Agenda

- General Introduction (Andrew Chang)
- M4R(2): An Opportunity for a Global Quality Dossier (Sarah Miksinski)
- Current state of Q12 implementation
  - US experience (Mahesh Ramanadham)
  - Updates and a Perspective on ICH Q12 Implementation in Japan (Yasuhiro Kishioka)
- Open discussion

Ground Rules for the Workshop

- Encourage open discussion
- Not use the session to ask what’s going on in the EWG

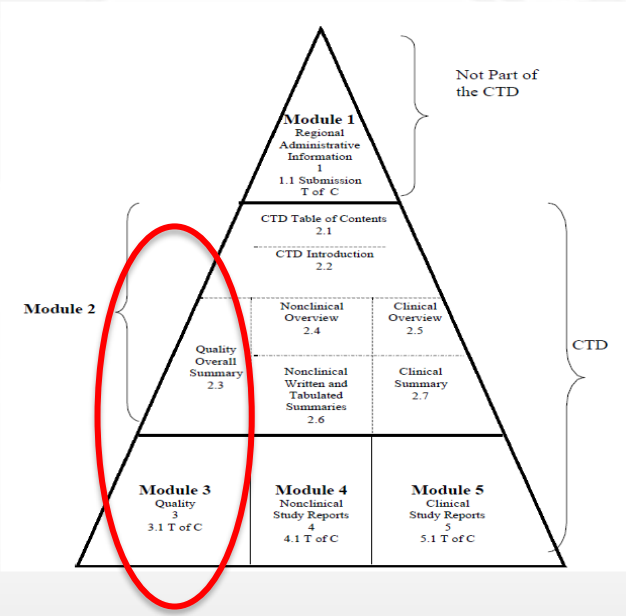
M4Q(R2): An Opportunity for a Global Quality Dossier

ICH M4Q(R2) Expert Working Group (extracted content)

Presented by: Sarah Pope Miksinski
Date: 23 Jan 2024
Conference: CASSS/WCBP

What's M4Q Designed to Do?

- **Provides a harmonized structure and format for presenting quality information in Common Technical Document (CTD)/electronic CTD for registration of pharmaceuticals for human use**
  - **Module 2 Quality Overall Summary (QOS)**
  - **Module 3 Quality**
- **M4Q(R1) was developed in 2002**
- **Major improvement over paper/local submission formats**



M4Q(R2) Objectives

- **M4Q(R2) guideline will improve submission and assessment efficiency, resulting in accelerated access to pharmaceuticals by (6Es):**
  1. Encouraging global convergence of science- and risk-based regulatory approaches in the preparation of dossiers.
  2. Explaining and defining the organization and positioning of information for Modules 2 and 3.
  3. Enriching communication between regulators and applicants and enhancing lifecycle and knowledge management.

M4Q(R2) Objectives (Continued)

4. Embracing product and process innovation.
5. Enabling efficient use of digital tools for submission and assessment and preparing for the closely linked, upcoming ICH guideline on structured pharmaceutical quality submission.
6. Elucidating regulatory expectations and supporting efficient assessments, decision-making, and actions.

ICH
harmonisation for better health

Thank You!

ICH Q12: FDA Implementation Experience

WCBP 2024

CDR Mahesh Ramanadham, Pharm.D., MBA
Deputy Director
FDA/CDER/OPQ/OPPQ


Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Scope

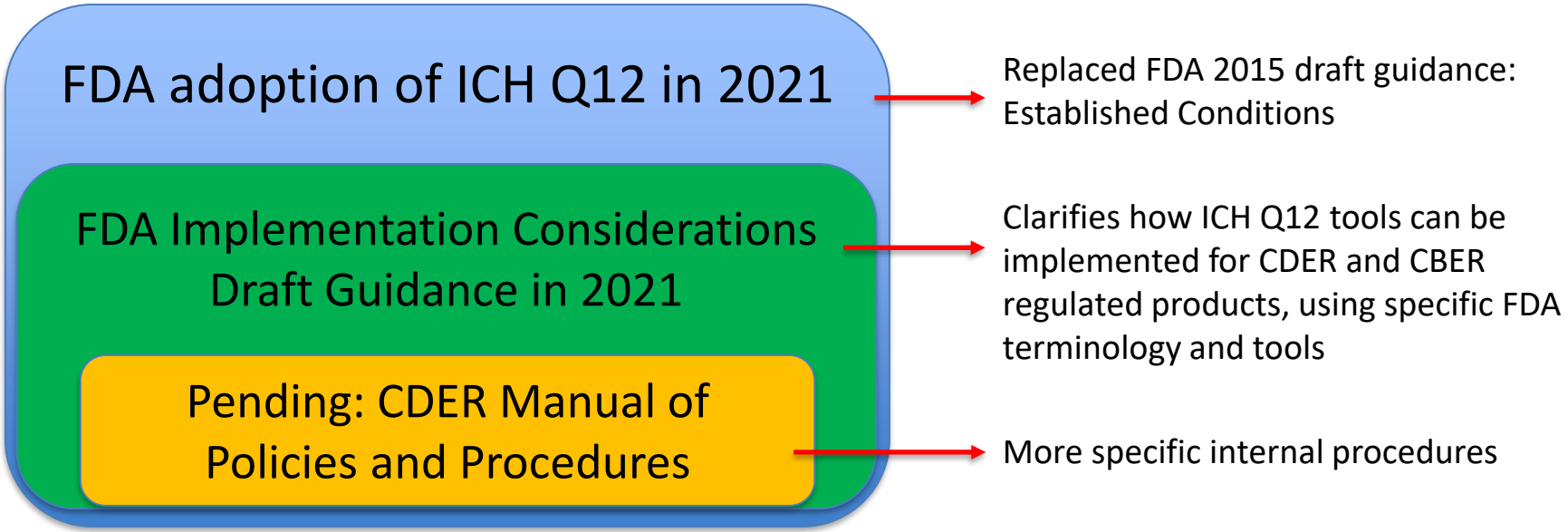
- Pharmaceutical drug substances and products that require a marketing authorization
- Drug-device combination products that meet the definition of a pharmaceutical or biological product

Fully Implemented

Tools

- Established Conditions (EC)
- Post-approval Change Management Protocols
- Product Lifecycle Management Document
- Pharmaceutical Quality Systems (PQS)
- Relationship between Regulatory Assessment and Inspection
- Structured Approaches for Frequent CMC Post-Approval Changes

ICH Q12: FDA Implementation



ICH Q12 FDA Implementation: Application Demographics

Application Type	Original	Supplement	Approved
Biologic License Application	4	15	11
New Drug Application	2	6	7
Abbreviated New Drug Application	0	0	0
Total	6	21	18

- Table includes applications from FDA's established conditions pilot (2019) and post implementation (2021 – present)

Examples of Approved ECs

- Reduced volume of ECs, with reporting categories consistent with regulation & guidance, or with reduced reporting categories
- Both parameter-based and performance-based approaches for manufacturing process and analytical methods
- Manufacturing facility specific ECs
- ECs for device constituent part for a drug-device combination product (e.g., CCS, performance specification)

Reflections from FDA's Initial Experience

- Clarity in the application cover letter that ECs are proposed is pivotal to success
- Clear scientific justification for ECs and reporting categories is critical
- PLCM has been a pivotal tool for clarity in proposed and approved ECs and reporting category
- FDA assessment of PQS driven by understanding which facilities will implement ECs, and whether the proposed reporting categories differ from regulation & guidance

Applicant Interactions

- Responsive to FDA information requests, e.g.:
  - Additional clarity in PLCM (e.g., specific reporting categories, facilities)
  - Additional information to justify ECs or reporting categories
  - Requested EC and reporting category revisions
- Some applicants did not provide requested clarifications, rather, withdrew proposals for ECs
- To date, FDA has not denied approval of an application due to Q12

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Updates and a Perspective on ICH Q12 Implementation in Japan

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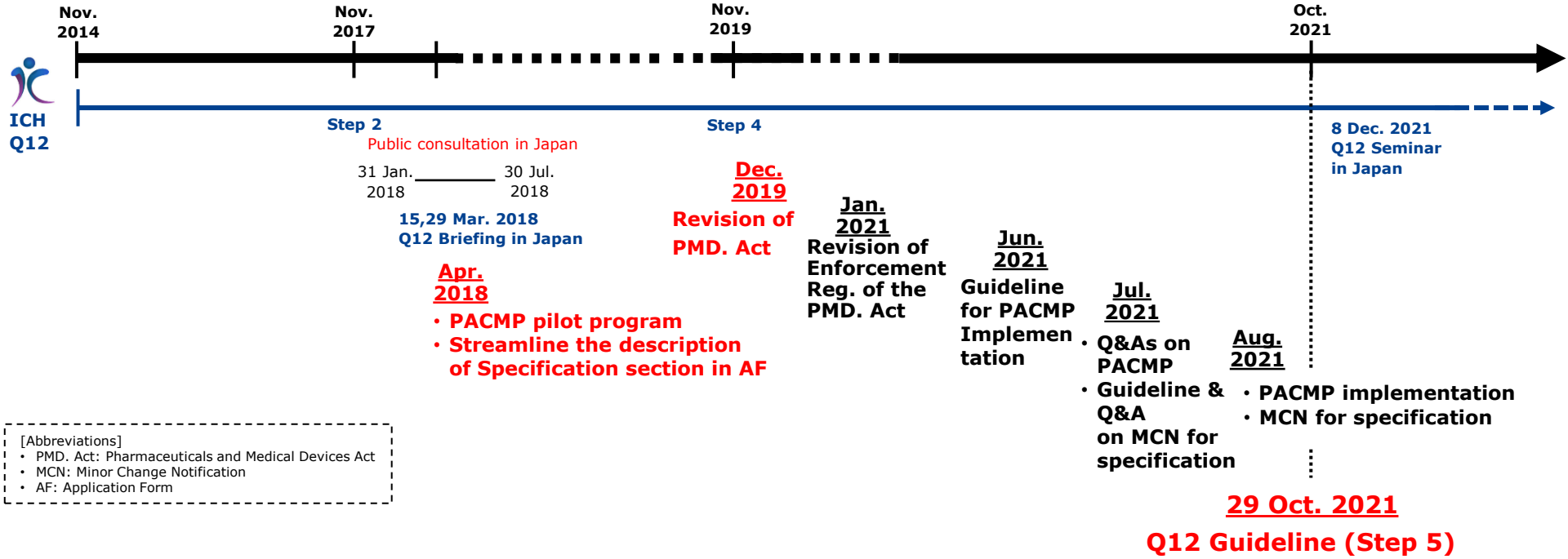
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

ICH Q12 Implementation in Japan



[Abbreviations]
- PMD. Act: Pharmaceuticals and Medical Devices Act
- MCN: Minor Change Notification
- AF: Application Form

Major Challenges toward Successful/Harmonized Implementation

- Effective **Pharmaceutical Quality System (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**
  - Harmonized document across regions (e.g., format; how each element should be presented)

Recent MHLW's Initiatives

(MHLW; Minister of Health Labour and Welfare)

9. Jun, 2023
Report of the Panel of Experts on Comprehensive Measures to Achieve Rapid and Stable Supply of Pharmaceuticals
https://www.mhlw.go.jp/stf/newpage_33548.html (in Japanese)

- Ensure stable supply
- Strengthen drug discovery capabilities
- Resolve the issues of "drug lag/loss"
- Efforts toward appropriate distribution of pharmaceuticals

10. Jul, 2023～
Review Committee on Pharmaceutical Regulation for Strengthening Drug Discovery Capabilities and Securing Stable Supply
https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html (in Japanese)

- Promotion of pharmaceutical development
- Clinical trials
- Post-marketing safety measures
- Dissemination of information
- **Quality**

  Review the description of manufacturing process in Application Form and post-approval CMC changes, taking into account international consistency

Future Opportunity for further Convergence

- Adopted direction at 4th review committee (13 Oct. 2023)

https://www.mhlw.go.jp/stf/newpage_35743.html (in Japanese)

Post-Approval Change Reporting Categories

ICH Q12 Classification	Japan	US	EU
Prior Approval	PCA (Partial Change Application)	PAS	Type II Variation
Notification Moderate		CBE-30	Type IB Variation
Notification Low	MCN (Minor Change Notification)	CBE-0	Type IA_{IN} Variation
		Annual Report	Type IA Variation
Not Reported	Not Approved Matters		

- Introduce "middle-category" (pilot program)
- Introduce "annual report" (pilot program)
- Review the description of Application Form
  - to achieve internationally harmonized & risk-based approach for post-approval CMC changes
  - discuss the need for the overhaul of "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law in 2005"

https://www.pmda.go.jp/files/000153677.pdf (in English)

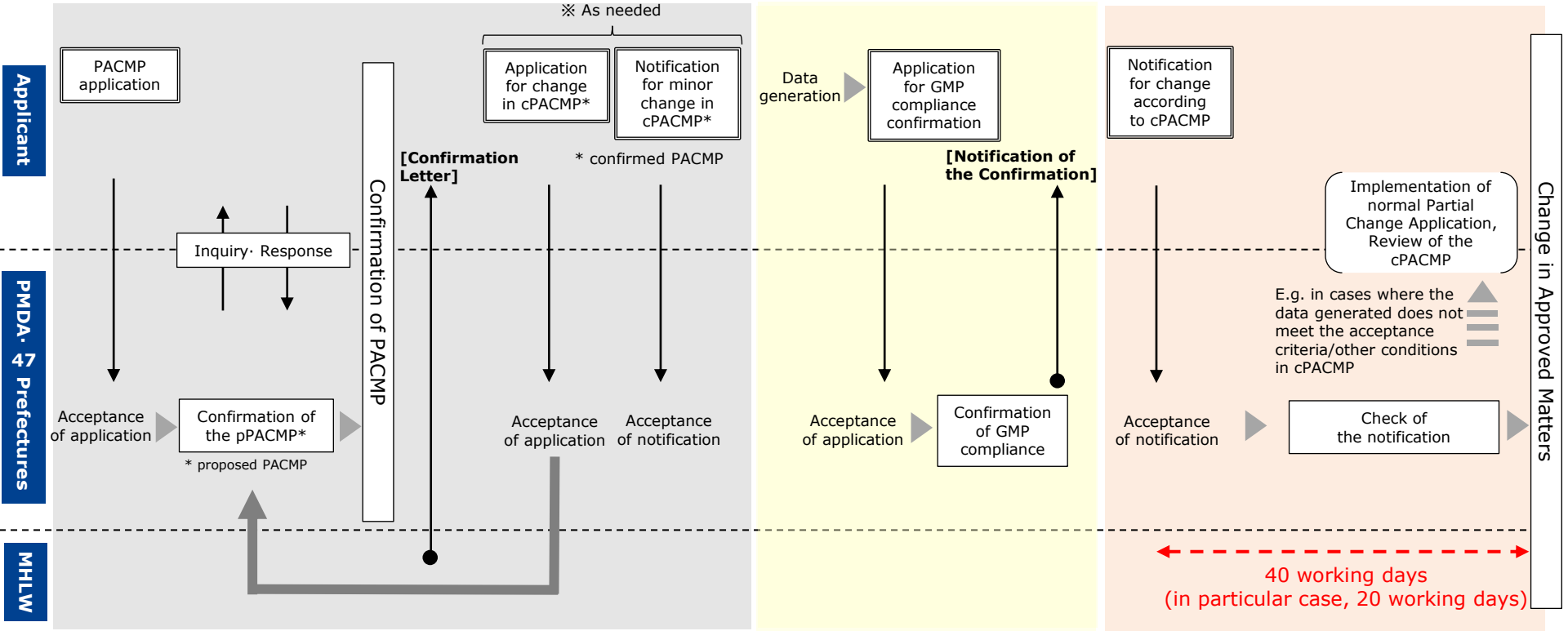
in a very early stage of discussion

Thank you & look forward to panel discussion!

KISHIOKA Yasuhiro
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency

Back-up

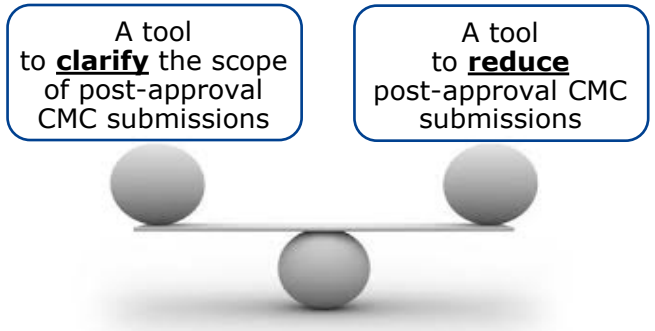
PACMP: Guideline (MHLW PSEHB/ELD Notification 0616-14, 16 Jun. 2021)



https://www.mhlw.go.jp/hourei/doc/tsuchi/T210618I0010.pdf (in Japanese)

Divergent Views/Expectations on ECs

- ICH Q12
  - The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed. *(Chapter 1.3)*
  - ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority. *(Chapter 3.2.1)*

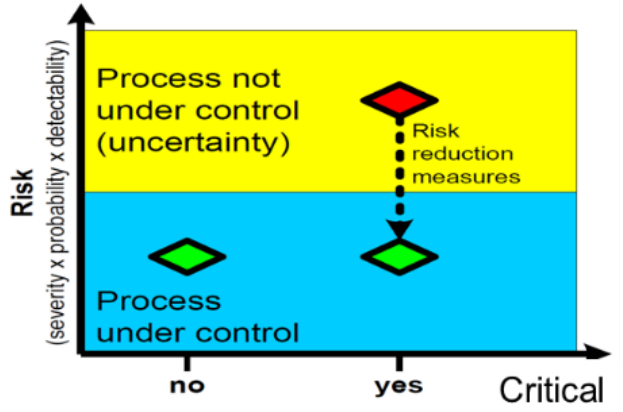


To what extent can enhanced understanding of product and process reduce ECs?

ECs for manufacturing process parameters

- ICH Q12 Chapter 3.2.3.1

Process parameters that need to be controlled to ensure that a product of required quality will be produced should be considered ECs. These ECs are identified through an initial risk assessment and application of knowledge gained from executed studies, prior knowledge, and a criticality assessment that determines the level of impact that a process parameter could have on product quality. The criticality assessment should account for severity of harm and whether the ranges studied sufficiently account for the expected variability in the EC. CPPs and other process parameters where an impact on product quality cannot be reasonably excluded should be identified as ECs.



ICH Q-IWG Discussion (2013)

Facilitation Questions for M4Q(R2) Topic

1. What is meant by efficiency? Is it only time-based, or are there other efficiencies to explore with M4Q revision?

2. Q9 was recently revised. What are some of the potential key interfaces between Q9 and M4QR2? (I see this as a risk comms question…perhaps there are others).

3. The scope of M4Q has expanded in the revision (as per the approved concept paper). Can the panel comment on how this expanded scope has presented opportunities and/or challenges?

Facilitation Questions for Q12 Topic

1. How to identify ECs?
   - e.g., can ECs be identified by using platform knowledge?

2. How QMS fits into ICH Q12 implementation?

3. How to engage with different functional units in your company for implementing ICH Q12?
   - Lessons learned – good, bad, and ugly.
   - Are the benefits of using ICH Q12 tools fully recognized across your organization?