

ICH M4Q(R2) and the Way Forward

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ICH Guideline Training by National Institute of Food and Drug Safety Evaluation,
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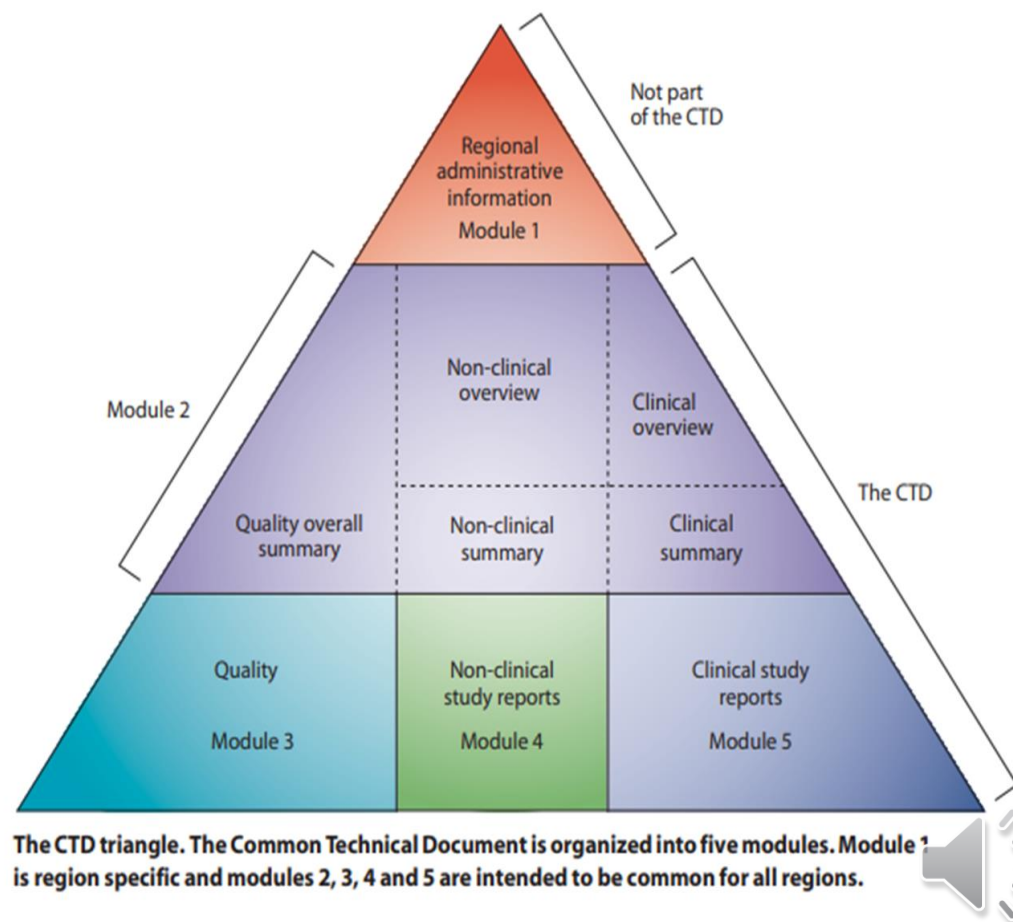


International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

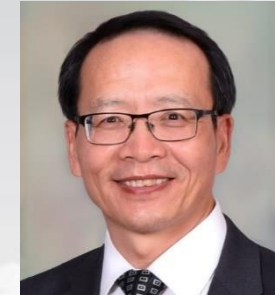
What was M4Q(R1) Designed to Do?



- 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) was a substantial improvement compared to the prior state with regional submission formats



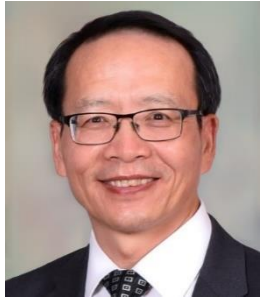
What Are Perceived Problems with M4Q(R1)?



- Global Implementation
 - Need to support global understanding and regulatory convergence
- Alignment with Modern Guidelines
 - Integration with contemporary quality guidelines (Q8-Q14)
 - Incorporation of other relevant ICH guidelines developed since 2002
- Product Coverage
 - Need to provide clear information location guidance for complex products such as antibody-drug conjugates, vaccines, ATMPs/Cell & Gene Therapies & Tissue Engineered Products or multiconstituent products that meet the definition of a pharmaceutical or biological product
- Digital Technology Integration
 - Leverage advances in digital tools and data management
 - Enhance regulatory submission and assessment efficiency



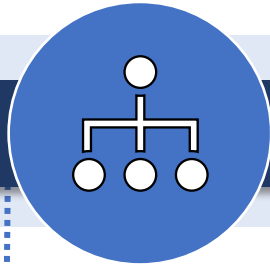
What are the Issues to be Resolved?



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



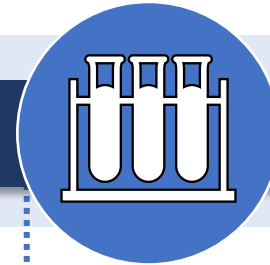
Establishing the role of M4Q(R2) as the main source of the structure and location of regulatory quality information.



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



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



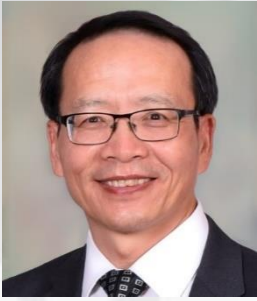
Better capturing the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure.



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



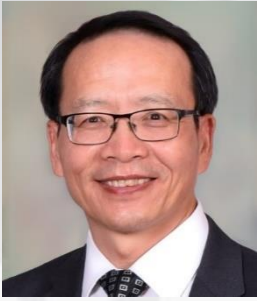
M4Q(R2) Objectives: The Six Strategic Elements (6Es)



- **Encouraging** global convergence of science- and risk-based regulatory approaches in dossier preparation
- **Explaining** clear organization and positioning of information for CTD Modules 2 and 3
- **Enriching** communication between regulators and applicants while enhancing lifecycle and knowledge management
- **Embracing** product and process innovation to support modern pharmaceutical development
- **Enabling** efficient use of digital tools for submission and assessment, preparing for upcoming structured pharmaceutical quality submission guidelines
- **Elucidating** regulatory expectations to support streamlined assessments, decision-making, and regulatory actions

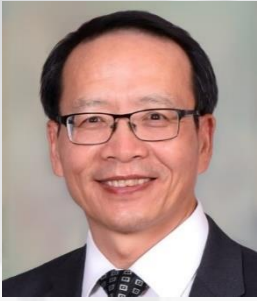


Evolution from M4Q(R1) to M4Q(R2)



- Enhanced Digitalization: Sufficient granularity to facilitate digital submissions
- Emerging Technologies: Accommodation of advanced manufacturing, AI/ML, bioinformatics
- Structured Data Management: Support for modern data management processes
- Lifecycle Management: Better integration of post-approval change management
- Flexibility: Adaptable structure for all types of medicinal products

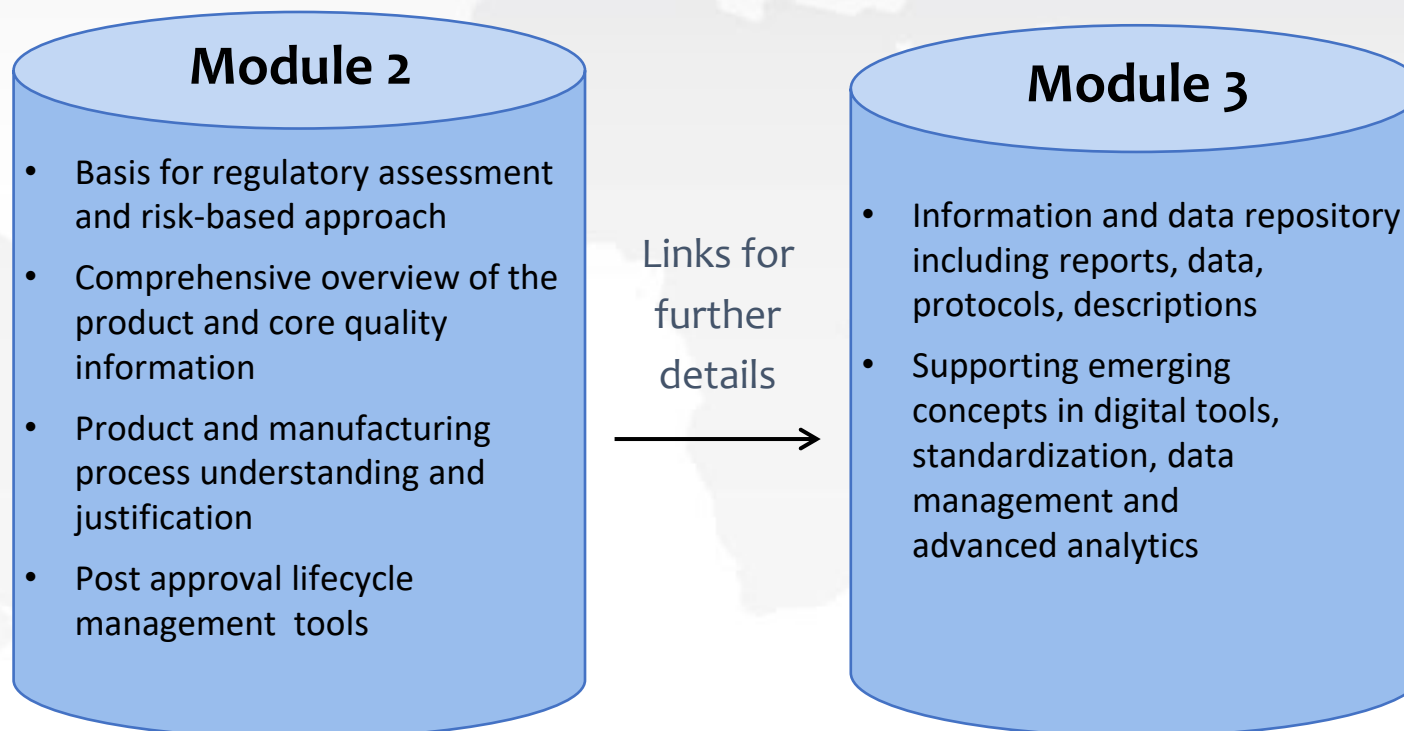
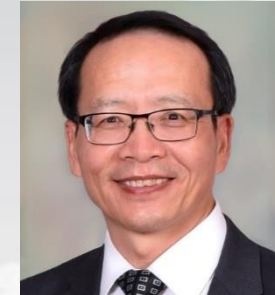




- All medicinal products for human use and their constituents
- Initial marketing authorization applications including master files
- Post-approval submissions
- Flexible accommodation of emerging product types
- Key Structural Elements:
 - Module 2.3: Quality Overview to provide the “What” and “Why”
 - Module 3: Body of Data to provide the “How” and detailed data



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



M4Q(R2) enabling:

- ✓ efficient, effective, patient-centric and globally harmonised submissions, assessment and lifecycle management, and minimize dossier redundancies
- ✓ various types of submission and product modalities
- ✓ future implementation of structured product quality submissions





Overall Development and Overall Control Strategy

Provide a holistic view of the medicinal product and submission

Development Summary and Justifications

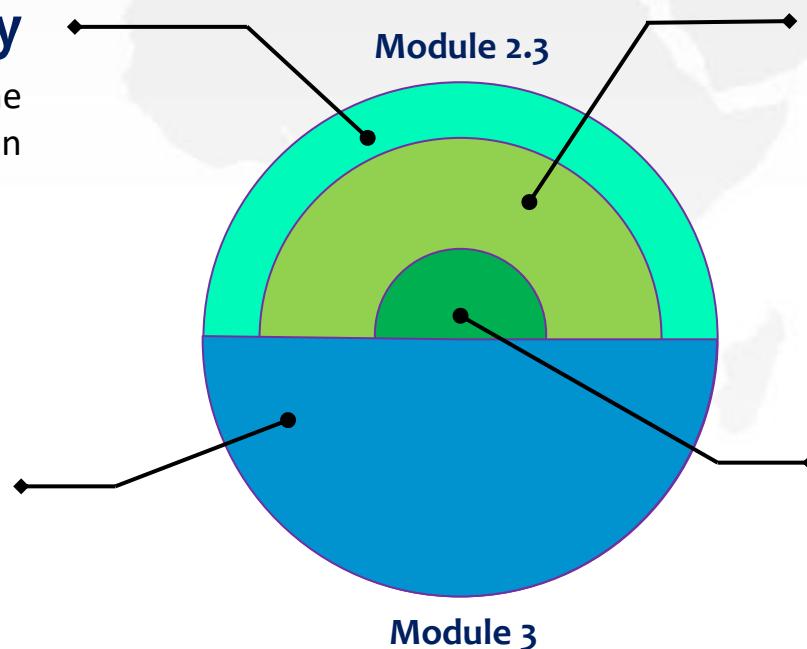
Summarizes the development process and provides justifications

Body of Data

Offers additional in-depth information to support the submission

Core Quality Information

Focuses on the essential quality aspects of the product



Module 2.3: Quality Overview to provide the “What” and “Why”
Module 3: Body of Data to provide the “How” and detailed data



M4Q(R2) Structure Overview



Module 2

2.3.1 General Information

{ Essential product details, optionally supported by a schematic

2.3.2 Overall Development and Overall Control Strategy

{ High level summary of the development and overall control strategy, including the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and how control elements ensure consistent quality

2.3.3 Core Quality Information (CQI)

{ Information needed to support a science- and risk-based review for product approval and ongoing lifecycle management

2.3.4 Development Summary and Justification (DSJ)

{ Scientific and risk-based rationale for development, including justifications for specifications and control strategies

2.3.5 Product Lifecycle Management (PLCM)

{ Strategy for managing post-approval changes, including a summary of changes, the PLCM, and any associated protocols or commitments

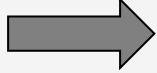
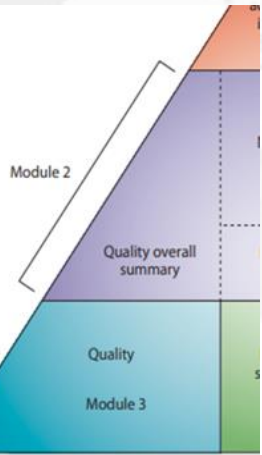
2.3.6 Product Quality Benefit Risk (Optional)

{ Optional summary of how quality-related risks are mitigated and justified in the context of the product's therapeutic benefits, especially relevant for expedited review pathways

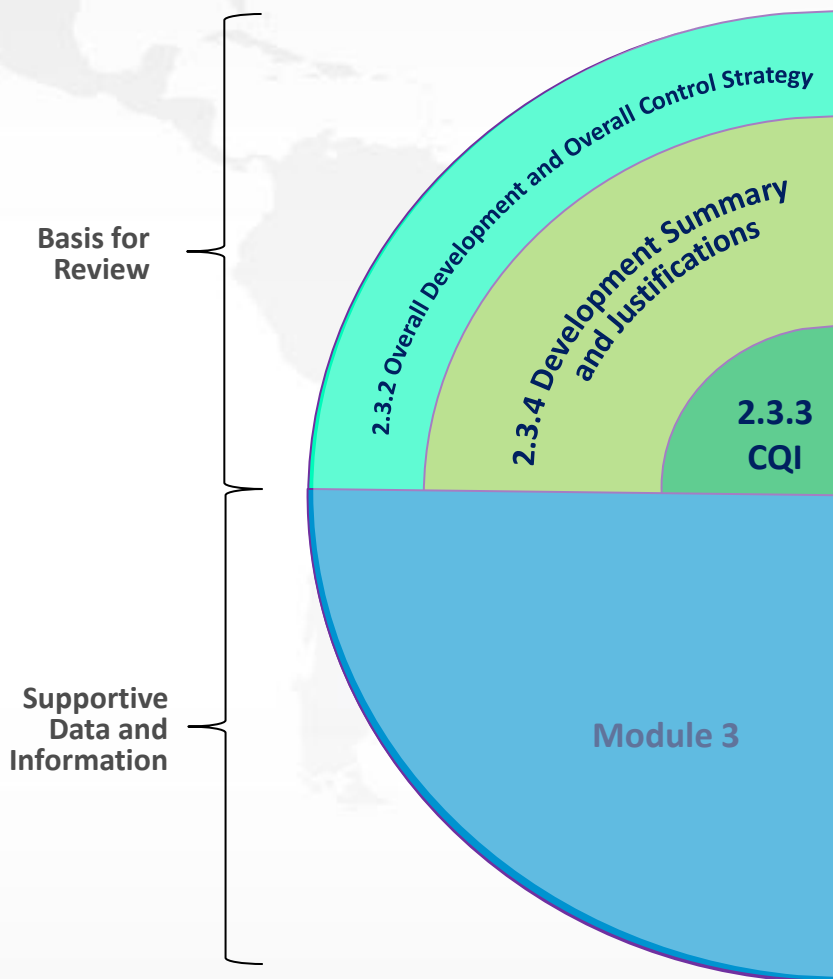
Module 3

3.2 Body of Data

{ Detailed descriptions of methods, data, and other relevant quality information that supports Module 2.3



M4Q(R2) – How Sections Work Together



Function During Initial Marketing Authorisation

Facilitates overall understanding and supports an efficient assessment

Describes how the product and manufacturing process were developed, including science- and risk-based justifications

Information considered necessary to support a science- and risk-based regulatory assessment

Repository for detailed descriptions of methods, data, and other assessment-relevant quality information

Function During Lifecycle Management

The integrated Module 2.3 sections and Development Summary and Justifications are supportive and may be supplemented or amended due to a Post-approval change

The content of Core Quality Information (CQI) should be maintained throughout the product lifecycle to ensure that product quality information remains current.

The M3 content is supportive and may be supplemented or amended due to a Post-approval change



M4Q(R2) Structure: 2.3.1 General Information



Information should be provided, when applicable:

- Drug substance(s): Non-proprietary or common name
- Drug product(s): Non-proprietary or common name
- Dosage form(s) and drug release profile(s)
- Strength(s) and form of drug substance for strength expression
- Administration: Route(s) and methods
- Primary packaging description
- Medical device(s) or co-packaged item(s)
- Maximum daily dose

Optional Enhancement:

- Schematic representation (picture) illustrating product components and functional relationships

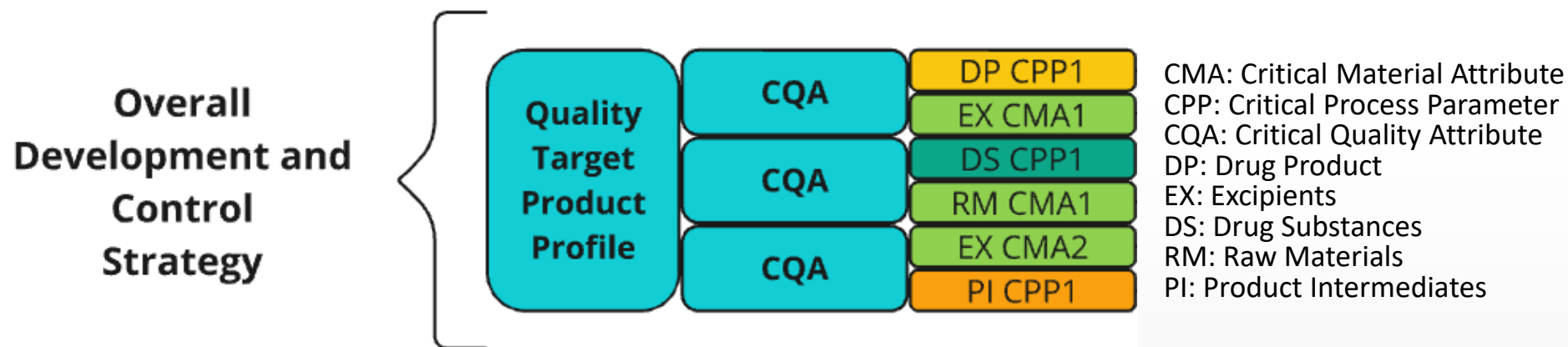


M4Q(R2) Structure: 2.3.2 Overall Development and Overall Control Strategy

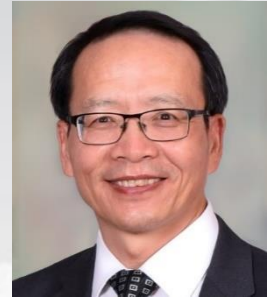


- Strategic Purpose:
 - High-level overview facilitating understanding and efficient assessment
 - Built upon ICH Q8, Q10 concepts considering patient needs
 - Reflects the Core Quality Information content

- Three Integrated Components:
 - Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)
 - Overall Product Development Strategy
 - Overall Control Strategy Representation



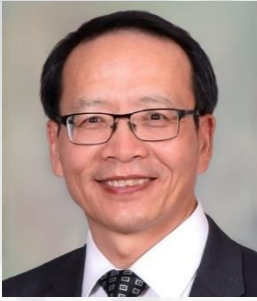
M4Q(R2) Structure: 2.3.3 Core Quality Information



- Definition and Scope:
 - Information considered necessary to support a science- and risk-based regulatory assessment to enable marketing authorization and facilitate lifecycle management.
- Key Characteristics:
 - Assessment Basis: Supports regulatory decision-making
 - Lifecycle Management: Subject to regional post-approval change requirements
 - Current Information: Must be maintained throughout product lifecycle
 - Comprehensive: Includes all information subject to lifecycle management
- Important Principle:
 - Identification of Established Conditions (ECs) per ICH Q12 should NOT result in reduction of information submitted in marketing authorization application



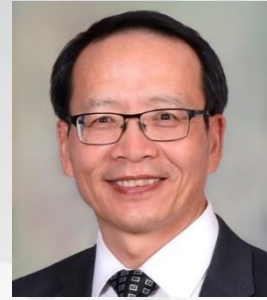
M4Q(R2) Structure: 2.3.4 Development Summary and Justification



- Primary Purpose:
 - Describe how drug substance, product, components if applicable, and manufacturing process were developed
 - Include main choices made throughout development
 - Provide science- and risk-based justifications for commercial process and control strategy
- Key Content Areas:
 - Process Development: How commercial manufacturing was established
 - Control Strategy Justification: Why specific controls were selected
 - Development Choices: Rationale for key decisions affecting product quality
- Content Nature:
 - Supportive - may be amended or supplemented for post-approval submissions



M4Q(R2) Structure: 2.3.5 Product Lifecycle Management



- Purpose: Framework for managing changes throughout product lifecycle
- 2.3.5.1 - Change Summary and Justifications (Post-Approval):
 - Summary of proposed change and background
 - Table with present vs. proposed content
 - Updated CTD sections with cross-references
 - Justification for proposed updates
- 2.3.5.2 - Product Lifecycle Management Document (PLCM):
 - List of Established Conditions and Reporting Categories (Optional)
 - Post-approval Quality Commitments, if Applicable
 - List of Post-Approval Change Management Protocols (PACMPs), if Applicable
- 2.3.5.3 - Content of PACMPs, if Applicable

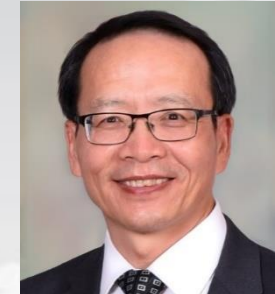


M4Q(R2) Structure: 2.3.6 Product Quality Benefit Risk (Optional)

- Purpose: Support overall benefit-risk discussion in clinical overview (Module 2.5)
- When Particularly Relevant:
 - Expedited Review Pathways: High unmet medical need situations
- Key Content:
 - Risk Mitigation Approach: How quality risks are addressed
 - Patient-Centric Benefits: How benefits outweigh residual risks or uncertainties
 - Impact Assessment: Effect on safety and/or effectiveness
 - Adequacy Explanation: Why product quality is considered adequate for intended use



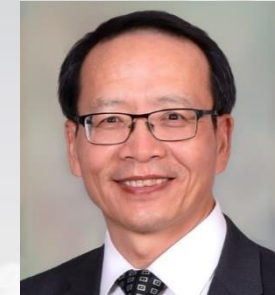
M4Q(R2) Structure: Module 3



- Module 3 serves as a repository for detailed descriptions of methods, data, and other relevant quality information that supports Module 2.3
- Information in Module 3 is supportive and may be amended or supplemented as a result of post-approval changes



M4Q(R2) introduces specific subsections for materials/components



- Facilitates re-use of information/ minimises duplication
- Alignment with ISO IDMP standards
- Information organised in defined substructure (DMCS)
- Information on analytical procedures and facilities applies across materials and is presented in dedicated sections with separate substructure



Drug Substance (DS)



Substance Intermediate (SI)



Raw Material (RM)



Starting / Source Material (SM)



Excipient (EX)



Reference Material (RS)



Impurities (IM)



Drug Product (DP)



Product Intermediate (PI)



Packaged Medicinal Product for multiconstituent products (PM)



Pharmaceutical Product after transformation (PH)



Medical Device (MD)



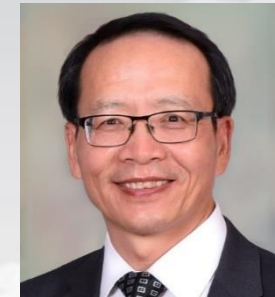
Facilities



Analytical Procedures



M4Q(R2) Organization – Standard Subsections



Most subsections of M4Q(R2) follow a standardized Description, Manufacture, Control, Storage (DMCS) model for information about materials, such as 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/shelf-life |

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



Example of DMCS Model for Drug Product

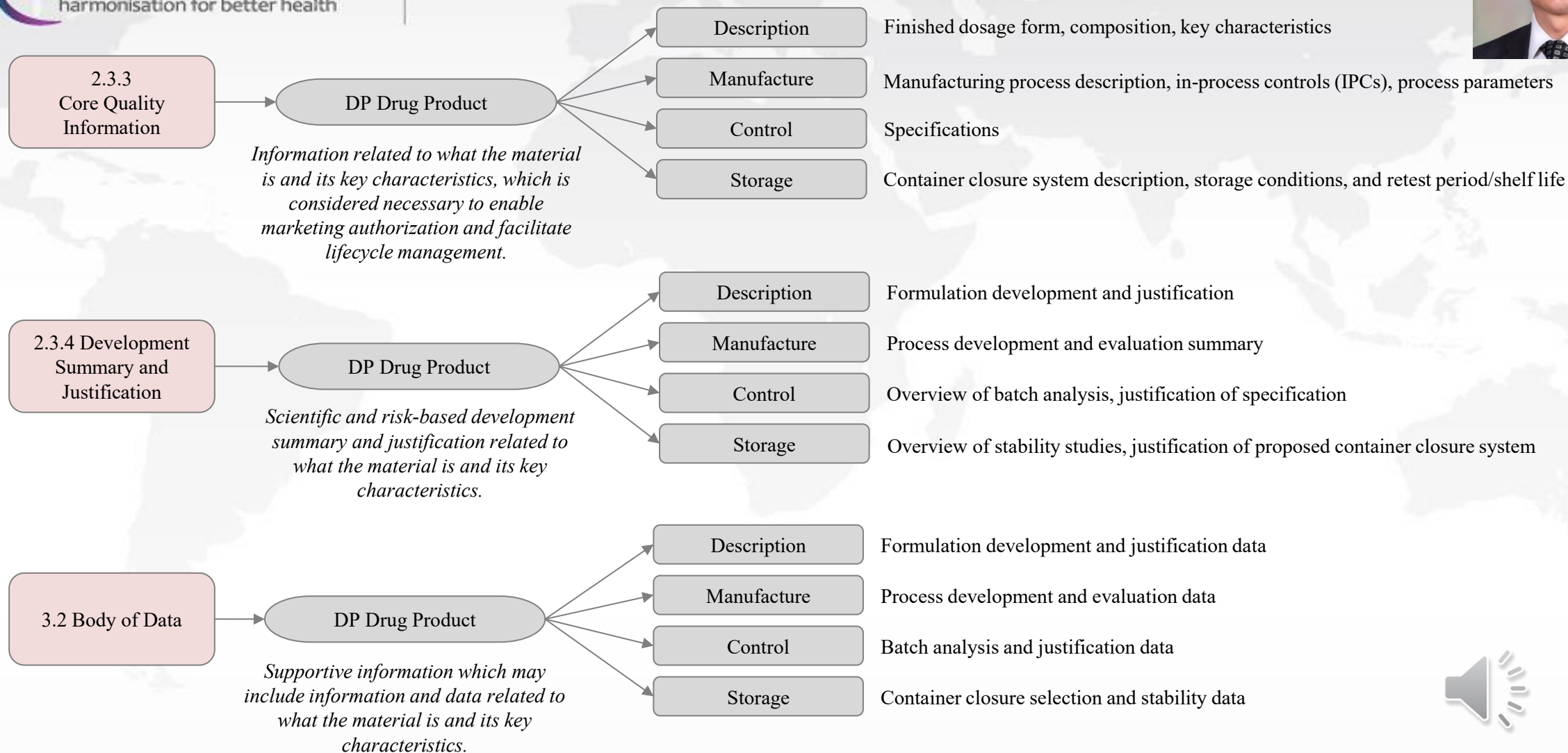
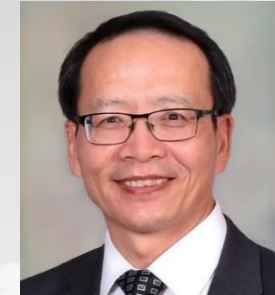


Figure 1: Illustration of relationships among sections 2.3.3 Core Quality Information, 2.3.4 Development Summary and Justifications, and Module 3.2 Body of Data in the context of DMCS Model used for materials.



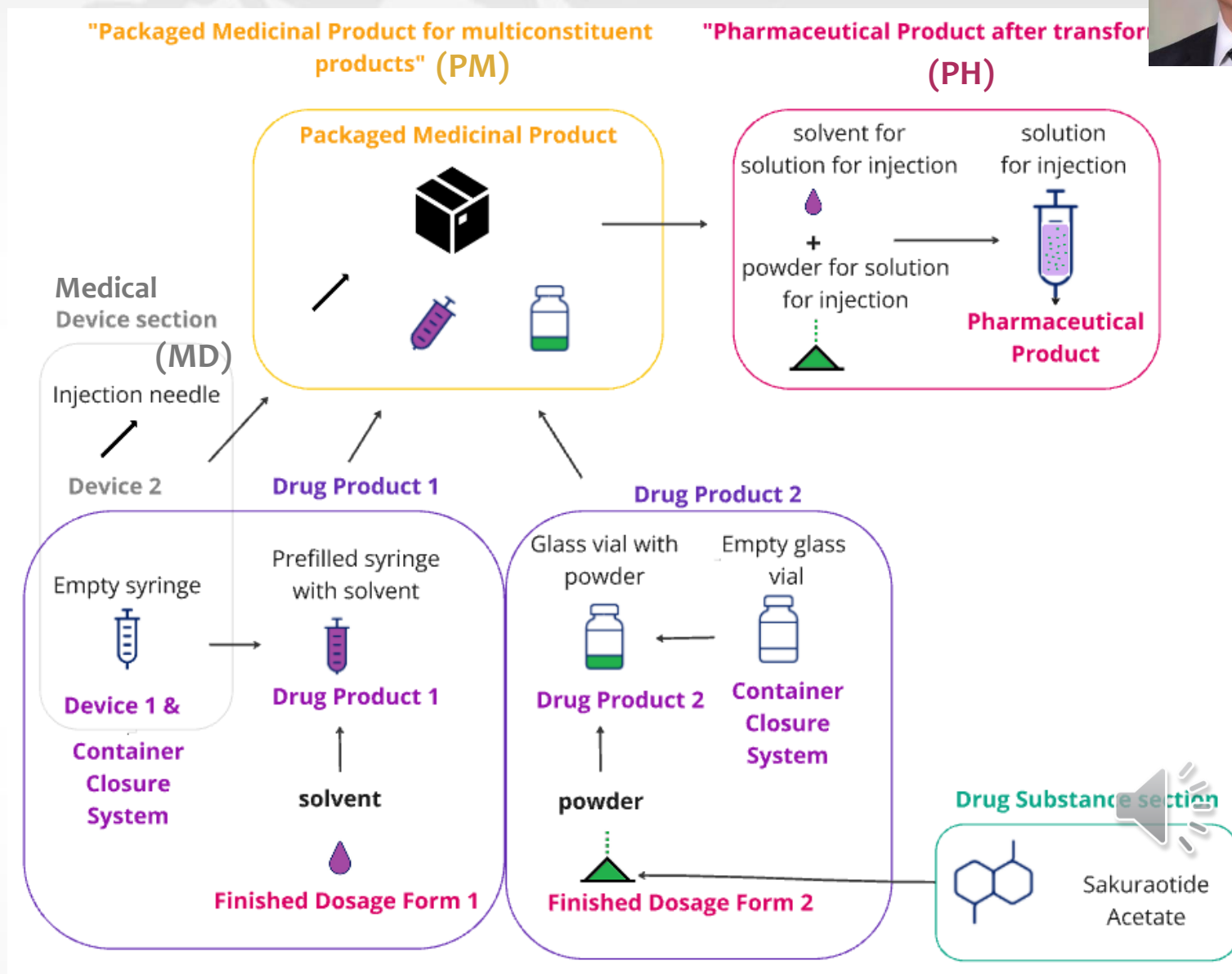
- **Drug Product (DP)**
 - The Finished Dosage Form in the final immediate packaging intended for sale or supply
- **Medicinal Product**
 - Pharmaceutical product or combination of pharmaceutical products that can be administered to human beings or animals for treating or preventing disease, with the aim of making a medical diagnosis or to restore, correct or modify physiological functions
- **Packaged Medicinal Product**
 - Medicinal Product in a container being part of a package, representing the entirety that has been packaged for sale or supply
- **Multiconstituent products (PM)**
 - Multiconstituent products consist of two or more constituents that are intended to be used together for a specific therapeutic, diagnostic or preventive purpose, and that are packaged in a container or in a unit as a marketing pack. Multiconstituent products may include one or more drug product constituents, or a combination of these with additional finished dosage forms and/or medical device(s).
- **Pharmaceutical Product**
 - Qualitative and quantitative composition of the product as administered to the patient in line with regulated product information.

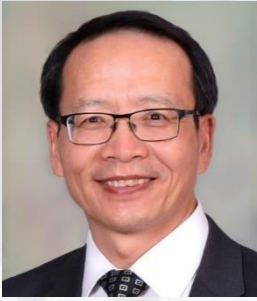


Illustration for explanation of DP, PM, PH, MD



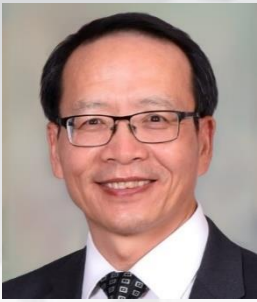
- **DP1** PFS (prefilled syringe)
- **DP2** Powder in glass vial
- **PM section:** information about the packaging configuration/ packaging process/ packaging material as necessary and applicable: needles + PFS + powder for solution for injection
- **PH section:** description of the preparation of the solution for injection (transformation of the powder in glass vial to the solution for injection), compatibility studies, in-use stability as applicable
- **MD section:** information about empty devices (syringe and injection needle) in accordance with regional requirements





- M4Q(R2) aims to foster harmonization/convergence of the Quality dossier content, ideally enabling the submission of a single dossier across ICH member countries
- When legally obligated, the applicant should provide any additional information specific to the region directly in the relevant section in a separate document as an addendum to the harmonized core document used across ICH regions
- Maintains global harmonization while respecting regional legal requirements





Industry

- Clearer regulatory expectations
- Streamline submission preparation
- Support lifecycle management and post-approval changes

Patients

- Accelerated access to new medicines
- Improved lifecycle management reducing supply issues

Regulators

- Improve assessment efficiency
- Facilitate science- and risk-based assessment
- Support global reliance and work-sharing



ICH M4Q(R2) Work Plan



| Expected completion date | Milestone |
|--------------------------|--|
| ☑ | <i>Mar. 2025</i> <i>ICH interim meeting in Budapest, Hungary – discuss comments received during formal consultation</i> |
| ☑ | <i>May 2025</i> <i>ICH meeting in Madrid, Spain - Step 1 Expert sign off</i> |
| ☑ | <i>May 2025</i> <i>Step 2a Endorsement by Members of the Assembly</i> <i>Step 2b Endorsement by Regulatory Members of the Assembly</i> <i>Release for public consultation</i> |
| <i>2025 - 2026</i> | <i>Public workshops/presentations on introduction of M4Q(R2) Step 2</i> |
| <i>Nov. 2026</i> | <i>Review and resolve public comments</i> |
| <i>Jun. 2027</i> | <i>Step 3 Sign-off and Step 4 Adoption of Final Guideline</i> |



EWG recommendations for implementation of M4Q(R2)



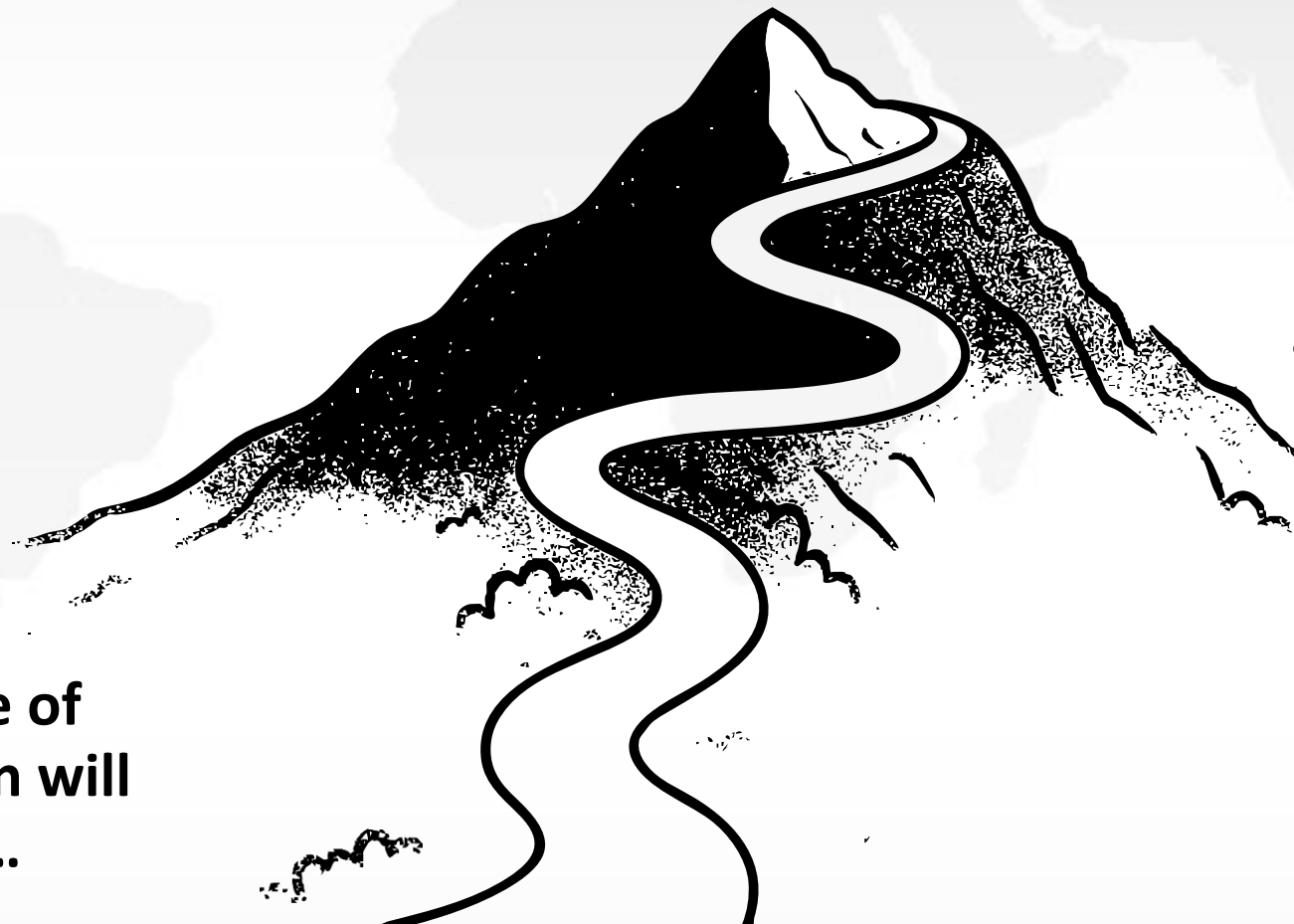
- **Global Coordination:**
 - Establish plans for implementation of eCTD 4.0, if not yet
 - Align adoption timelines across ICH regions; allow optional early adoption
- **Adequate Transition Period:** Ensure sufficient time post-Step 4 for adapting systems, processes, and vendor-supported tools without disrupting regulatory operations
- **Balanced Approach:** Aim to support digital advancement while minimizing disruption for industry and regulators



ICH M4Q(R2): A path towards Greater Efficiency and Patient Access



**...M4Q(R2) will
combine innovation,
efficiency, and global
harmonization to help
patients receive
treatments faster.**



**The uphill stage of
implementation will
be challenging...**





ICH M4Q(R2) Draft Guideline:

[https://database.ich.org/sites/default/files/ICH%20M4Q%28R2%29 Draft Guideline 2025 0514.docx](https://database.ich.org/sites/default/files/ICH%20M4Q%28R2%29%20Draft%20Guideline%202025%200514.docx)

ICH M4Q(R2) Concept Paper:

[https://database.ich.org/sites/default/files/ICH M4Q-R2 ConceptPaper Endorsed 2021 1115.pdf](https://database.ich.org/sites/default/files/ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf)

ICH Public Consultations webpage:

<https://www.ich.org/page/public-consultations>



ICH M4Q(R2) Expert WG



Thank you!

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

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