



Updates and a Perspective on ICH Q12 Implementation in Japan

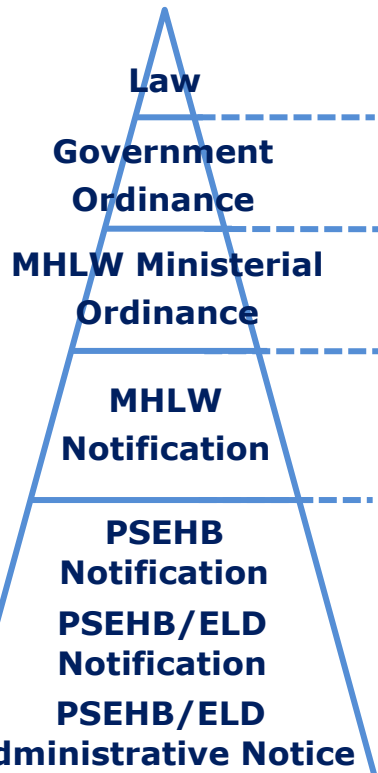
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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

- Overview of Recent Revision of Japanese Regulation
- Introduction of PACMP* into Our Regulation
 - * PACMP: Post Approval Change Management Protocols
- Perspective on Harmonized Implementation of ICH Q12 Guideline

Regulatory Framework in Japan



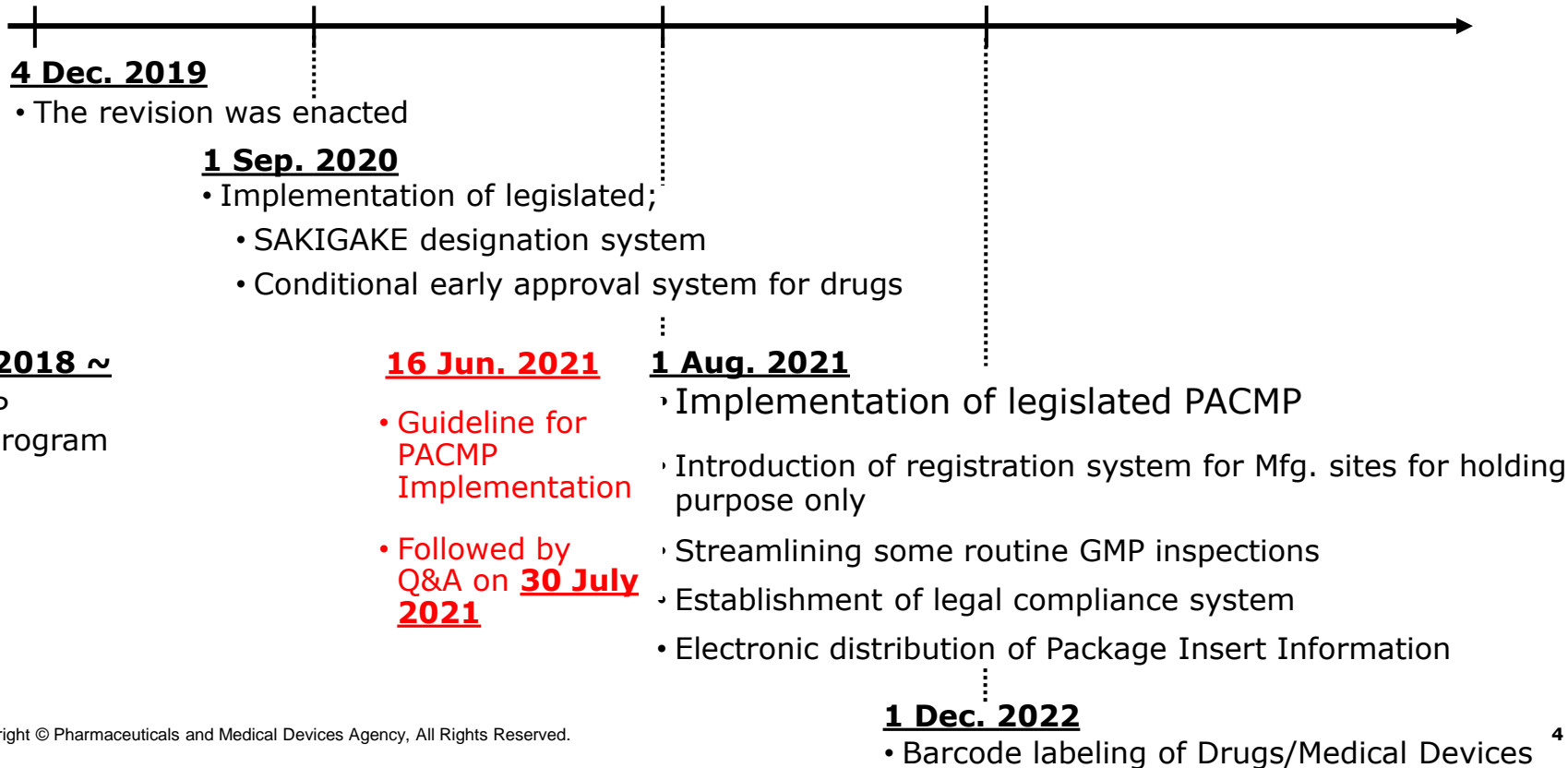
- Pharmaceuticals and Medical Devices Act (PMD. Act)
(Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulation of the PMD. Act
- GMP, QMS, GCTP, GQP
 - GMP: Good Manufacturing Practice
 - QMS: Quality Management System
 - GCTP: Good Gene, Cellular, and Tissue-based Products Manufacturing Practice
 - GQP: Good Quality Practice
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH Guidelines
- Guideline for Descriptions (of Mfg. process section) in Application Forms for Marketing Approval of Drugs, Quasi-drugs and Cosmetics (10 Feb 2005)
- ...

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

Latest Revision of PMD. Act

- Purpose
 - Deliver better medical products in a safer, more prompt and more efficient manner
 - Improve the system to allow patients to use drugs without anxiety in their familiar community
- Three major pillars
 - Modernize regulation throughout product lifecycle
 - Revise the role of community pharmacies/pharmacists
 - Establish more reliable legal compliance system

Implementation Schedule for some major revisions



Other Key Updates (1) (in relation to ICH Q12 implementation)

- Revision of Enforcement Regulation of the PMD. Act (enacted on 29 Jan. 2021)

(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

Other Key Updates (1) (in relation to ICH Q12 implementation) **cont.**

- Guideline and relevant Q&A
(MHLW PSEHB/ELD Notification 0730-6, PSEHB/ELD Administrative Notice, 30 Jul. 2021)

Guideline: <https://www.mhlw.go.jp/hourei/doc/tsuchi/T210802I0040.pdf> (in Japanese)
Q&A: <https://www.mhlw.go.jp/hourei/doc/tsuchi/T210802I0050.pdf> (in Japanese)

- Introduce Minor Change Notification (MCN) mark (“ ”) in Specification section of Application Form
- Provide MCN examples and descriptions for Specification section of Application Form

Excerpt from Glycoprofiling Example

.....
.....
Reaction condition: 37°C for “17 - 19 hours”
.....

Other Key Updates (2) (in relation to ICH Q12 implementation)

- Revision of GMP (enacted on 28 Apr. 2021)
 - Incorporate Pharmaceutical Quality System (PQS) into MHLW Ministerial Ordinance
 - Ensure thorough compliance with Approved Matters
 - ...

Outline

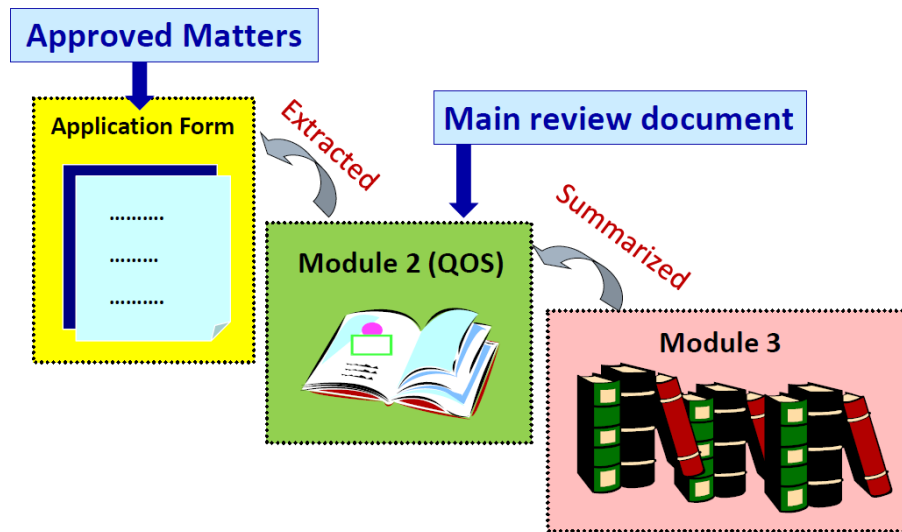
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Background: Post-Approval CMC changes in Japan

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)	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)

Relationship between Application Form and ICH CTD



PACMP: Legal Basis

- PMD Act.

(**Confirmation of plan** for making a change of approved matters of pharmaceuticals, Quasi-Pharmaceutical Products and Cosmetics)

Article 14-7-2 (1) ~ (11):

(Application, Mutatis Mutandis)

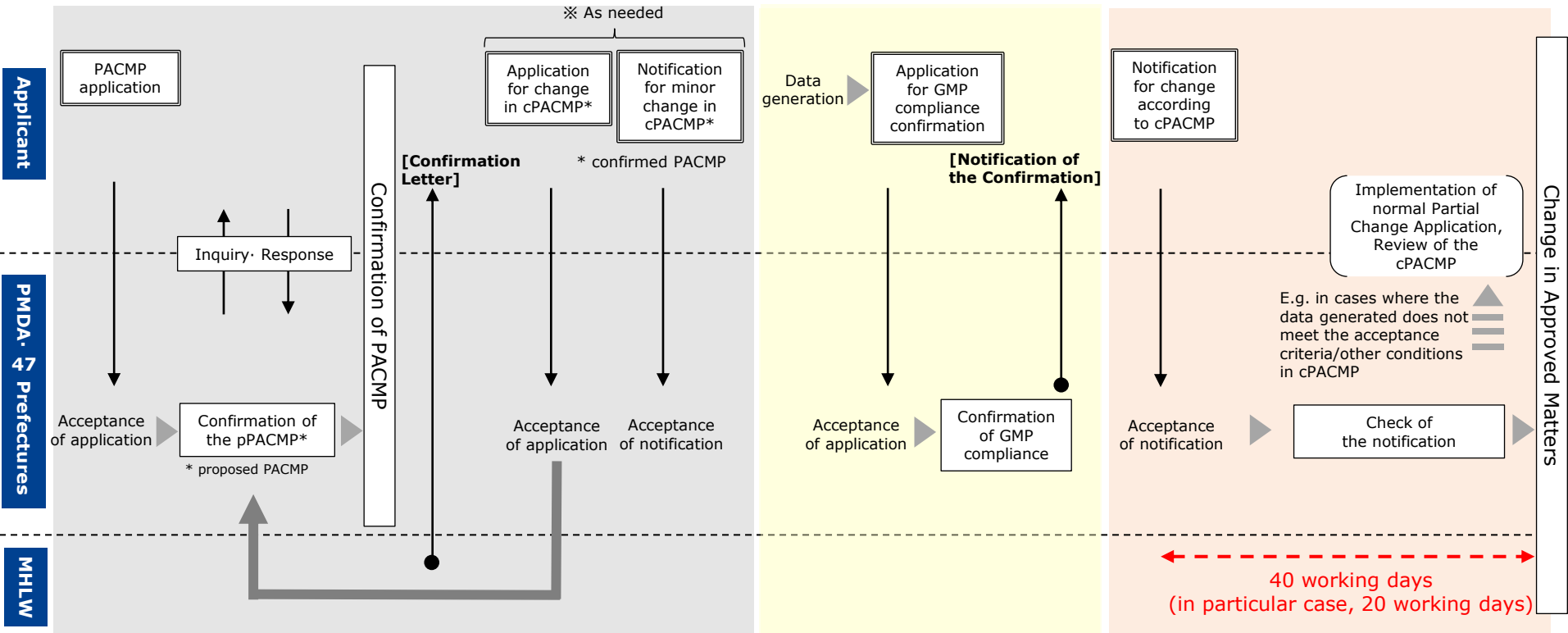
Article 19-4 The provision for “designated holder of marketing authorization for foreign-manufactured pharmaceuticals, quasi-pharmaceutical products or cosmetics” shall apply mutatis mutandis to Article 14-4 ~ 14-8 and ...

- Enforcement Ordinance of the PMD. Act
- Enforcement Regulation of the PMD. Act.

Article 68-1 ~ 68-15

➡ Scope, Procedures (such as “step1”, “step2” and GMP inspection), Timeline and Fee

PACMP: Guideline (MHLW PSEHB/ELD Notification 0616-14, 16 Jun. 2021)



PACMP: Key Aspects in comparison with pilot program

	Legislated PACMP	Pilot program (Apr. 2018 ~ Jul. 2021)
Scope	Prescription drugs, Regenerative medical products, OTC drugs, Quasi-drugs, and Cosmetics that require approval by MHLW (Pharmaceuticals approved by 47 Prefectures are excluded) Note: Changes in Master File are excluded for the time being	Prescription drugs
Step 1 procedure	Application for confirmation to MHLW	PMDA Consultation
Step 1 timeline	Same as normal PCA in general (6 months (median) for chemicals, 12 months (median) for biologics)	4 months (PACMP Quality consultation)
PACMP in MAA	Available Note: Need a separate application. Application timing should be consulted with relevant contact point	Not available
GMP inspection	PMDA or 47 Prefectures	PMDA
Step 2 procedure	Notification (Prior notification before implementation of the change)	PCA* or MCN *: shorter timeframe compared to normal PCA
Step 2 timeline	40 working days (in particular case*, 20 working days) *:if it meets both of the following conditions; <ul style="list-style-type: none"> • there is no notification for minor change submitted since lastly confirmed PACMP, • there is no minor Change Notification in relevant Approved Matters submitted since last approval 	3 months (median) in case of PCA required

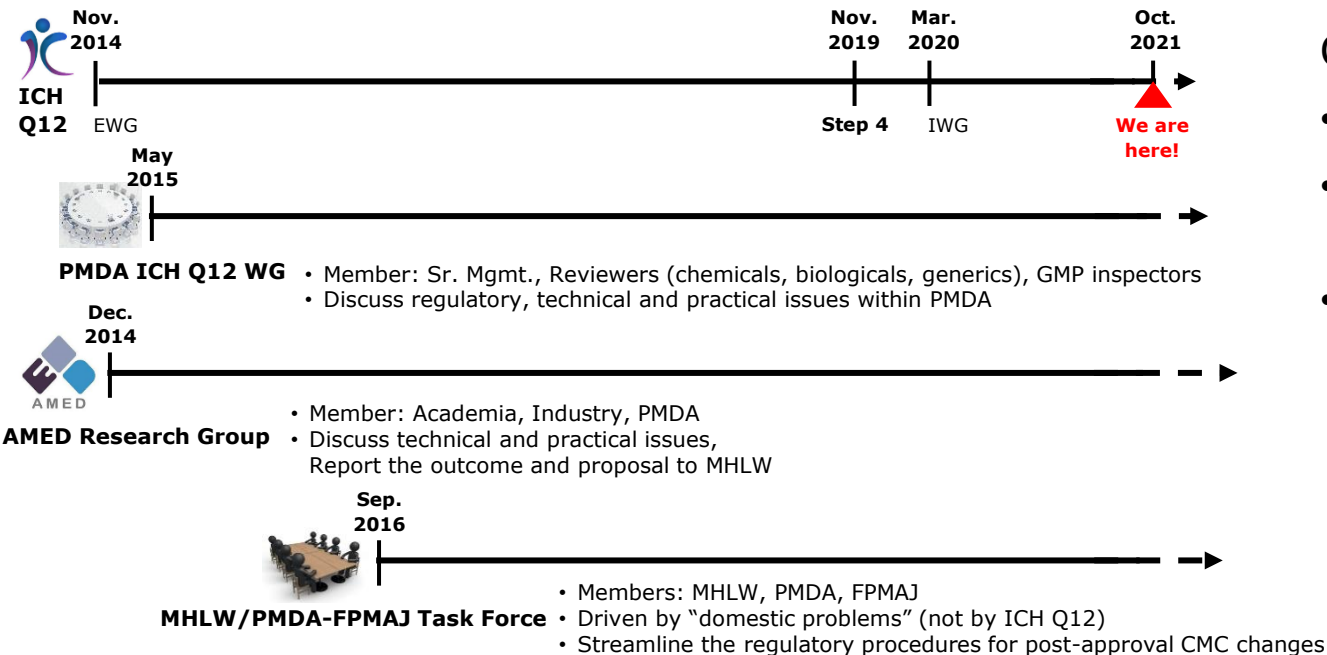
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Major Challenges

- Effective PQS incl. Change Management
- Identification of Established Conditions (ECs) and Associated Reporting Categories (RCs)
 - Criticality assessment vs. Risk assessment
 - Risk Tolerance
 - Can PQS maturity reduce the details of ECs?
 - Feasibility of unified ECs/RCs across regions based on current RC systems in all regions
- PACMP
 - Need to accumulate experience for both regulators and the industry
- Product Lifecycle Management (PLCM) document
 - How a tabular format covers all elements of ECs?

An Enabler: Prospective and Continuous Dialogues with Stakeholders



Communication;

- within an organization
- between regulators and the industry
- among regulators



For more details:

https://cdn.ymaws.com/www.casss.org/resource/resmgr/cmc_japan_speaker_slides/2017_CMCJP_Kishioka.pdf

Apr. 2018 **PACMP** **pilot program**

Dec. 2019 **Revision of PMD. Act**

Aug. 2021 **PACMP**

Summary

- PMDA has achieved some major milestones to implement ICH Q12 guideline in collaboration with stakeholders.
 - Revised PMD. Act provides additional flexibility in terms of post approval CMC changes.
 - Legislated PACMP has started since 1 August, 2021.
- “Ba” is necessary in order to reach the stage of adherence to ICH Q12 guideline.

Acknowledgements

- PMDA ICH Q12 IWG (YAGI Satomi, OKUDAIRA Shinichi, HARA Kentaro)
- PMDA Q12 Working Group
- AMED Research Group
- MHLW/PMDA-FPMAJ Task Force

AMED: Japan Agency for Medical Research and Development

MHLW: Minister of Health Labour and Welfare

FPMAJ: The Federation of Pharmaceutical Manufacturers' Associations of JAPAN

Thank you for your attention!

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