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Post-Approval Changes of Biologicals in Japan: CMC

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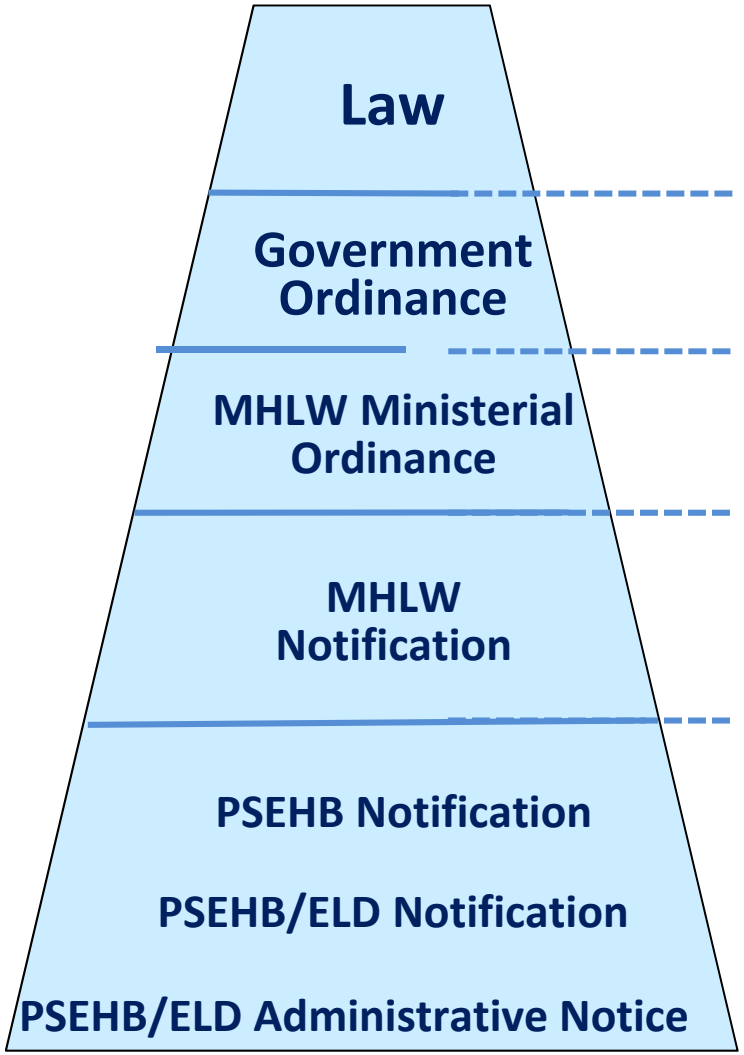
The views and opinions expressed in this presentation are those of the presenter

Outline

- **Regulatory Framework of Common Technical Document**
- **Regulatory Pathway for Post Approval Changes**
- *...and* Future

Regulatory Framework in Japan

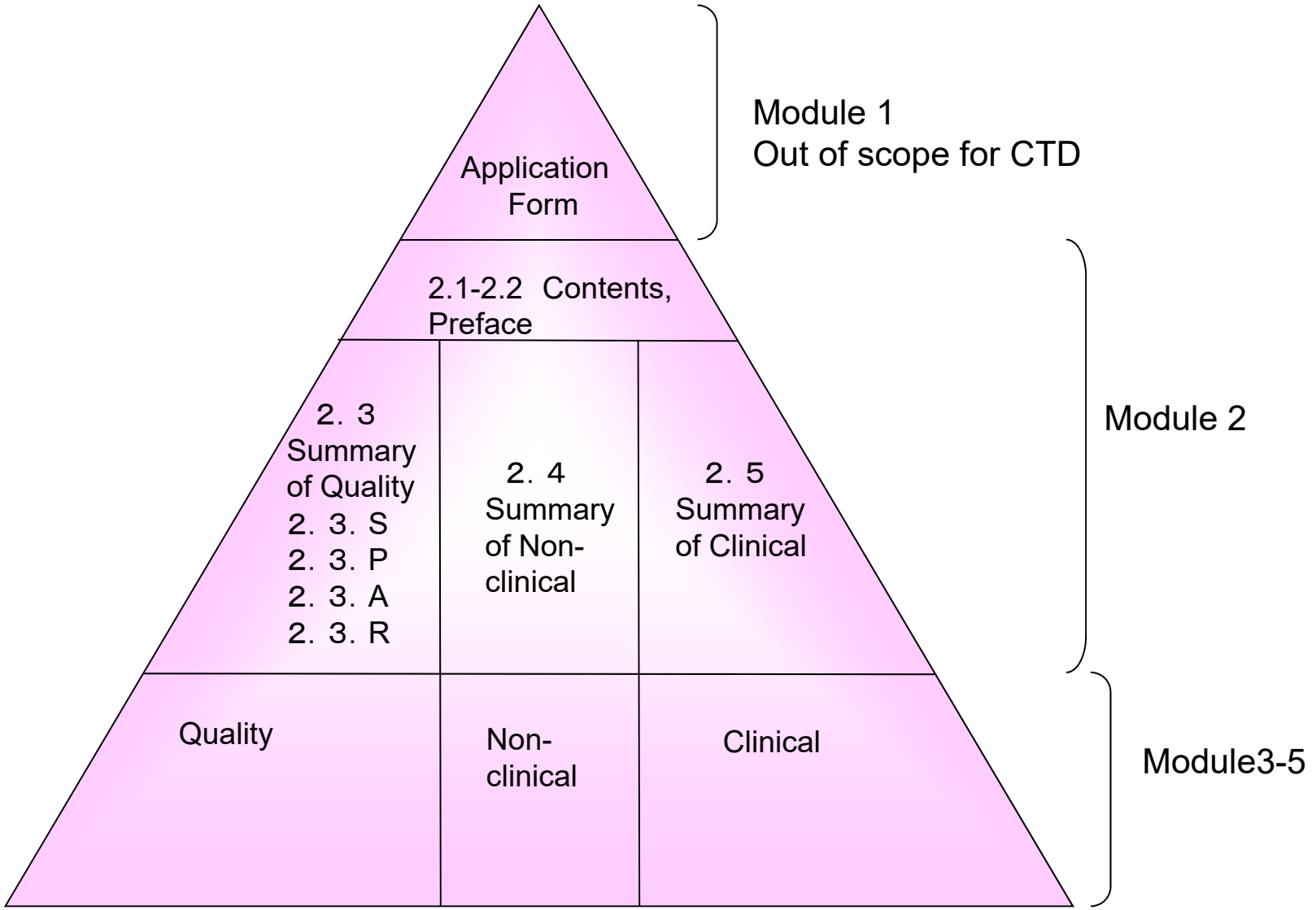
-Focus on biologics CMC-



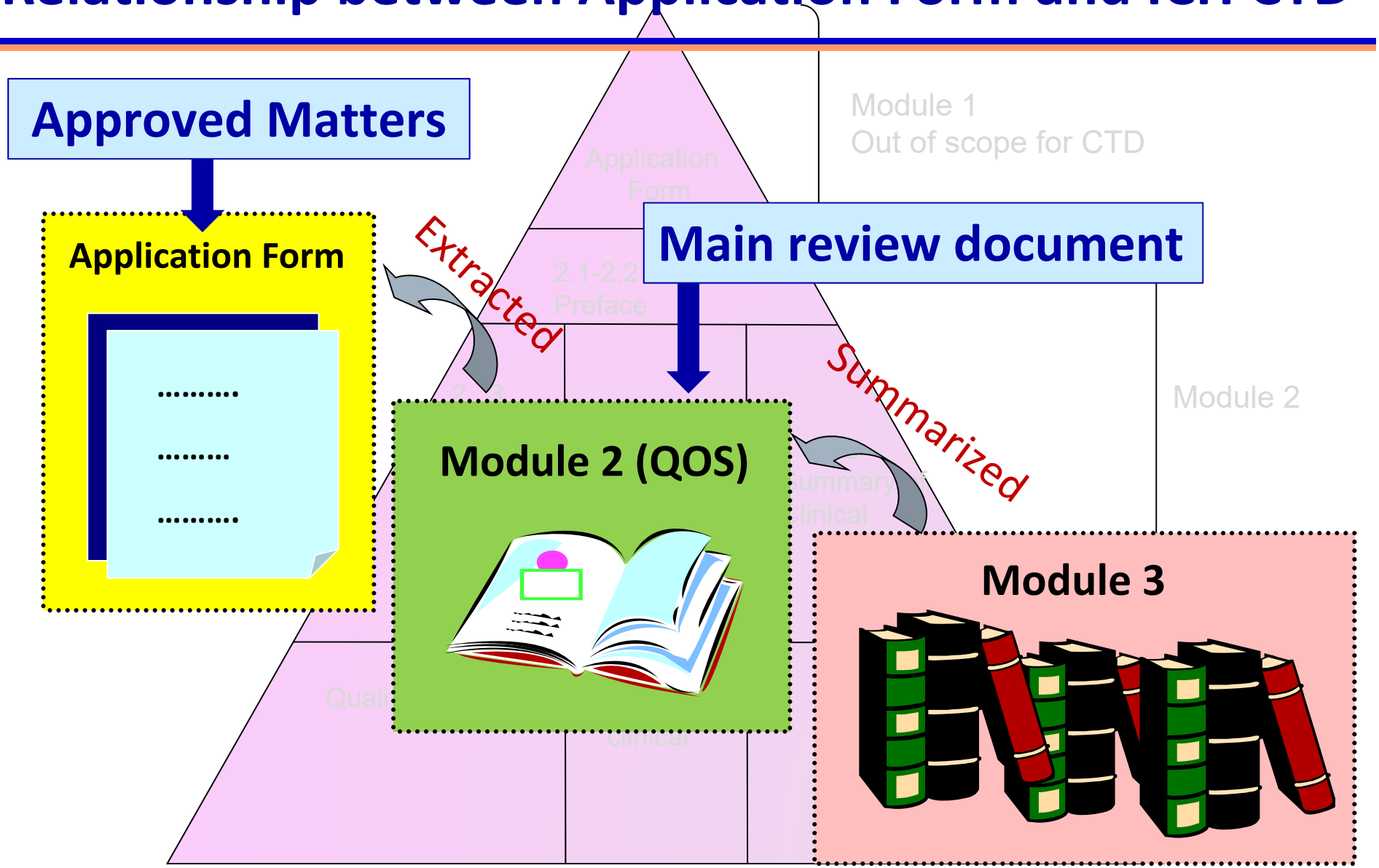
- **P**harmaceuticals and **M**edical **D**evices (**PMD**) Act.
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients (vaccine, Blood Products)
- Minimum Requirements for Biological Products
- ICH guidelines
- Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law
- Etc.

- MHLW: Minister of Health Labour and Welfare
- PSEHB: Pharmaceutical Safety and Environmental Health Bureau
- ELD: Evaluation and Licensing Division

Structure of Common Technical Document



Relationship between Application Form and ICH CTD



Section of Application Form

- General name (JAN)
- Brand name
- Composition
- Manufacturing process, incl. control of materials
- Specifications
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information

PMD. Act

(Marketing approval to drug etc.)

Article 14 Persons intending to market a drug …… must obtain approval of the Minister for marketing of each item.

Partial Change Application (PCA)

9 When persons who have received approval as specified in Paragraph 1 wish to make a partial change of approval items (excluding cases where such changes are minor changes as specified by MHLW Ordinance), approval of the Minister must be obtained for such cases. In such cases, the provisions of the preceding paragraphs shall apply *mutatis mutandis*.

Minor Change Notification (MCN)

10 A person who has obtained approval specified in Paragraph 1 shall submit a notification of minor changes specified by MHLW Ordinance in the preceding paragraph to the Minister as specified by MHLW Ordinance.

Enforcement Regulations of the PMD. Act

(Range of minor change in the approval items)

Article 47 The minor changes specified by MHLW Ordinance pursuant to the provisions of Article 14, Paragraph 10 of the Act shall be changes other than those specified below.

(1) Changes in the manufacturing methods, etc. that will affect the nature, properties, performance, or safety of a product

(2) Deletion of items from the specifications and changes in the specifications

(3) Changes concerning methods for the inactivation or elimination of pathogenic factors

(4) Addition, changes or deletions concerning the dosage and administration, or the indications

(5) In addition to those specified in the preceding items, any changes that could potentially affect the quality, efficacy, or safety of a product

Outline

- Regulatory Framework of Common Technical Document
- **Regulatory Pathway for Post Approval Changes**
- *...and* Future

Regulatory change in Application Form (1)

Chemicals

Specifications

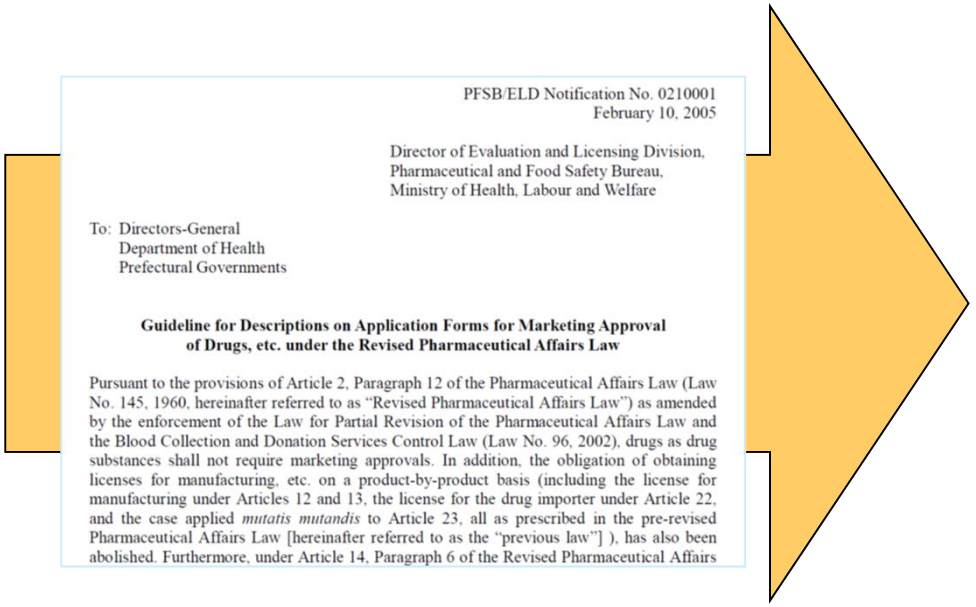
Mfg. process

Biologics

Specifications

Mfg. process

- Mandatory for all products



PFSB/ELD Notification No. 0210001
February 10, 2005

Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

To: Directors-General
Department of Health
Prefectural Governments

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law

Pursuant to the provisions of Article 2, Paragraph 12 of the Pharmaceutical Affairs Law (Law No. 145, 1960, hereinafter referred to as "Revised Pharmaceutical Affairs Law") as amended by the enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and the Blood Collection and Donation Services Control Law (Law No. 96, 2002), drugs as drug substances shall not require marketing approvals. In addition, the obligation of obtaining licenses for manufacturing, etc. on a product-by-product basis (including the license for manufacturing under Articles 12 and 13, the license for the drug importer under Article 22, and the case applied *mutatis mutandis* to Article 23, all as prescribed in the pre-revised Pharmaceutical Affairs Law [hereinafter referred to as the "previous law"]), has also been abolished. Furthermore, under Article 14, Paragraph 6 of the Revised Pharmaceutical Affairs

- Discussions in research groups
- Guideline incl. mock for chemicals

Specifications

Mfg. process

Specifications

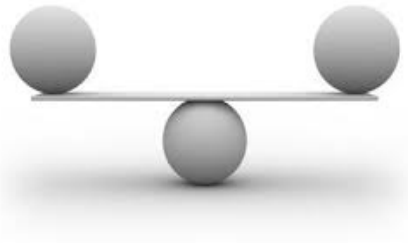
Mfg. process

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law in 2005
http://www.pmda.go.jp/files/000153677.pdf (in English)

Regulatory change in Application Form (2)

- Minor Change Notification in manufacturing process section was introduced.

- Harmonization among ICH regions was considered.
  - CBE30/Type1B, Annual Report/Type1A, Comparability Protocol were NOT introduced.
  - Information/elements classified as Annual Report/ Type1A were considered as non-Approved Matters.



Post-Approval Change Reporting Categories

Impact on quality	Japan	US	EU
High	**Partial change Application** (prior approval for change)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	**Minor change Notification** (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**(Non-approved matters)**	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

In Japan, according to the impact of MFG changes on quality, safety and efficacy, sponsor should submit the partial change application or minor change notification.

Concept of the Revised PAL for Biologicals

- Because biological drugs are produced by utilizing biosynthesis processes in biological bodies, it may be possible that materials that are inhomogeneous in molecular structure are produced. Furthermore, as some changes in the higher structure of the molecule that are difficult to be determined by physicochemical analyses can affect biological activity, evaluation of the impact by changes in the manufacturing method on the quality, safety, and efficacy of the product is considered as being different from that of ordinary chemical drugs. Since biological drugs consist of various kinds of materials such as proteins, glycoproteins, polypeptides, and their derivatives, and their controls also vary, **it is difficult to uniformly specify the matters to be addressed in a minor change notification for biological drugs.**
- Accordingly, in the case of biological drugs, changes in the matters described on an approval application form shall, in principle, be addressed in a partial change approval application.

A partial change approval application and a minor change notification for the manufacturing method

- As **changes in** the matters entered in the **Manufacturing Method** should be adequately controlled, they shall therefore be **addressed in a partial change approval application, in principle.**
- When there is an extremely low possibility of the change having an adverse impact on the quality/safety of the final product, and in the following confirmed cases, a minor change notification may be applicable;
- For the applicable cases, the applicant may make such a proposal when submitting an approval application; the proposal will be judged during the review as to whether it can be accepted.
- In cases where in-house in-process control tests and similar target values are described.
- Etc.

Manufacturing Method (Process parameter)

- **Expression of minor notification and partial change approval application**

- Among the standard batch sizes or the process parameters that serve as target values/set values, the matters to be addressed in **a minor change notification** shall be expressed as enclosed in 『 〇 〇 』.
- The standard batch sizes or the process parameters to be addresses in **partial change approval application** shall be expressed as enclosed in 《 〇 〇 》.
- The matters to be addressed in **a minor change notification** other than target values/set values shall be enclosed in “ 〇 〇 ”.

Update Remaining Challenges

- Our 2005 GL has provided the basic principle of approved matters in the manufacturing process and helped both regulators and the industry.

- However, there still remain some challenges, including;
  - Adverse effects of mock
    - Some just followed the mock described in the guideline to meet deadline.
    - Both regulators and the industry tend to follow the mock *(?)*, although the description in the AF is on a product-by-product basis.
  - Document management
    - The discrepancy between the actual situation (e.g. MBR) and AF is caused by multiple factors.
  - Others
    - Some tend to lose sight of the original purpose of the AF.
    - Some tend to think MAHs manufacture and control their products only according to the AF.
    - There had been no detailed discussion on Specification.

Outline

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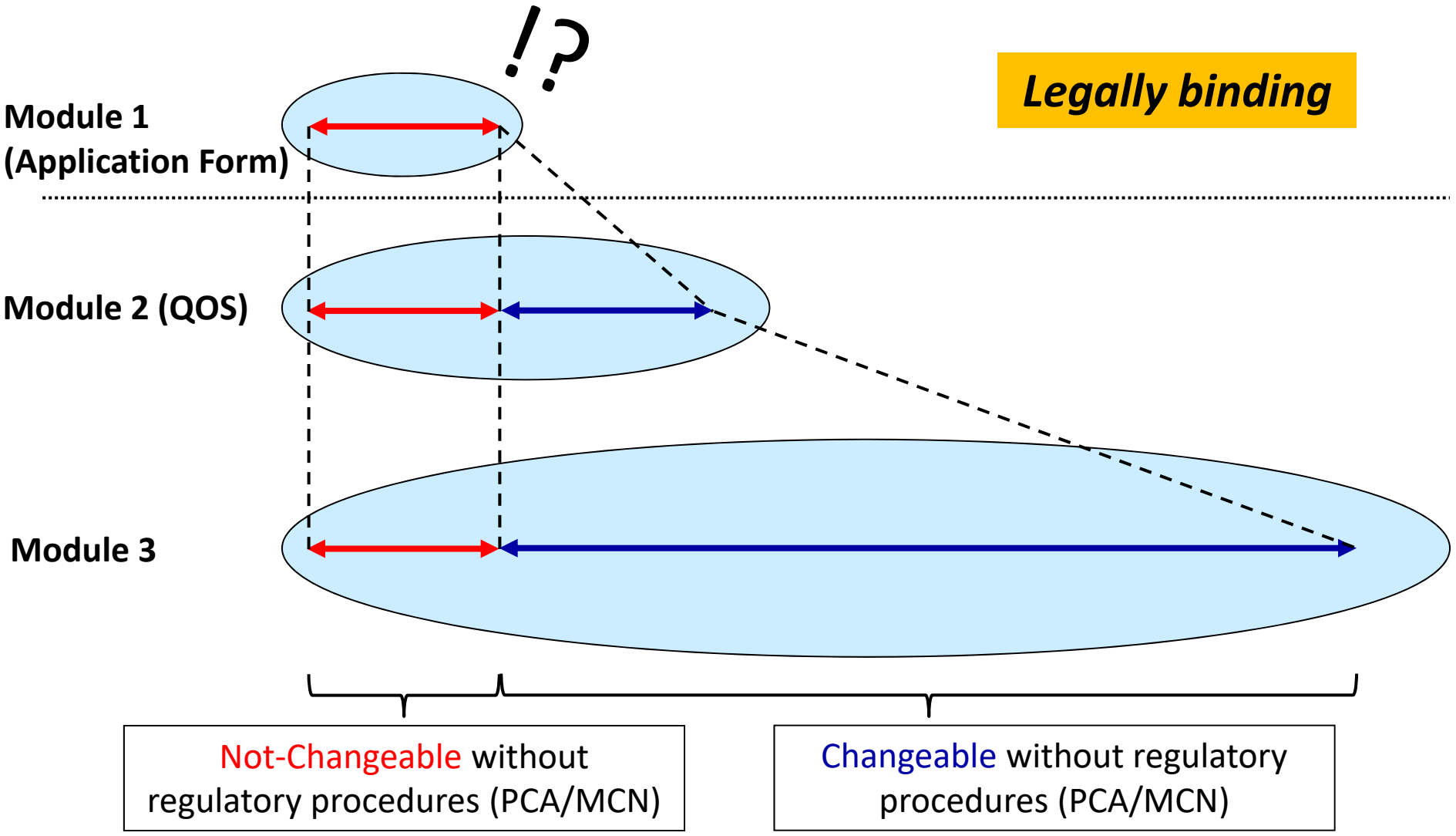
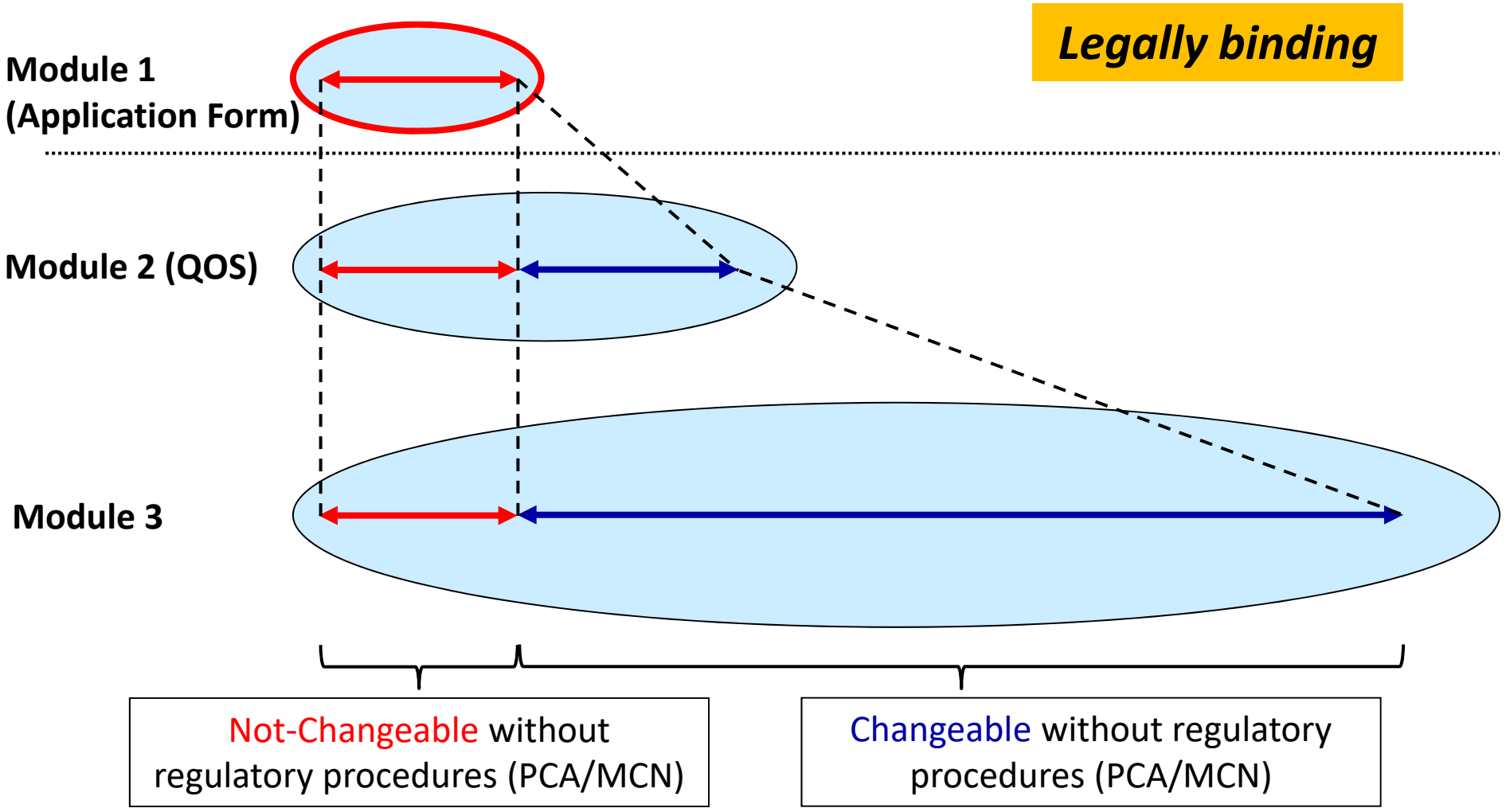
Japan's Effective/Efficient/Flexible Quality Regulation



Thank you for your attention

Japan's Effective/Efficient/Flexible Quality Regulation



Outline

- Past, Present
- ...*and* Future

Reminder!
Some of the content are currently under discussion.
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Issues to be addressed in ICH Q12

- Regulatory Dossier
  - Explore the development of a harmonised approach to "regulatory commitments" for inclusion in the guideline. Such approaches could enable post approval changes that facilitate continual improvement and encourage the adoption of innovative technologies.
  - Delineate the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier, in order to create a more enabling post approval change management system.
- Pharmaceutical Quality System (PQS) aspect
  - Establish criteria for a harmonised risk-based change management system based on product, process and/or clinical knowledge that effectively evaluates the impact of change on quality, and, as applicable to safety and efficacy.
  - Clarify expectations and reinforce the need to maintain a knowledge management system that ensures continuity of product and process information over the product lifecycle.
- Post-Approval Change Management Plans and Protocols
  - Introduce the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (Assessors and Inspectors)
  - Establish criteria for post-approval change management protocols that can be adopted by the ICH regions (enabling a harmonised proactive approach for lifecycle management)
  - Encourage enhanced product development and control strategy approaches (Quality by Design (QbD)) providing opportunities for scientific and risk based foundations for post-approval change management plans.

From ICH Q12 Concept Paper

Approved Matters ≈ Established Conditions

Japan

Module 3

Summarized

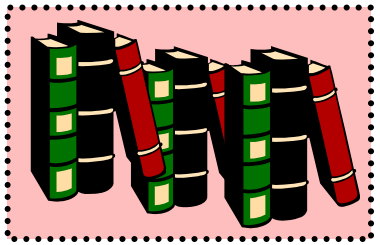
Module 2 (QOS)

Extracted

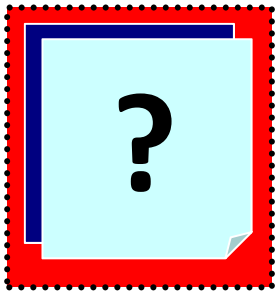
Approved Matters

Module 1(AF)

ICH



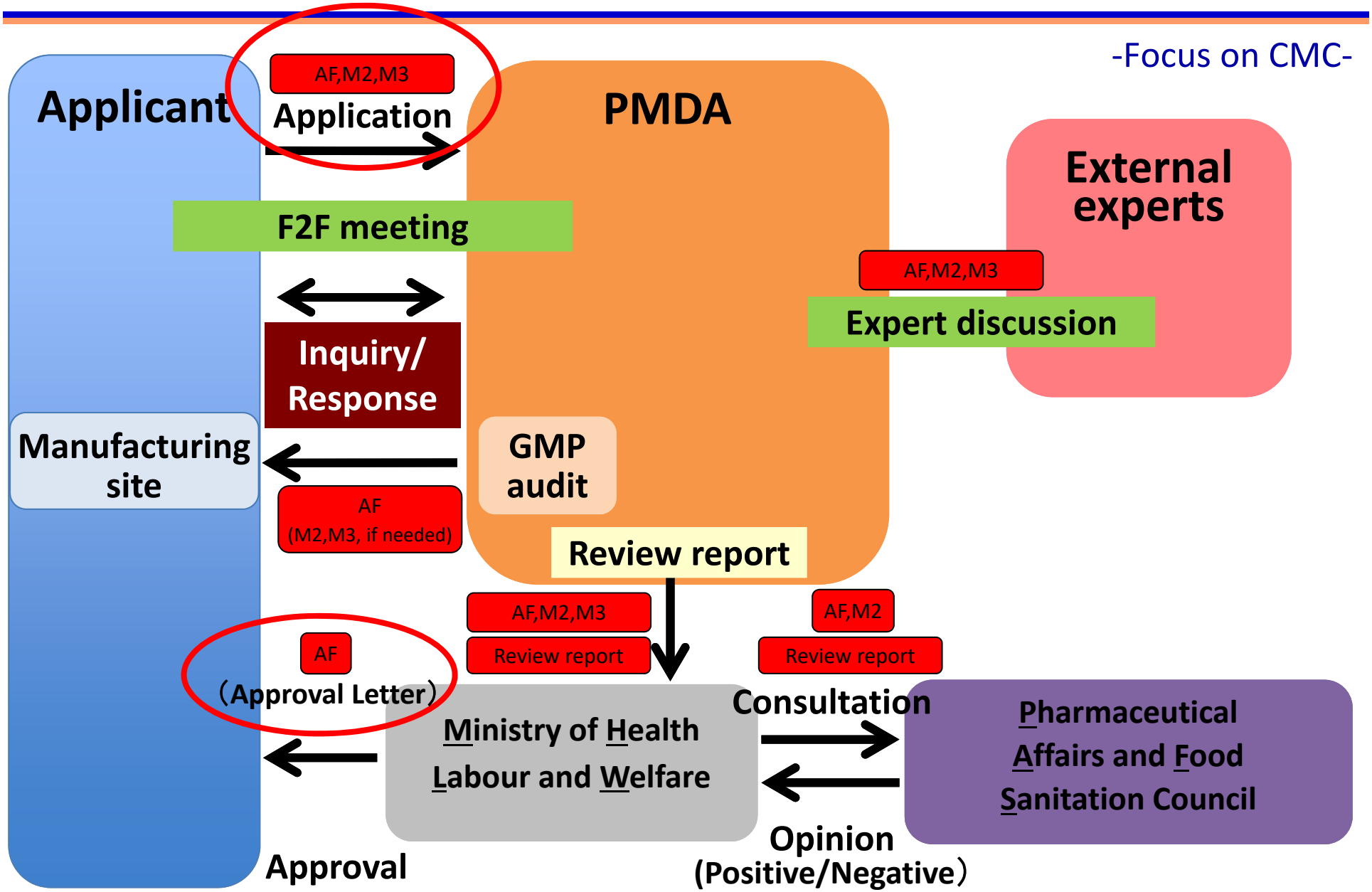
Module 3



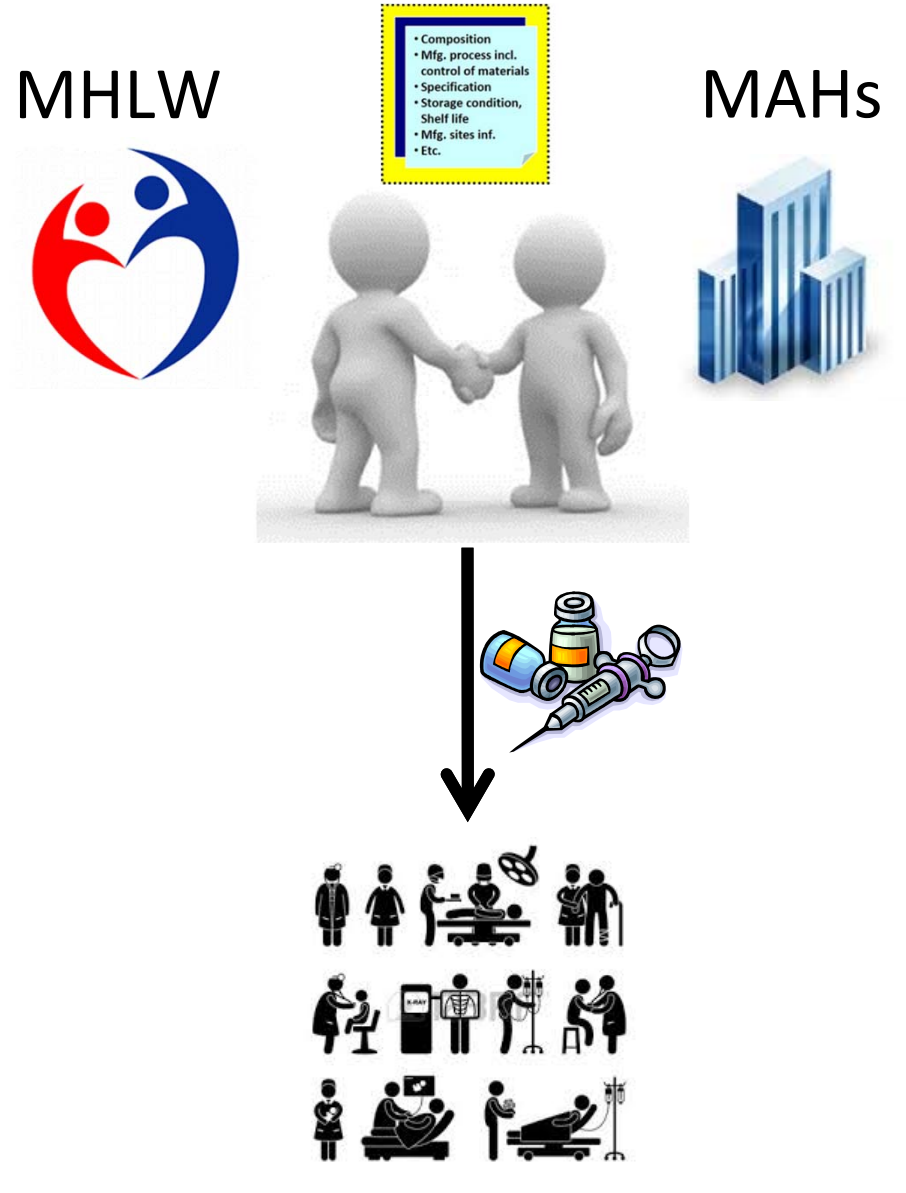
Established Conditions

Review Process of MAA with document flow

-Focus on CMC-



Japanese Application Form

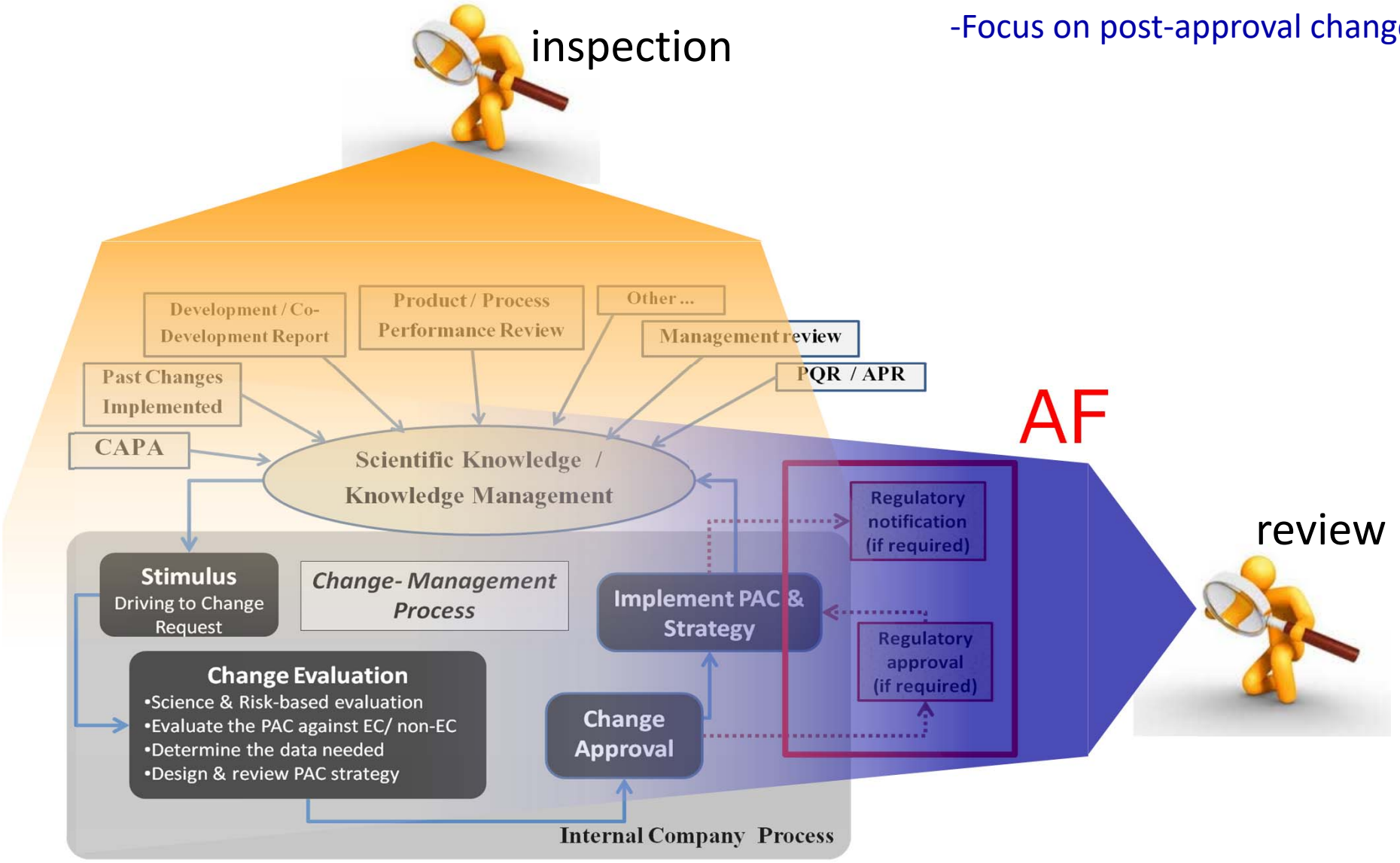


Japanese Application Form/Approved Matters

- AF, found in Module 1.2, is a legally binding document in Japan.
- Essential elements to ensure pharmaceutical quality should be described in AF.
- A post-approval regulatory action is required if a MAH changes the content in the AF (Approved Matters; AMs).
- AMs (incl. PCA/MCN) are determined on a product-by-product basis.
- AF provides the transparency and flexibility in terms of post-approval changes.

AF and Review/Inspection

-Focus on post-approval change-



Modified from draft Q12 document

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