M4Q(R2) Common Technical Document on Quality Guideline Update

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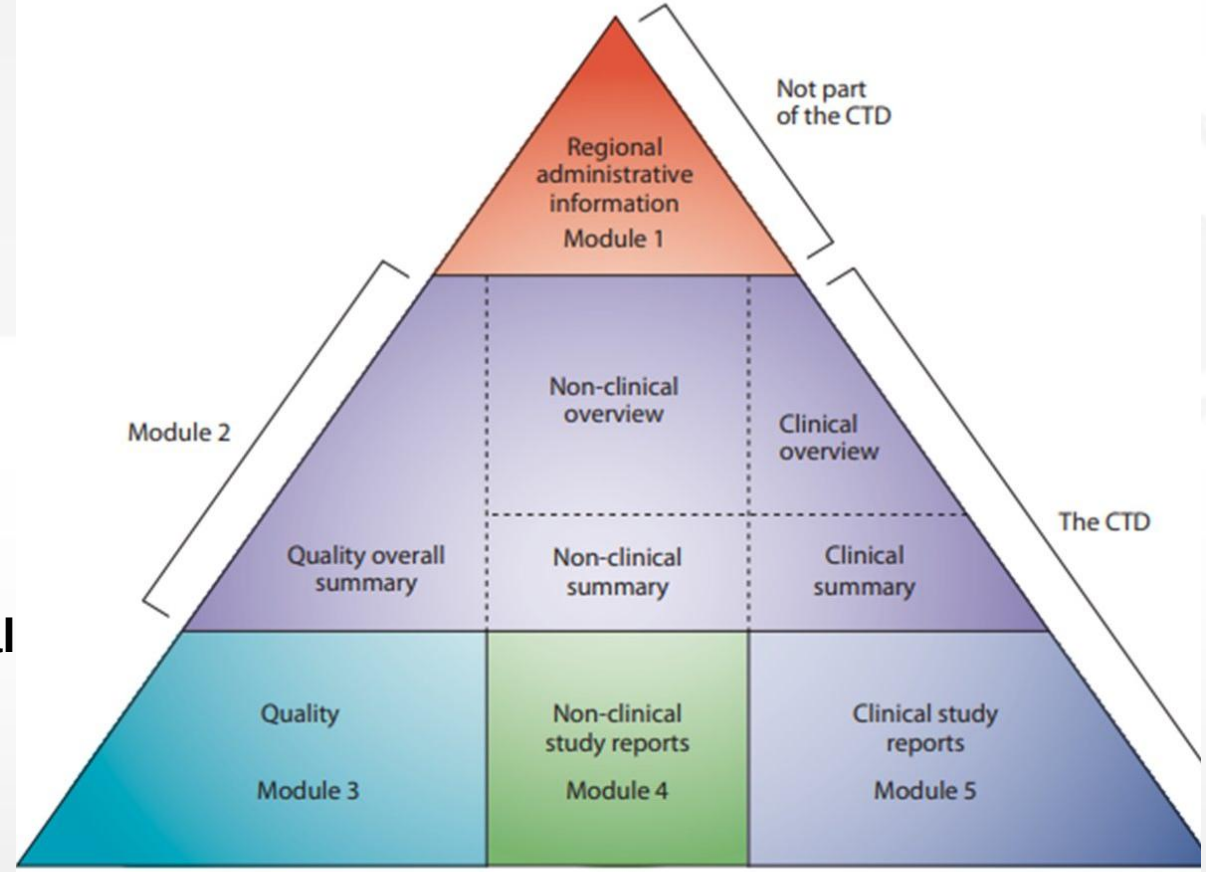
Outline

- 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

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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

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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.

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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

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M4Q(R2) Benefit Conceptual thinking

Industry

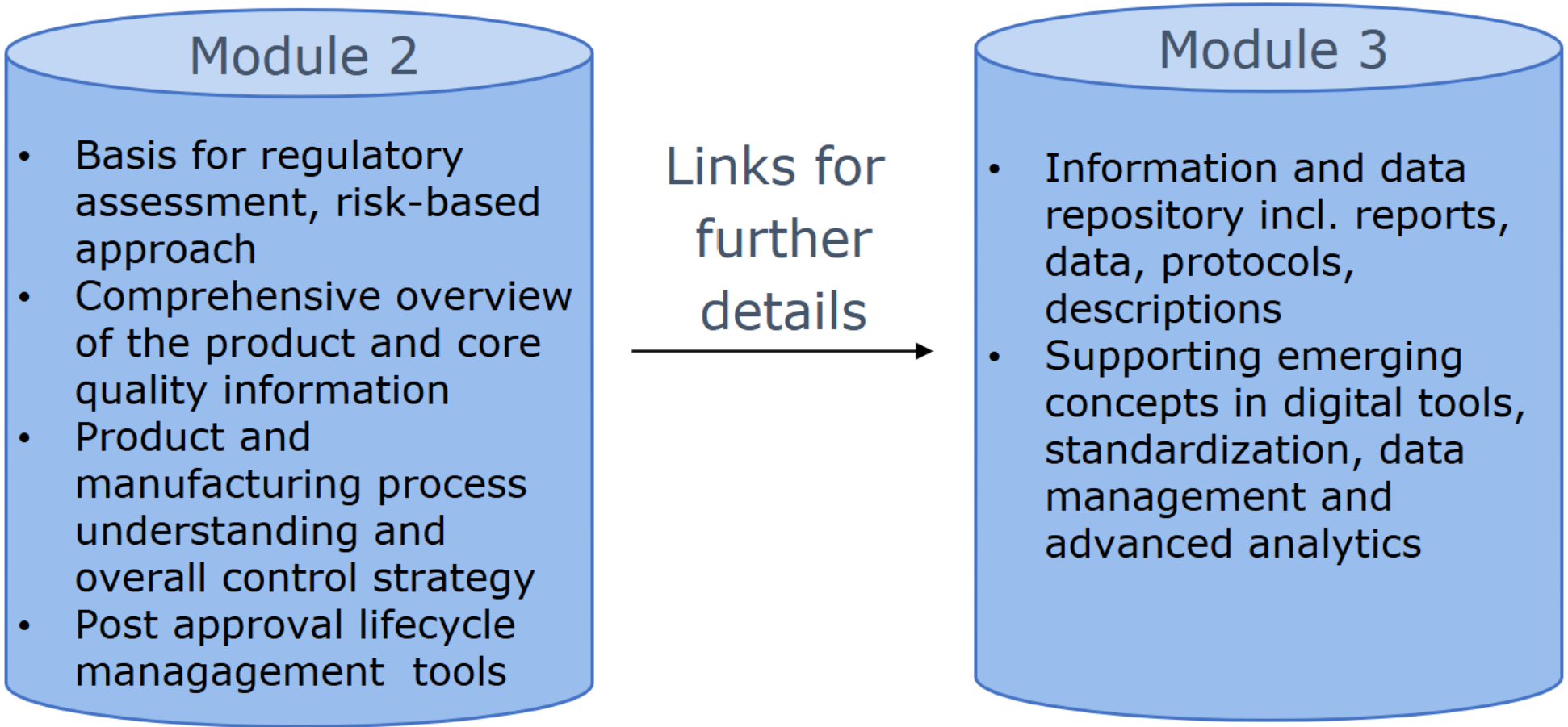
- Regulatory expectations more clear
- Facilitates applying enhanced ICH quality vision
- Quality of submissions higher
- Aligning preparations for applications
- Promotes communication with regulators
- Facilitates data and information management

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



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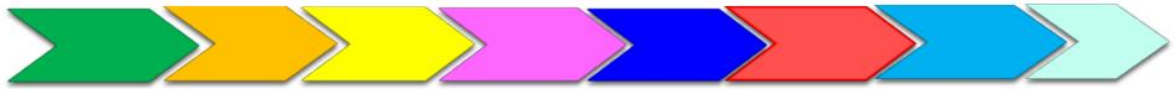
Structure of Module 2

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)

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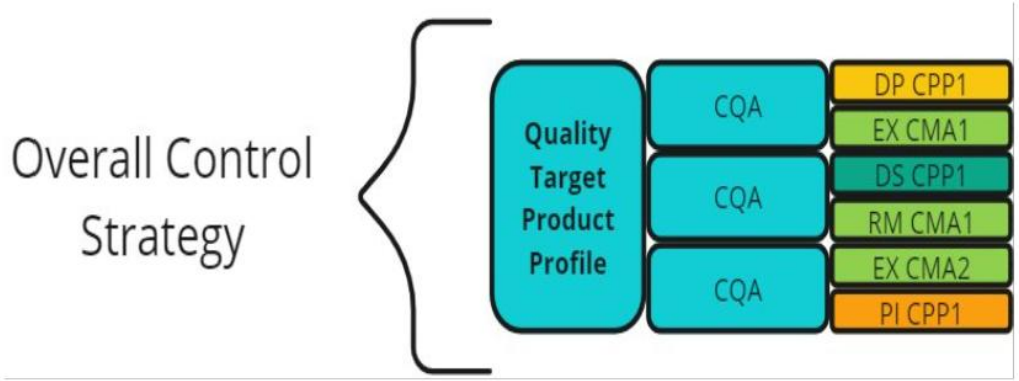
2.3.2 Overall Development and Control Strategy

- 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



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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

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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.

2.3.4 Development Summary and Justification (DSJ)

- **Additional Sections in Module 2.3 Development and Justifications**
  - Integrated Development and Justifications, if applicable
    - Overview of comparability during development
  - Integrated Discussion
    - Integrated justifications of extractables and leachables, if applicable
    - Integrated justifications of control of adventitious agents, if applicable
    - Development and justifications for products without a defined and/or isolated drug substance
      - Continuous manufacturing
      - ATMP
    - Integrated justifications of specific items, if applicable (Optional)
      - Justify commercial manufacturing process and control strategy
      - Justify specifications, nitrosamines, residual solvents, and elemental impurities

2.3.4 Development Summary and Justification (DSJ)

- **Additional Sections in Module 2.3 Development and Justifications**
  - Comparability and similarity with a reference product
    - Summary and Justifications of analytical and in vitro comparability with a reference product (generics and biosimilars), if applicable
    - Summary and Justifications of sameness with a product approved in a reference country if a reliance procedure is used

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.

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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.

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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.

Relationships among Module 2 Core Quality Information, Development Summary and Justifications, and Module 3 Body of Data

	2.3.3 Core Quality Information	2.3.4 Development Summary and Justification	3.2 Body of Data
	Information related to what the material is and its key characteristics, which is considered necessary to enable marketing authorization and facilitate lifecycle management.	*Scientific and risk-based development summary and justifications related to what the material is and its key characteristics.*	*Supportive information including reports and data related to what the material is and its key characteristics.*
Description	Nomenclature, structure, composition, key characteristics	Characterization summary, formulation development and justification	Characterization data, formulation and justification data
Manufacture	Manufacturing process description, IPCs, critical process parameters	Process development and evaluation summary	Process development and evaluation data
Control	Specifications	Summary of batch analysis, justification of specifications	Batch analysis and justification data
Storage	Container closure system description, storage conditions, and retest period/shelf life	Summary of stability studies, justification of proposed container closure system	Container closure selection data, stability data

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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

→ 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

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)

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

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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

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

M4Q(R2) - Document history

Version	History	Date
Version 1	First draft guideline based on subWGs' input	14/Feb/2024
Version 2	EWG's review and revision	21/Feb/2024
Version 3	EWG's endorsement for constituents' initial consultation	14/Mar/2024
Version 4	Changed the order of DSJ and CQI, revised (working) definition of CQI, and removed the statement of DSJ and Module 3 in post-approval communications (working)	08/Jun/2024
Version 5	EWG subWGs revised the draft guideline per constituents' initial consultation	25/Oct/2024
Version 6	EWG's endorsement for constituents' formal consultation	02/Dec/2024

Work plan: Expected future key milestones

Expected future completion date	Milestone
Nov. 2024	*ICH meeting in Montreal, Canada – EWG agrees on the second draft of M4Q(R2) guideline*
Jan. 2025	*Plenary Working Party (PWP) and Stakeholder Consultation (Formal)*
May 2025	*ICH meeting in Madrid, Spain – Step 1 Sign off*
Jun. 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*
Nov. 2026	*Review and resolve public comments*
Jun. 2027	*Step 3 Sign-off and Step 4 Adoption of Final Guideline*

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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.

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ICH M4Q(R2) Expert Working Group

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Thank You!

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use