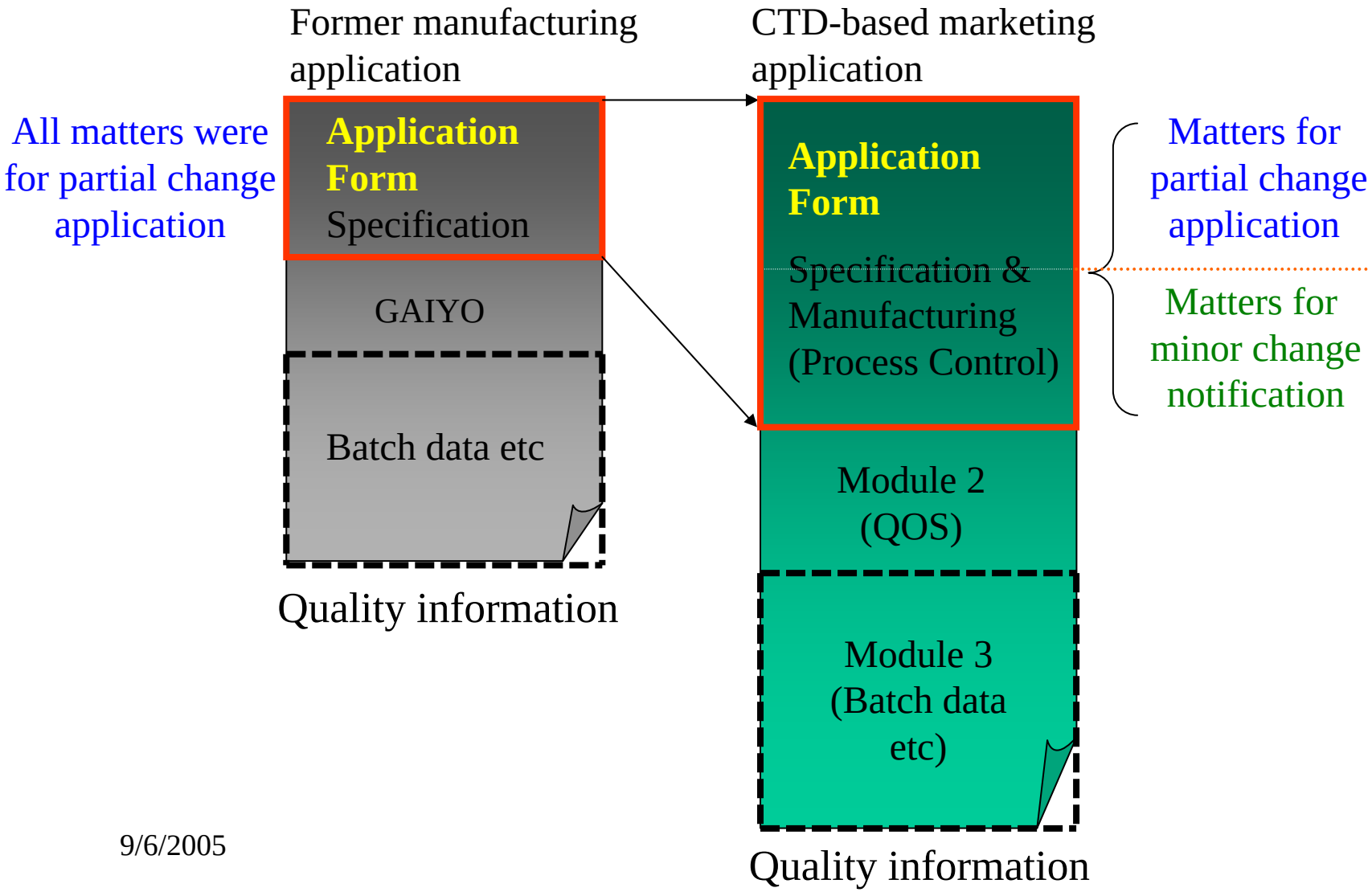
Basis for Quality(CMC) Review

- 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

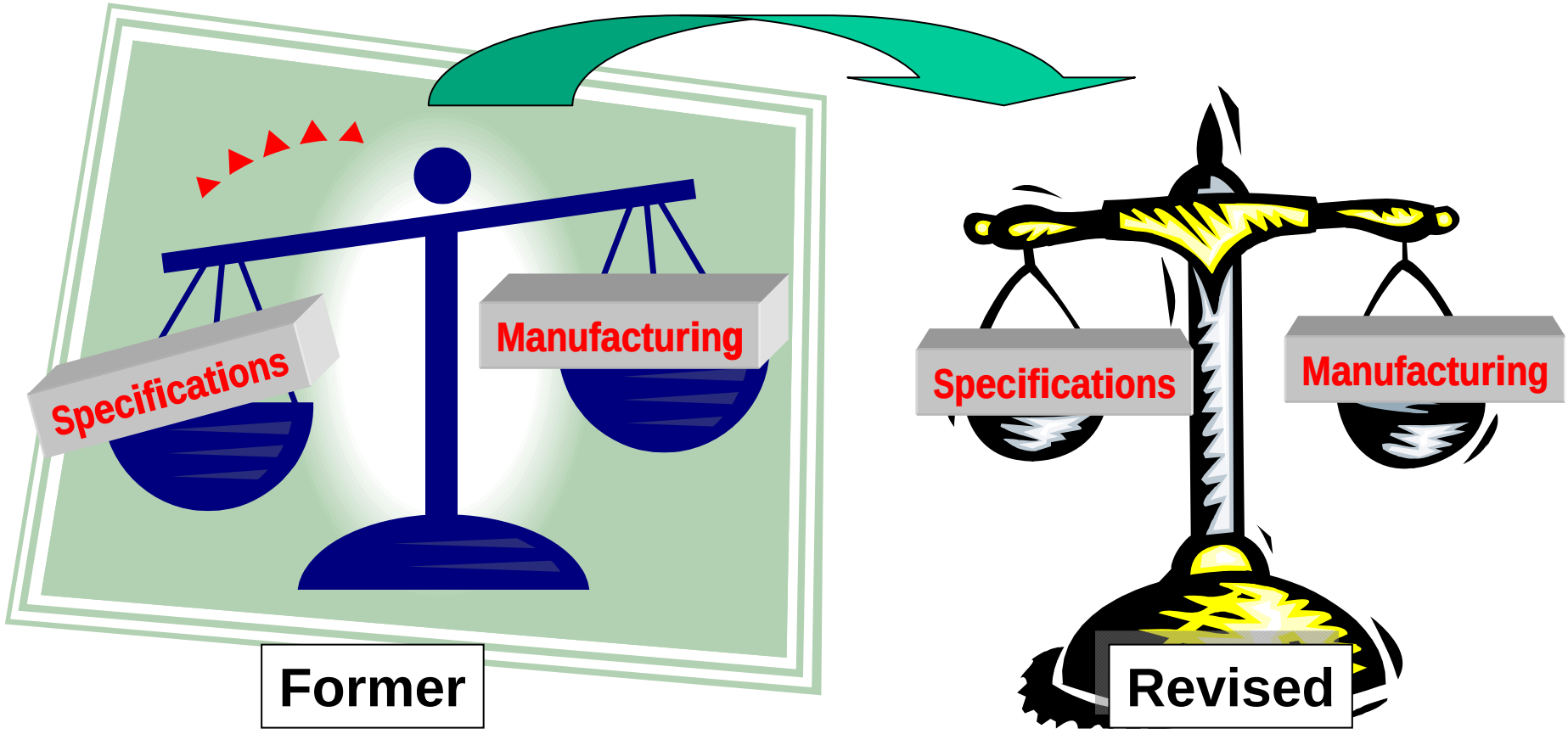
- ICH Q8 concept (minimum; identify risk, additional; Design Space) may be used to classify approval matters in the manufacturing process.

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

- **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.**

Japan

- **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?

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

Former 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

CTD-based NDA Dossier

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.

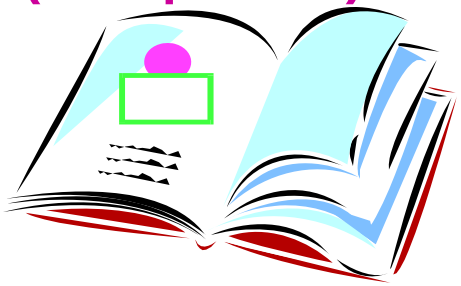
Relationship between Application Form and CTD Documents

Application form (in Japanese)

Analytical procedures (JP style) & acceptance criteria

Manufacturing process

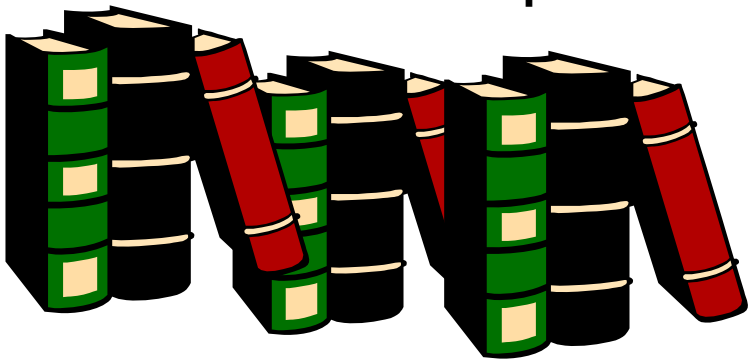
Module 2 (QOS) (in Japanese)



- 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



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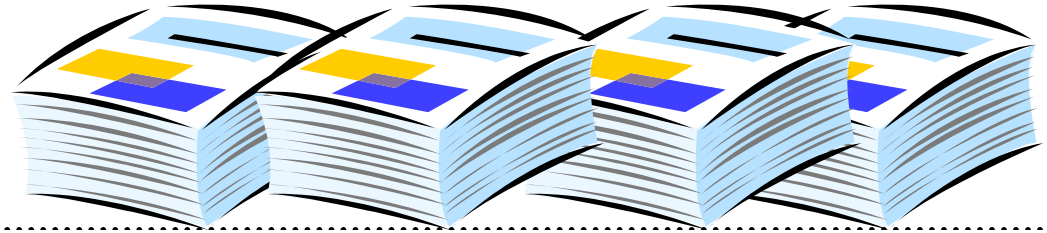
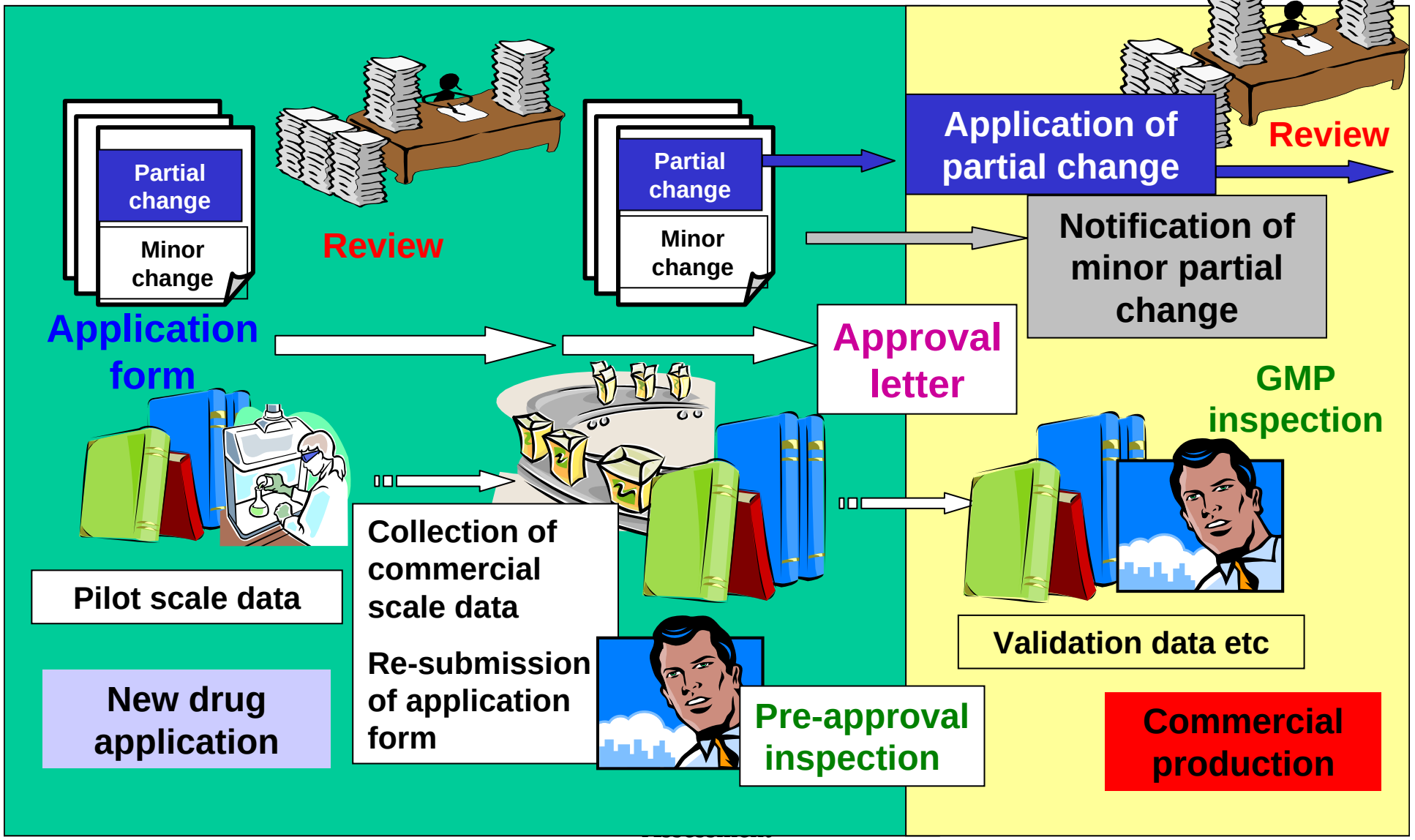


Revised Framework for Review and GMP Inspection



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

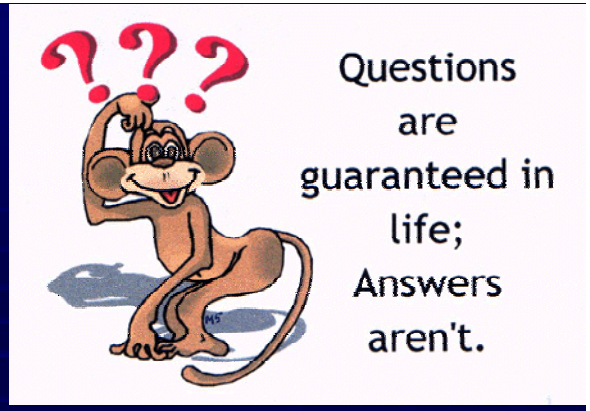
Norman Schmuff, US FDA

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