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

Updates on ICH M4Q(R2)

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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 or ICH M4Q(R2) EWG.

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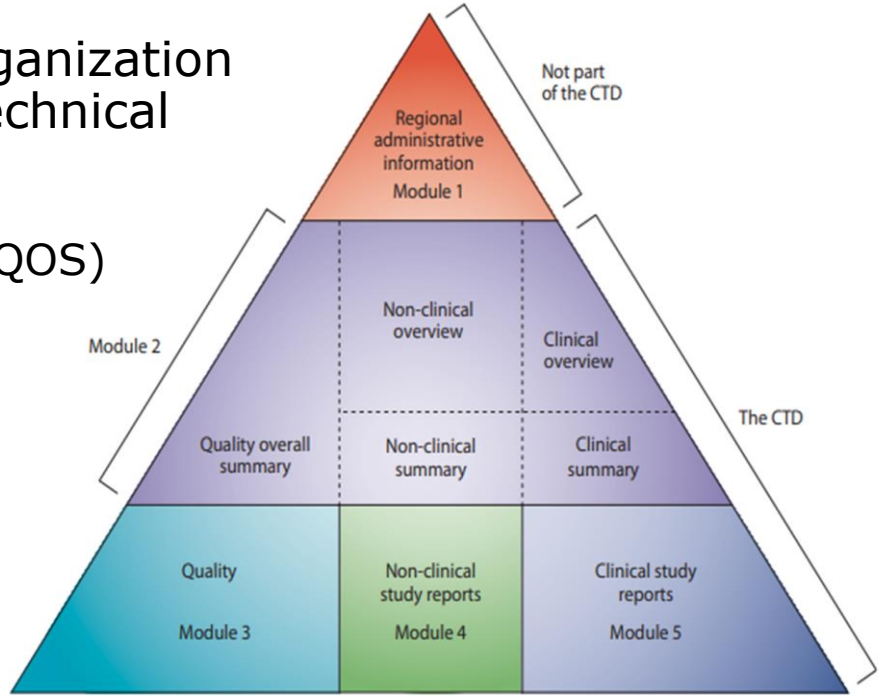
Outline

- Background & M4Q(R2) objectives
- Current EWG thinking
- Future Plan

ICH Quality Submission: M4Q(R1)

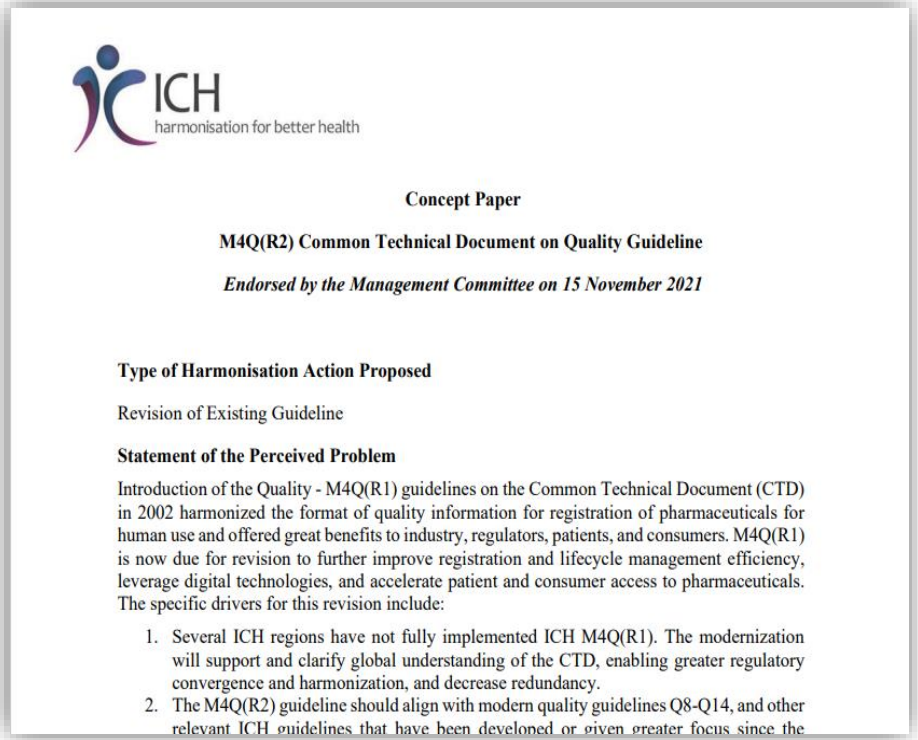
- Globally harmonized content and organization of quality information in Common Technical Document (CTD)/eCTD
  - Module 2.3 Quality Overall Summary (QOS)
  - Module 3 Quality
- M4Q(R1) published in 2002 was a substantial improvement compared to the prior state with range of submission formats and shift from paper to electronic



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

ICH M4Q(R2) Concept Paper

ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf



ICH
harmonisation for better health

Concept Paper

M4Q(R2) Common Technical Document on Quality Guideline

Endorsed by the Management Committee on 15 November 2021

Type of Harmonisation Action Proposed

Revision of Existing Guideline

Statement of the Perceived Problem

Introduction of the Quality - M4Q(R1) guidelines on the Common Technical Document (CTD) in 2002 harmonized the format of quality information for registration of pharmaceuticals for human use and offered great benefits to industry, regulators, patients, and consumers. M4Q(R1) is now due for revision to further improve registration and lifecycle management efficiency, leverage digital technologies, and accelerate patient and consumer access to pharmaceuticals. The specific drivers for this revision include:

1. Several ICH regions have not fully implemented ICH M4Q(R1). The modernization will support and clarify global understanding of the CTD, enabling greater regulatory convergence and harmonization, and decrease redundancy.
2. The M4Q(R2) guideline should align with modern quality guidelines Q8-Q14, and other relevant ICH guidelines that have been developed or given greater focus since the

What are the Issues to be Resolved?

Establishing the role of M4Q(R2) as the main source of the structure and location of regulatory quality information.

Incorporating concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines.

Enhancing the Quality Module 2 to facilitate the efficiency and effectiveness of regulatory submissions and assessments.

Expanding the scope of M4Q(R1) guideline to include all pharmaceutical drug substances and products (both chemical and biological)

Organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management.

Better capturing the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure.

ICH M4Q(R2) Objectives

- M4Q(R2) guideline will improve submission and assessment efficiency, resulting in accelerated access to pharmaceuticals by (6Es):
  - Encouraging global convergence of science- and risk-based regulatory approaches in the preparation of dossiers.
  - Explaining and defining the organization and positioning of information for Modules 2 and 3.
  - Enriching communication between regulators and applicants and enhancing lifecycle and knowledge management.
  - Embracing product and process innovation.
  - Enabling efficient use of digital tools for submission and assessment and preparing for the closely linked, upcoming ICH guideline on structured pharmaceutical quality submission.
  - Elucidating regulatory expectations and supporting efficient assessments, decision-making, and actions.

ICH elected a step-wise approach to modernize CTD Module 2 and 3

ICH M4Q(R2) will define the new structure of Module 2.3 and Module 3

When M4Q(R2) has reached step 2,
a concept paper outlines for the work on
Structure Product Quality Submission (SPQS) will be made

M4Q(R2) will think ahead but not work on implementation of structure data

M4Q(R2) Benefit Conceptual thinking

Industry

- Regulatory expectations more clear
- Facilitates applying enhanced ICH quality vision
- Quality of submissions higher
- Aligning preparations for applications
- Promotes communication with regulators
- Facilitates data and information management

Regulators

- Increased consistency in decision making
- Higher efficiency in review
- Enhances benefit-risk considerations
- Better oversight of pharmaceutical product development and quality
- Promotes communication with Industry
- Promotes communication and efficiencies among regulators

=> Faster access for patients !!!

M4Q(R2) Milestones

[Abbreviations]
- WG: Working Group
- EWG: Expert Working Group
- F2F: face to face
- PWP: Plenary Working Party

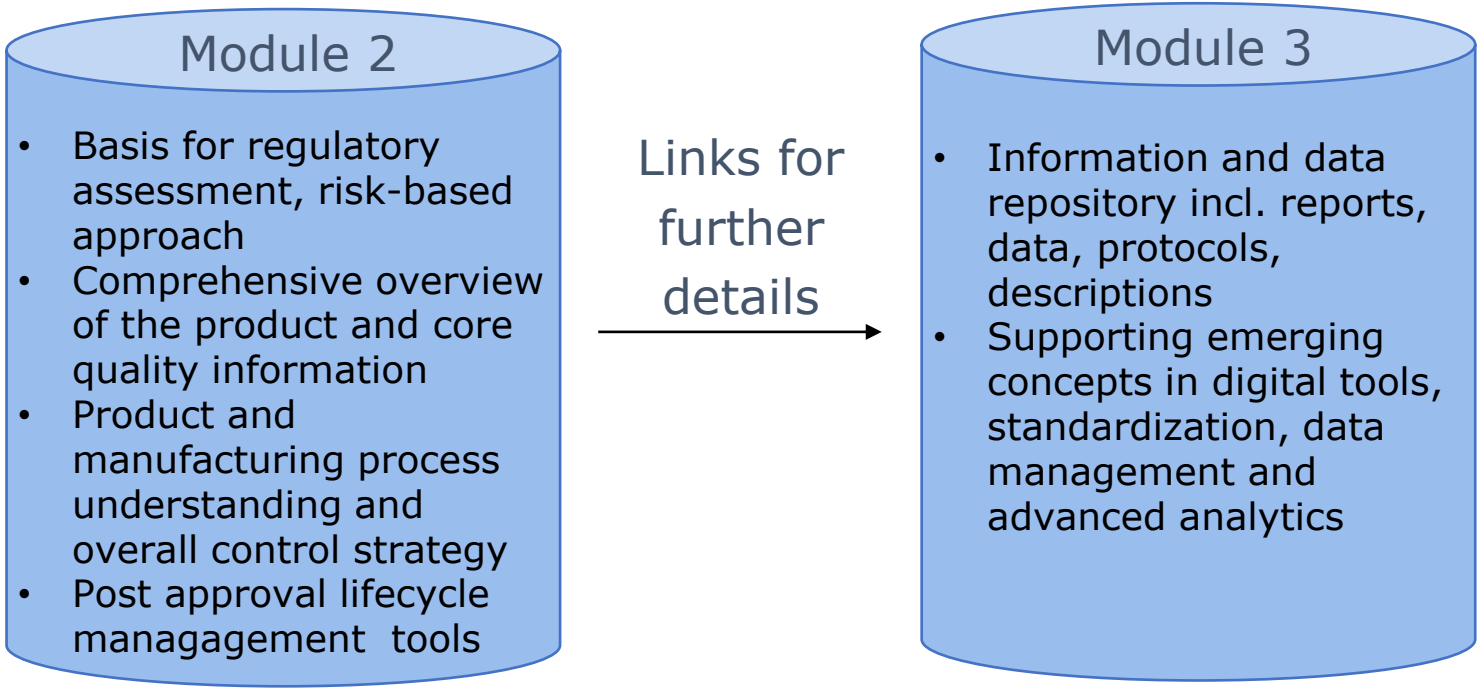
Completion date	Milestone
November 2021	ICH endorsed the Concept Paper and Business Plan and formed M4Q(R2) EWG
May 2022	F2F meeting in Athens, where the high-level conceptual thinking was defined
November 2022	F2F meeting in Incheon, where the EWG agreed on the definition of Overall Control Strategy, Roles and Objectives of Modules 2 and 3 document
March 2023	F2F (interim) meeting in Geneva, where the EWG agreed on the design of Module 3

M4Q(R2) Milestones (continued)

[Abbreviations]
- WG: Working Group
- EWG: Expert Working Group
- F2F: face to face
- PWP: Plenary Working Party

Completion date	Milestone
June 2023	F2F meeting in Vancouver, where the EWG discussed Module 2 design
November 2023	F2F meeting in Prague, where the EWG agreed on the design of Module 2 using mock examples
March 2024	informal consultation for major or show-stopper comments
June 2024	F2F meeting in Fukuoka, where the EWG addressed comments
November 2024	F2F meeting in Montreal, where the EWG reviewed and revised the guideline for PWP/constituent consultation

M4Q(R2) Establishes Module 2 as the Basis for Regulatory Assessment, Supported by Module 3



Structure of Module 2

2.3.1 Introduction

2.3.2 Overall Development and Overall Control Strategy

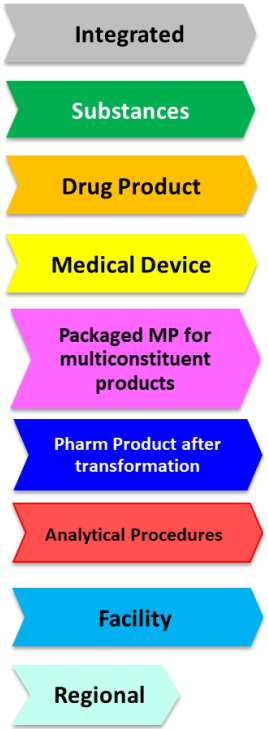
2.3.3 Core Quality Information (CQI)

2.3.4 Development summary and justifications (DSJ)

2.3.5 Product lifecycle management

- 2.3.5.1 Listing of Established Conditions (optional)
- 2.3.5.2 Reporting categories for Making Changes to Approved ECs (optional)
- 2.3.5.3 Post-approval change management protocols (PACMP), if applicable
- 2.3.5.4 Post-approval CMC Commitments, if applicable
- 2.3.5.5 Change Summary and Justification

2.3.6 Product Quality Benefit Risk (optional)

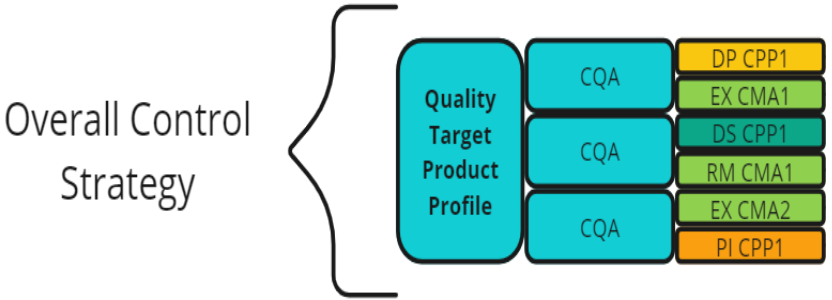


2.3.2 Overall Development and Control Strategy

- Overall development provides a concise overview of the development rationale, highlighting the critical decisions made to achieve QTPP/CQAs

- Overall control strategy aims to provide a comprehensive framework for ensuring overall product quality, rather than being a simple compilation of individual controls without consideration of their significance in assuring quality.

[Abbreviations]
- QTPP: Quality Target Product Profile
- CQA: Critical Quality Attribute
- CMA: Critical Quality Attribute



2.3.3 Core Quality Information (CQI)

- CQI supports a risk-based regulatory assessment to enable marketing authorization and facilitate lifecycle management. The information in this CQI section should include all information subject to lifecycle management per regional post-approval change requirements to ensure product quality

- The applicant should maintain the CQI throughout the product lifecycle to ensure that product quality information remains current
  - When ECs per Q12 are approved, they supersede CQIs for the purpose of lifecycle management
  - Identification of ECs does not alter the contents of the CQI section

2.3.4 Development Summary and Justification (DSJ)

- DSJ should describe how the drug substance and product, their further components (if applicable), and manufacturing process were developed, including the main choices made through development
- Should discuss all scientific and risk-based justifications, including discussion of the proposed commercial process and control strategy
- The structure of the DSJ includes a discussion and justification of the selected material used to produce them (starting materials, raw materials, excipients, etc.) and their corresponding CMAs* and CPPs as these justifications are relevant in the context of the final material targeted.
- The content of the DSJ is supportive. The applicant may amend or supplement it due to post-approval changes.

2.3.5 Product Lifecycle management

- The Product Lifecycle Management (PLCM) document serves as a central repository in the applications for Established Conditions (ECs) and other tools according to ICH Q12.

2.3.6 Product Quality Benefit Risk

- Optional, valuable in some exceptional cases (e.g. expedited reviews)
- Expected to support the overall benefit risk assessment
- Should facilitate understanding of how residual risks or uncertainties related to quality are mitigated and/or are outweighed by benefit to patients.

Module 3

- M3 serves as information and data repository that supports M2 and is presented in a globally standardized/harmonized format.
- M3 may comprise detailed information complementary to M2 and should be organized in a suitable format for easy access, analysis, and knowledge management.
- Module 3 is supportive and only amended as a result of post-approval changes.

M4Q(R2) Organization – Standard Subsections

- Most subsections of M4Q(R2) follow a standardized Description, Manufacture, Control, Storage (DMCS) model for information about materials such substances and products.

D	Description	Identifies the material and its key characteristics
M	Manufacture	Outlines the production process
C	Control	Describes quality control measures such as specifications
S	Storage	Provides stability, container closure information, and retest period/self-life

- This DMCS model applies across the main dossier sections to support efficient information management and retrieval.

Example 1

Module 2

- 2.3.1 Introduction
- 2.3.2 Overall Development and Control Strategy
- 2.3.3 Core Quality Information
- 2.3.4 Development Summary and Justifications
- 2.3.5 Product Lifecycle Management
- 2.3.6 Product Quality Benefit Risk

Module 3

6 backlinks

- 3.2.DS Drug Substance(s)
- 3.2.SI Substance Intermediate(s)
- 3.2.SM Starting Material(s)
- 3.2.RM Raw Material(s)
- 3.2.EX Excipient(s)
- 3.2.IM Impuritie(s)
- 3.2.RS Reference Standard(s)/Material(s)
- 3.2.DP Drug Product(s)
- 3.2.AP Analytical Procedures
- 3.2.FA Facilities

Relevant reports/data justifying the shelf life

2.3.3 Core Quality Information

10 backlinks

- 2.3.3.DS Drug Substance(s)
- 2.3.3.SI Substance Intermediates
- 2.3.3.SM Starting Material(s)
- 2.3.3.RM Raw Material(s)
- 2.3.3.EX Excipient(s)
- 2.3.3.DP Drug Product(s)
- 2.3.3.RS Reference Standard(s)/Material(s)
- 2.3.3.AP Analytical Procedures
- 2.3.3.FA Facilities

DP Shelf life

2.3.4 Development Summary and Justifications

Add cover

3 backlinks

- The Development Summary and Justifications describes how the product was developed including the main choices which were made through development.
- It summarises and justifies the comparability of different processes and formulations which have been used through development.
- It justifies the 2.3.2 Overall Control Strategy and the 2.3.3 Core Quality Information, as appropriate.

2.3.4.IN Integrated justifications and Overall Product Development

- 2.3.4.DS Drug Substance(s)
- 2.3.4.DP Drug Product(s)
- 2.3.4.AP Analytical Procedure(s)

Summary and discussion of the stability data that supports the shelf life

Example 2

Module 2

- 2.3.1 Introduction
- 2.3.2 Overall Development and Control Strategy
- 2.3.3 Core Quality Information
- 2.3.4 Development Summary and Justifications
- 2.3.5 Product Lifecycle Management
- 2.3.6 Product Quality Benefit Risk

Module 3

6 backlinks

- 3.2.DS Drug Substance(s)
- 3.2.SI Substance Intermediate(s)
- 3.2.SM Starting Material(s)
- 3.2.RM Raw Material(s)
- 3.2.EX Excipient(s)
- 3.2.IM Impuritie(s)
- 3.2.RS Reference Standard(s)/Material(s)
- 3.2.DP Drug Product(s)
- 3.2.AP Analytical Procedures
- 3.2.FA Facilities

Batch analysis data or CoA along with relevant data

2.3.3 Core Quality Information

10 backlinks

- 2.3.3.DS Drug Substance(s)
- 2.3.3.SI Substance Intermediates
- 2.3.3.SM Starting Material(s)
- 2.3.3.RM Raw Material(s)
- 2.3.3.EX Excipient(s)
- 2.3.3.DP Drug Product(s)
- 2.3.3.RS Reference Standard(s)/Material(s)
- 2.3.3.AP Analytical Procedures
- 2.3.3.FA Facilities

DP release/stability specifications

2.3.4 Development Summary and Justifications

Add cover

3 backlinks

- The Development Summary and Justifications describes how the product was developed including the main choices which were made through development.
- It summarises and justifies the comparability of different processes and formulations which have been used through development.
- It justifies the 2.3.2 Overall Control Strategy and the 2.3.3 Core Quality Information, as appropriate.

2.3.4.IN Integrated justifications and Overall Product Development

- 2.3.4.DS Drug Substance(s)
- 2.3.4.DP Drug Product(s)
- 2.3.4.AP Analytical Procedure(s)

Summary of justification for the specification

Work plan: Expected future key milestones

Expected future completion date	Milestone
January 2025	PWP and Constituent Consultation
March 2025	F2F (interim) meeting in Budapest
May 2025	F2F meeting in Madrid – **Step 1 Sign off**
June 2025	Step 2a Endorsement by Members of the Assembly Step 2b Endorsement by Regulatory Members of the Assembly Release for public consultation
2026	Public workshops on introduction of M4Q(R2) Step 2
June 2026	Review and resolve public comments
November 2026	Step 3 Sign-off and Step 4 Adoption of Final Guideline

Implementing M4Q(R2)

Implementing M4Q(R2) will take dedication and resources, but the effort we put in today will build the efficiencies of tomorrow--creating a faster, more reliable pathway for patients.

Acknowledgements

- ICH M4Q(R2) EWG members

Thank you for your attention!

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