PMDA Perspective on Regulatory Commitments

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Pharmaceuticals and Medical Devices Agency (PMDA)

Introduction of PMDA

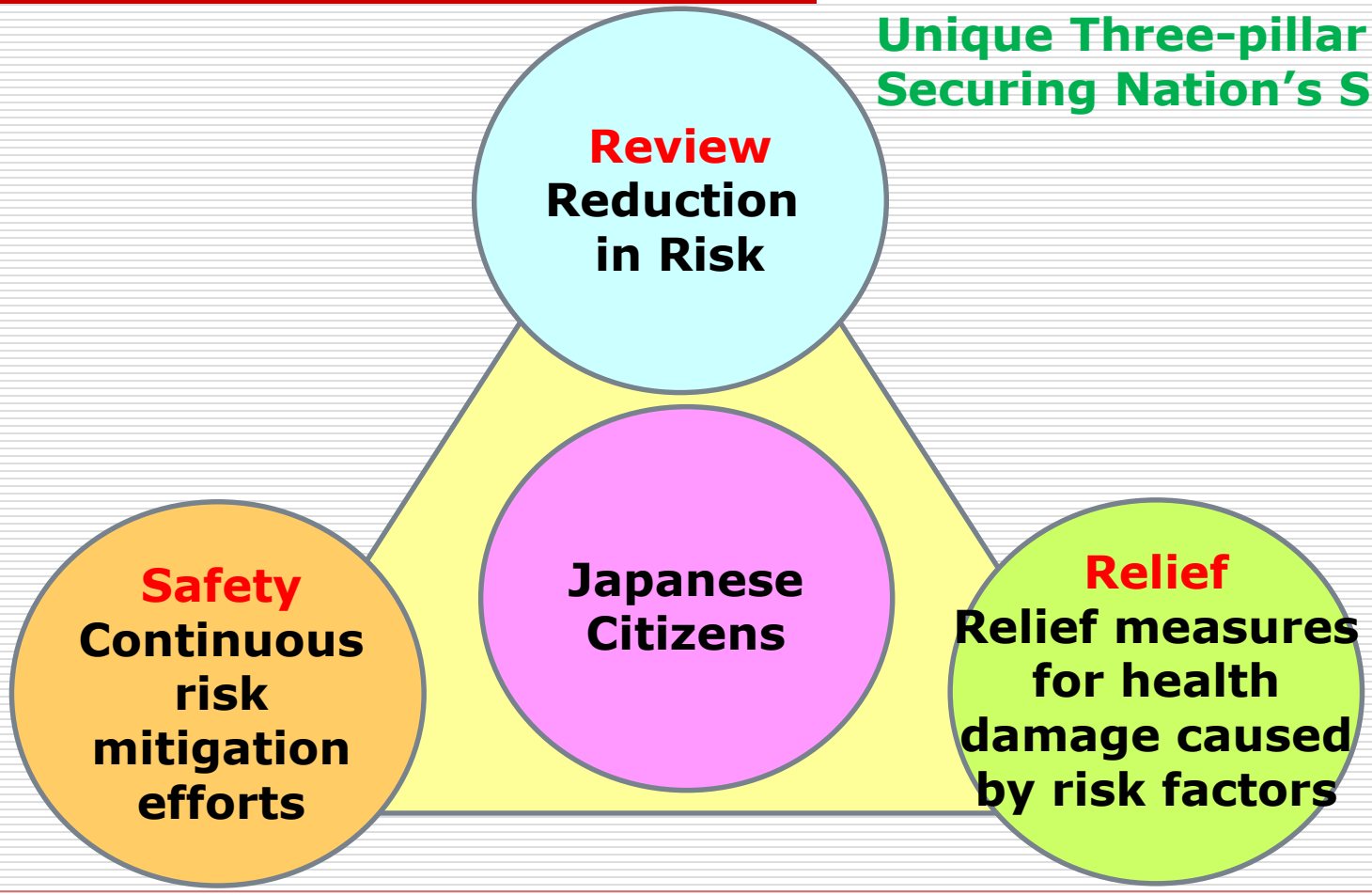
- Name : Pharmaceuticals and Medical Devices Agency
- Date of Establishment : In April 2004
- Established as an Incorporated Administrative Agency

http://www.pmda.go.jp/english/index.html

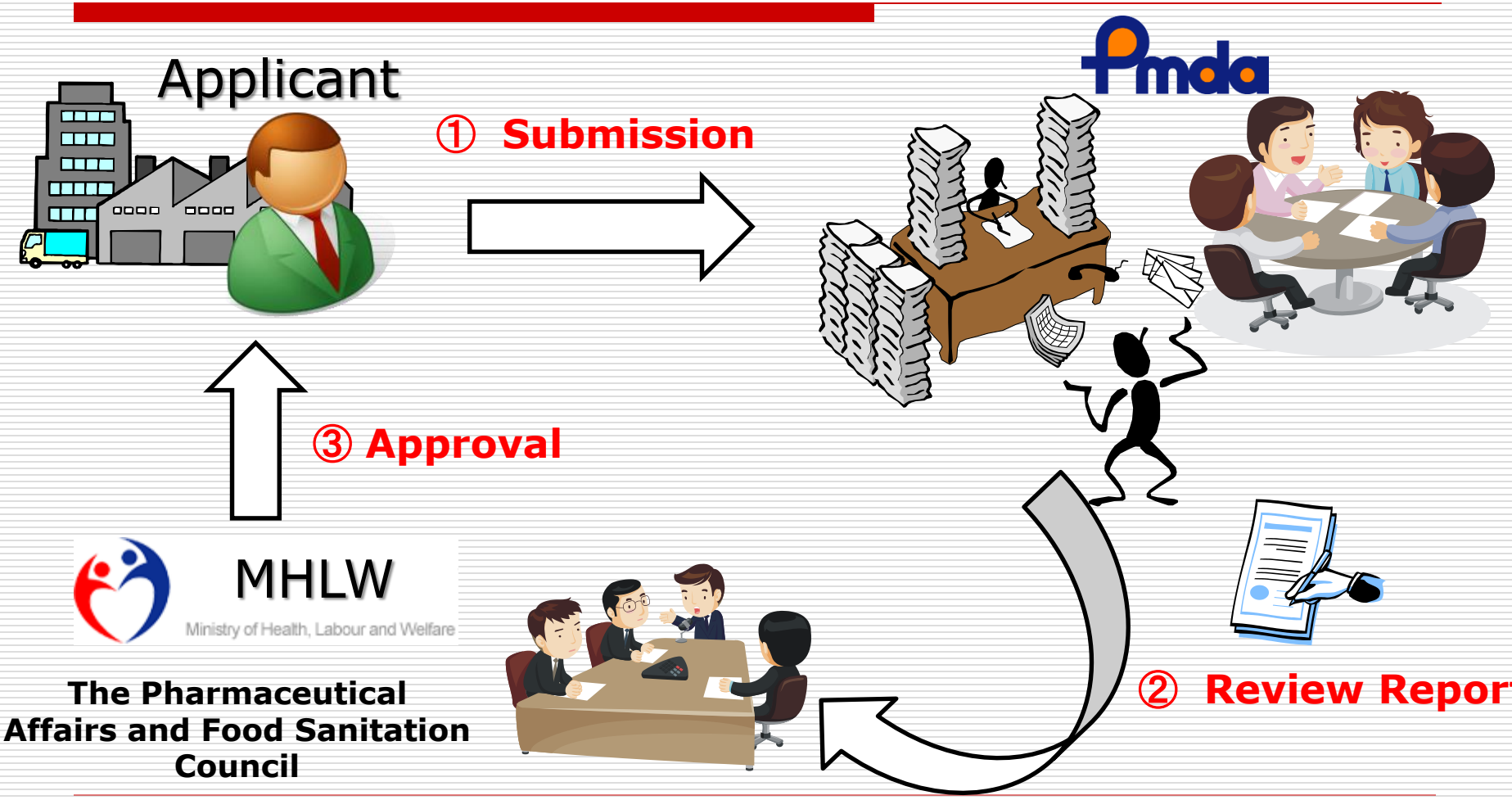
PMDA Organization

PMDA's Safety Triangle

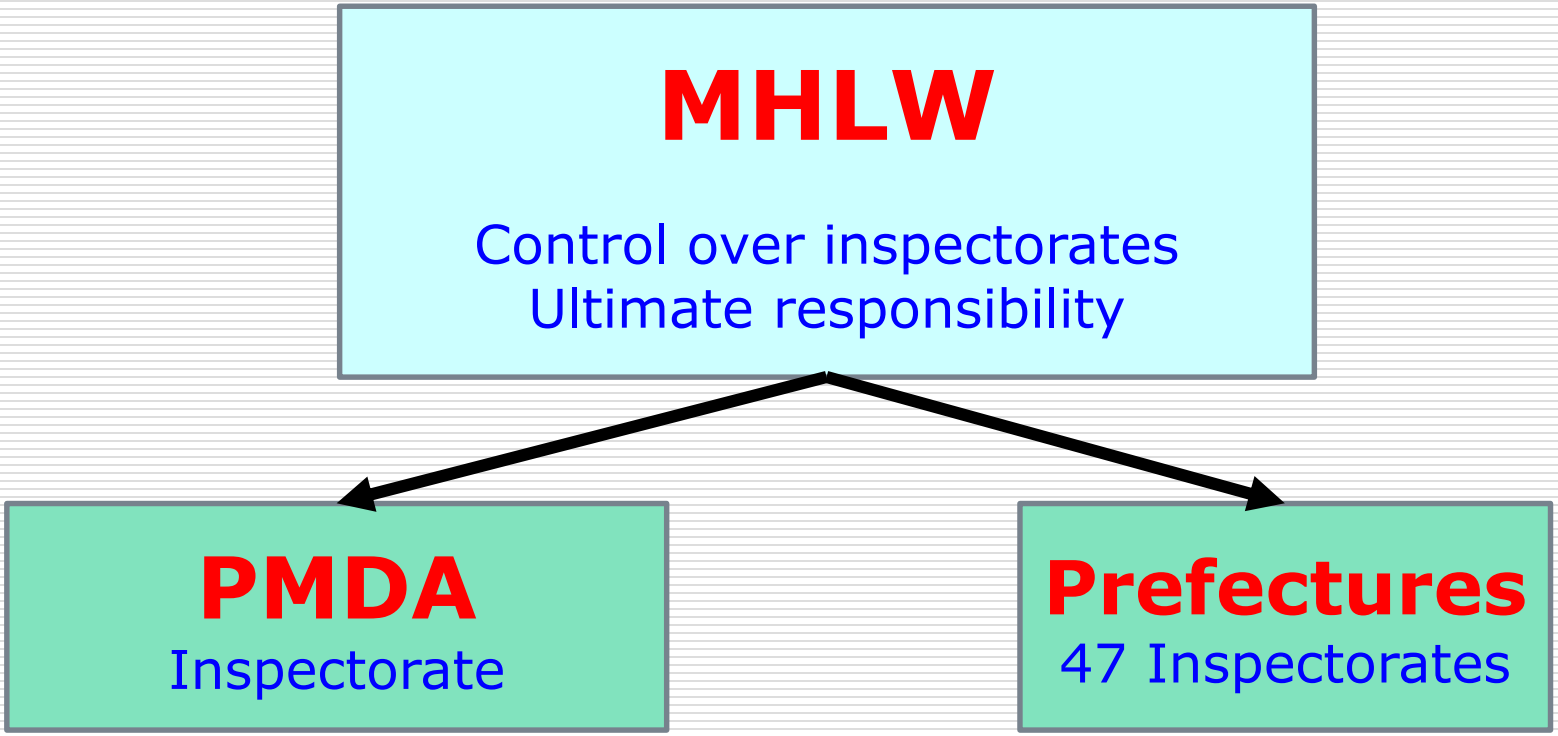
Unique Three-pillar System Securing Nation's Safety



Flowchart of Reviewing Process



GMP Inspection System



PMDA is partially vested with authority of MHLW

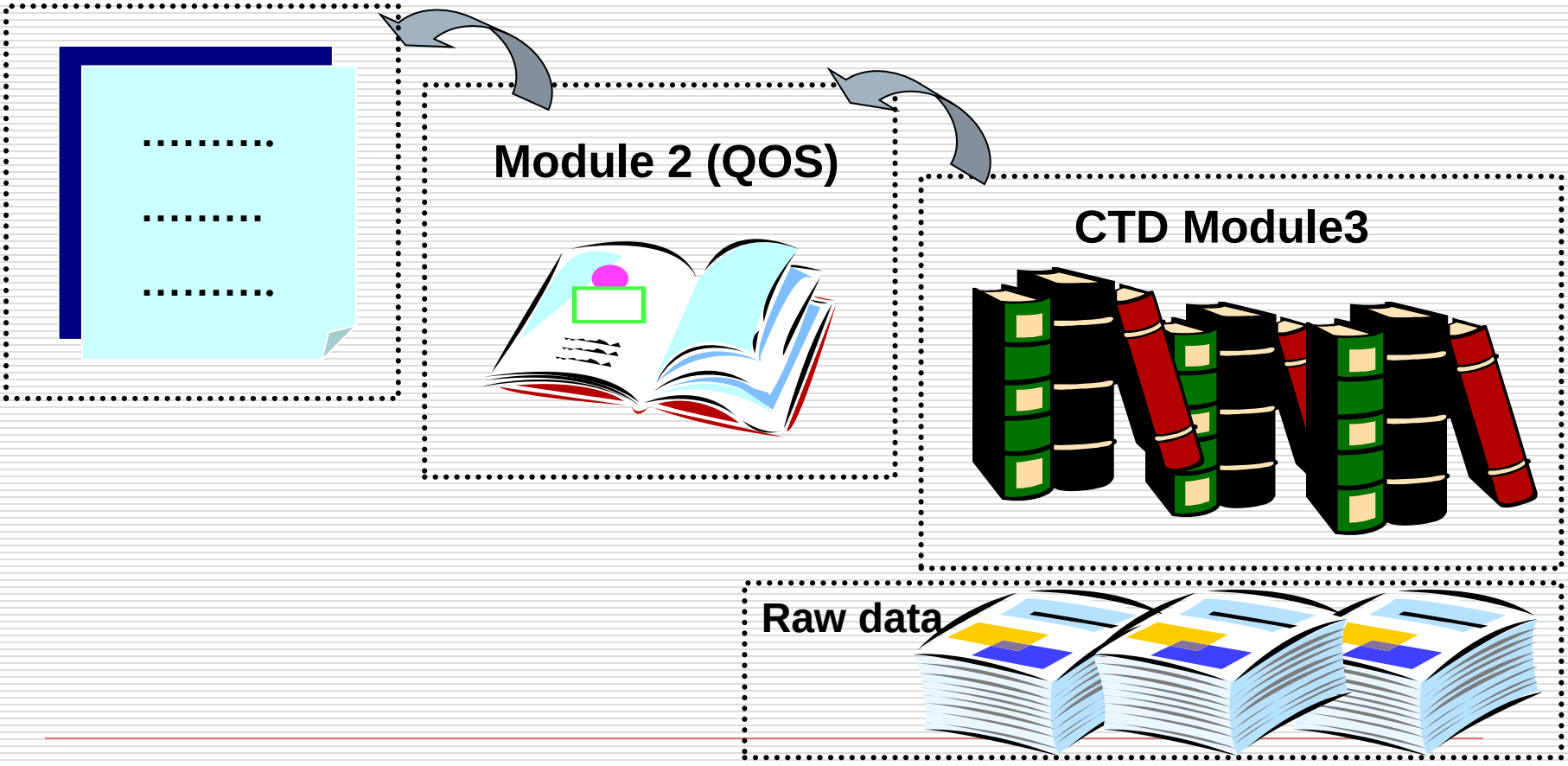
Prefectures are vested with part of MHLW's authority to exercise local autonomy.

GMP Inspections by PMDA and Prefectural Governments(47)

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	PMDA	PMDA
Other Drugs	Pref. Gov.	PMDA

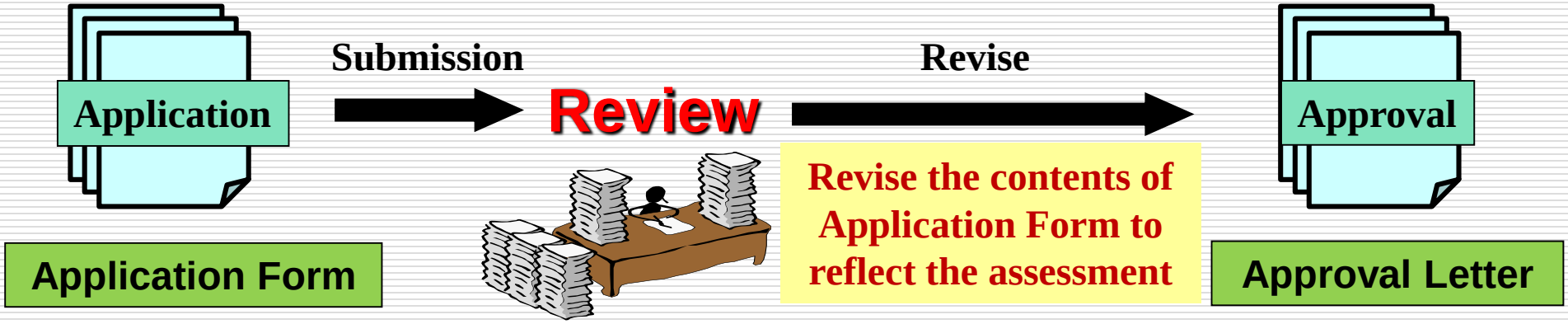
Relationship between Application Form and CTD Documents in Japan

Application Form (included in Module 1)



What is the Application Form?

- Contents provided in the Application Form by applicants are dealt with as "matters subject to approval."
- Contents described in Approval letter are "legally binding" approval matters.



Approval Matters

(Contents of Application Form)

- Japanese accepted name(non-proprietary name)
- Brand name
- Composition
- Manufacturing process, including control of materials
- Specifications and analytical procedures
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information

Matters to be described in manufacturing field of Application Form

- 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/Set Value)
  - A narrative description of manufacturing process
    - Acceptance criteria of starting material(s) and intermediate materials
    - In process control, Design Space and RTRT etc.

Post-authorization Procedure

Risk of Changes	Japan	US	EU
High	**Partial change** (Application for approval of variation)	**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		**Minor change** (Annual report)	**Type IA variation** (Notification within 12 months after implementation)

Examples of Matter Subject to a Partial Change Application

- Change in
  - principle of unit operation of critical process
  - materials of primary packaging component
  - matters for aseptic manufacturing
  - specification of intermediate product in case that the test is performed instead of release test of final drug product･･･etc.

But we can judge that on a case-by-case basis.

Flexibility

Flexible Assessment

- Only contents of Application Form will be legally binding matters as the approval letter.
- CTD Module 2 and 3 are just review documents.

- Assessors can set the post approval change classification for each procedure and process parameter on Application Form(Approval Letter).

How to describe partial change matters and minor change matters

- Enter target/set values of process parameters and standard charge-in amounts in
  - 《　》: partial change matter
  - 『　』: minor change matter
- Enter items other than target/set values in
  - “　”: minor change matter
  - No parentheses : partial change matter

Example of manufacturing description on Application Form

Step 1 (Critical Step)

CP-6『(230kg)』, tetrahydrofuran『(1300L)』, sodium carbonate『(42.4kg)』 are combined. Ethyl chloroformate "158～592kg" is added and the mixture is heated at temperature up to reflux. ・・・・

Water ("25 to 35%" *weight per weight of ethanol) is added and the mixture is stirred at 『20℃』.

* Water quantity is relative to the ethanol quantity, ethanol volume and crystallization temperature are parameters establishing Design Space which controls the quantity of total impurities.

Acknowledgement : Sakuramil (Sakuramil S2 mock)
http://www.nihs.go.jp/drug/section3/H23SakuramillMock(Eng).pdf

Benefits of Regulatory system in Japan

- **Transparency**
  - We can clearly share the regulatory commitments between the applicant and regulators .
  - Module 2 can be a good communication document because Module 2 is just a review document and applicants can write their narrative on Quality Overall Summary freely.
- **Efficiency**
  - Quality Overall Summary can facilitate our assessment because of the primary review document in Japan.
  - Members of a MHLW's council and external specialists can understand the contents of the application smoothly by the Quality Overall Summary.

Challenges

- It seems to be difficult to summarize the QbD approaches in Module 2 in brief.
- How to encourage continual improvement much more?

ICH Informal Quality Discussion Group(IQDG) in Minneapolis, 2014

- IQDG Quality Workshop
  - 2003 Quality Vision expectation achieved

However, more efforts needed to fully address challenges and strengthen product lifecycle management

ICH Q12 : Lifecycle Management

Lifecycle Management

- Problem statement
  - Implementation of ICH Q8/Q11, Q9 and Q10 provides opportunities for a more science and risk based approach to assessing changes across the lifecycle
    - Main emphasis is during the Development stage
  - Opportunities and benefits have not been fully realized (or enabled), and the envisioned operational flexibility has not been achieved
  - We now need to focus on the Commercial Manufacturing phase of the lifecycle

ICH Q12 Concept Paper

- Key words for Issues to be resolved
  - Regulatory commitments
  - Post approval change management system
  - Criteria for a harmonized risk-based change management system
  - Knowledge management system
  - Post-Approval Change Management Plans and Protocols

Regulatory Commitments

- The regions differ in their interpretation of "regulatory commitments" (e.g., manufacturing process and controls)

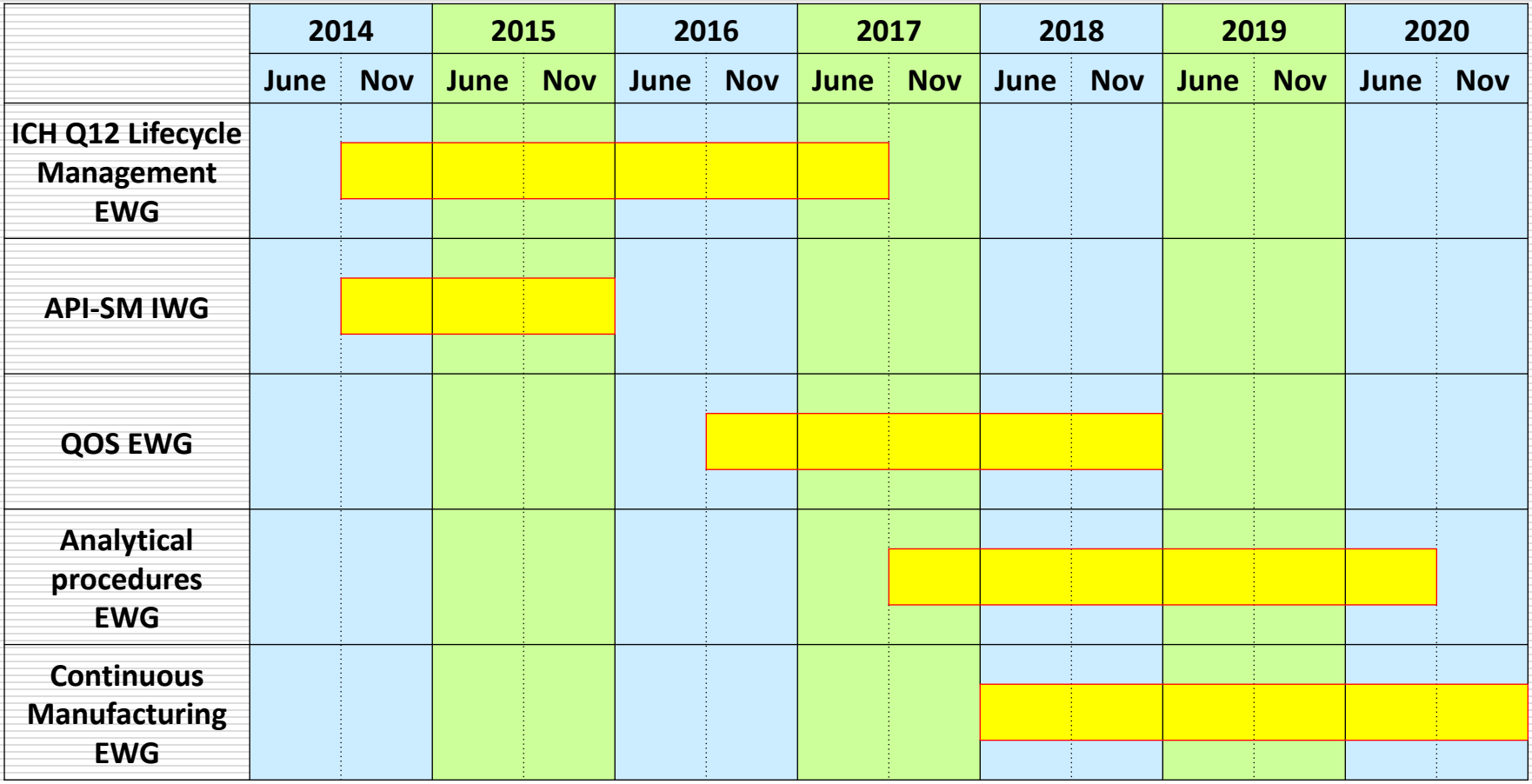
- In Japan, regulatory commitments are the contents of Application Form.
  - Regulatory commitments are clearly separated by Application Form because CTD M2 and M3 are references for a review.

Post approval change management system

- Enhance use of regulatory tools for prospective change management

- In Japan the application form can define a classification of post-authorization procedure during a review period.
- However we have no post-approval change management protocol or plan as in US/Europe.

ICH Future Quality Topics



Thank you for your attention