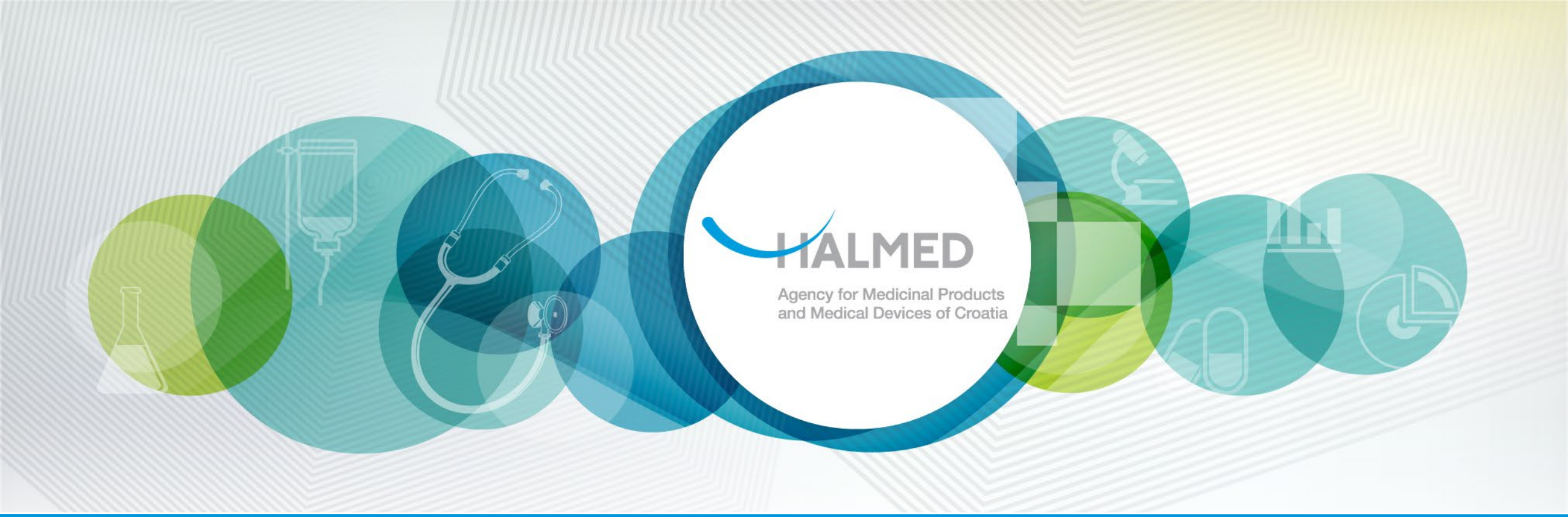


Finding your way with the new eCTD: ICH M4Q(R2)

Ivica Malnar
Agency for Medicinal Products and Medical Devices of Croatia

CERTIFIED FOR SUCCESS CONFERENCE
23-24 September 2025
Budapest, Hungary

Outline

- Introduction
- ICH M4Q(R1) Application Challenges
- M4Q Revision Objectives and Approach
- M4Q(R2) Design
- Looking Ahead

ICH M4: The Common Technical Document (CTD)
ICH M8: Electronic Common Technical Document (eCTD)

All the Quality, Safety and Efficacy information assembled in a common format

- Revolutionised the regulatory review processes

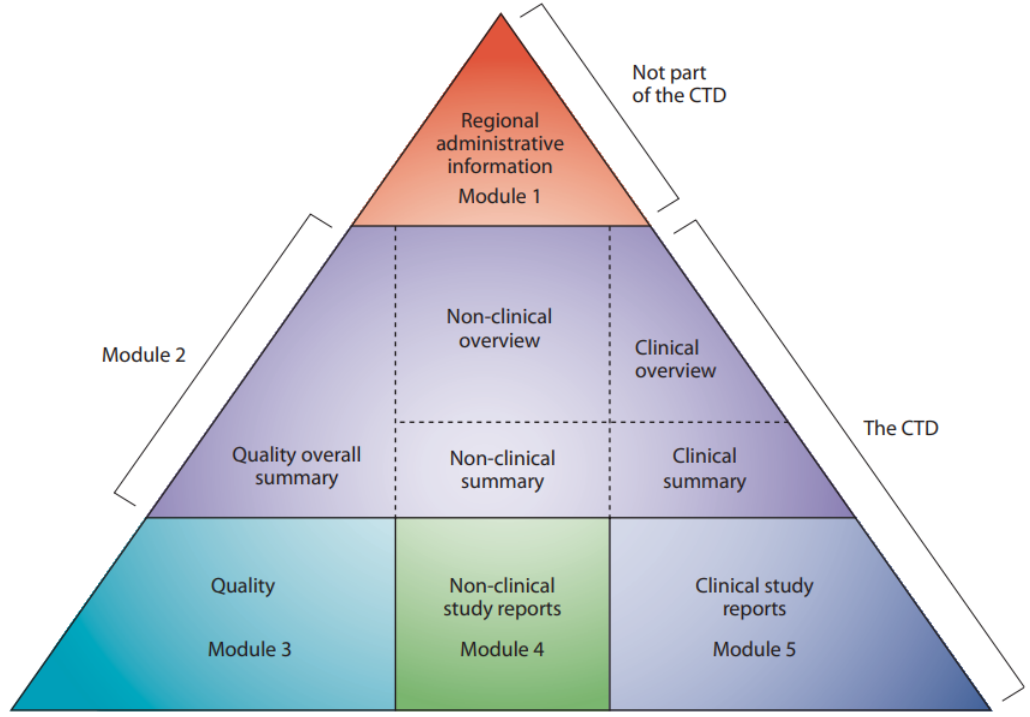
  → harmonised electronic submission

  → enabled implementation of good review practices

- For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities

- In July 2003, the CTD became the mandatory format for new drug applications in the EU

  - eCTD v.3.2.2 implemented in January 2010



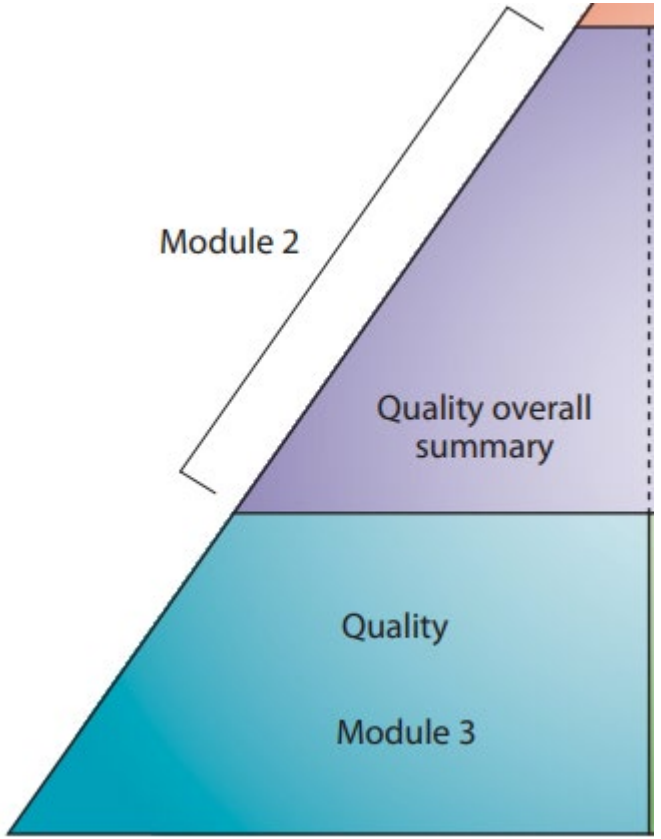
The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

ICH Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4, November 2000, current R4 version June 2016
ICH electronic Common Technical Document – eCTD v.3.2.2, July 2008

ICH M4Q(R1) – The CTD: Quality

- Globally harmonized content and organization of quality information in CTD format
  - **Module 2.3 Quality Overall Summary (QOS)**
  - **Module 3 Quality**
- In July 2003, M4Q(R1) became mandatory in the EU
  - Subsequently revised in conjunction with introduction of eCTD
- M4Q(R1) was a substantial improvement compared to the prior state with regional submission formats and shift from paper to electronic documents

  → great benefits to both industry and regulators
- No revisions have been made in over 20 years



ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality - M4Q(R1)
Quality overall Summary of Module 2, Module 3: Quality, September 2002

ICH M4Q(R1) Application Challenges

- Legacy CTD structure vs modern quality concepts
  - New guidelines ICH Q8–Q14 have been developed since M4Q(R1), introducing concepts such as Quality by Design (QbD), risk management and lifecycle approaches, continuous manufacturing
  - M4Q(R1) not designed for newer quality principles and their integration into the CTD format in not seamless

- Evolving technologies and product types
  - M4Q(R1) designed primarily with conventional small molecules in mind and organized around drug substance and drug product, with adaptations for biologics
  - Complex products and new therapeutic modalities (nanomedicines, oligonucleotides, and biologics like ADCs, vaccines, cell and gene therapies and tissue engineered products) and products made of multiple components (combination products) often don’t fit neatly into the framework

ICH M4Q(R1) Application Challenges

- Ambiguity in organization and placement of information
  - The required modular format (Module 2 summary vs. Module 3 detailed information) leaves interpretative gaps about what detail to put in the QOS vs the body of Module 3

    → often leads to repetition of information (QOS sometimes a copy-paste of M3)
  - Ambiguity on location and cross-referencing the information
  - Managing updates and variations while keeping consistency across the CTD structure

- Regional differences despite harmonisation
  - Even though ICH promotes harmonization, additional country/region-specific requirements often persist

    → reducing the benefit of having a single format

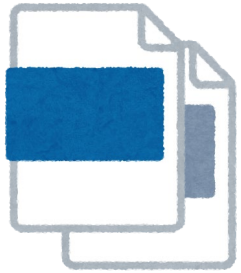
ICH M4Q(R1) Application Challenges

- Electronic and structured data demands (eCTD → next-gen)
  - Current trend is moving towards structured, machine-readable submissions and data standards, while M4Q(R1) was not built for structured content

    → complicating automation, preventing data re-use across submissions
  - MQ4 needs to adapt/respond to digitalization

    → enabling data management and standardization, promoting efficiency of review and approval process

Paper materials



eCTD

SPQS (Structured product quality submission)

Objectives identified in the M4Q(R2) Concept Paper

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

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

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

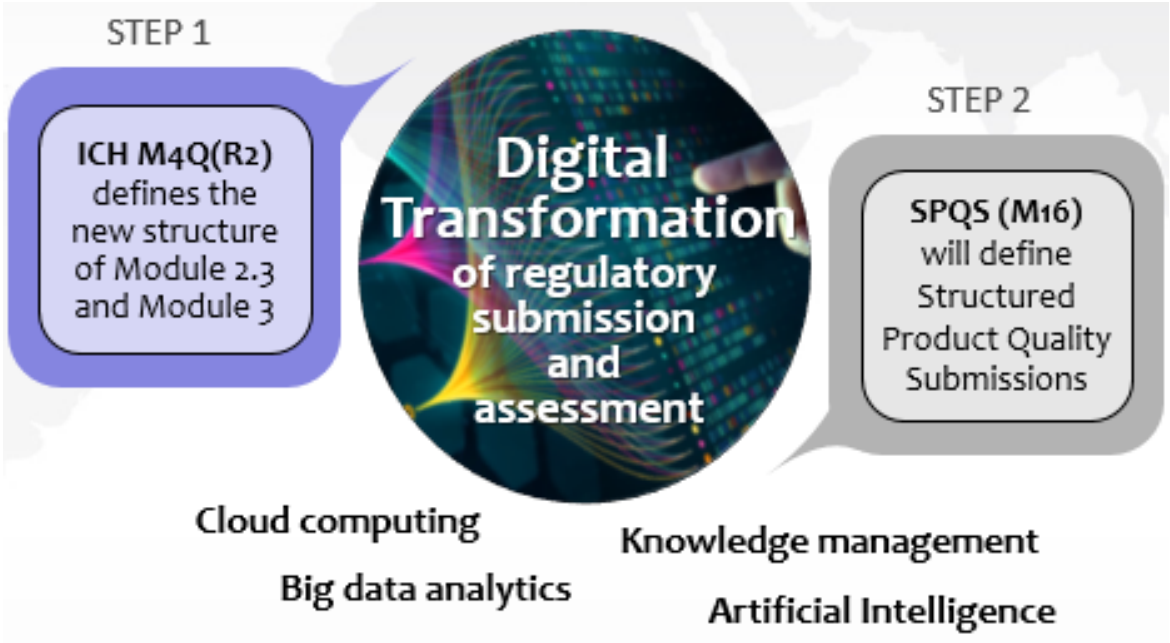
Incorporate concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines.

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

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

[ICH M4Q-R2 Concept paper]

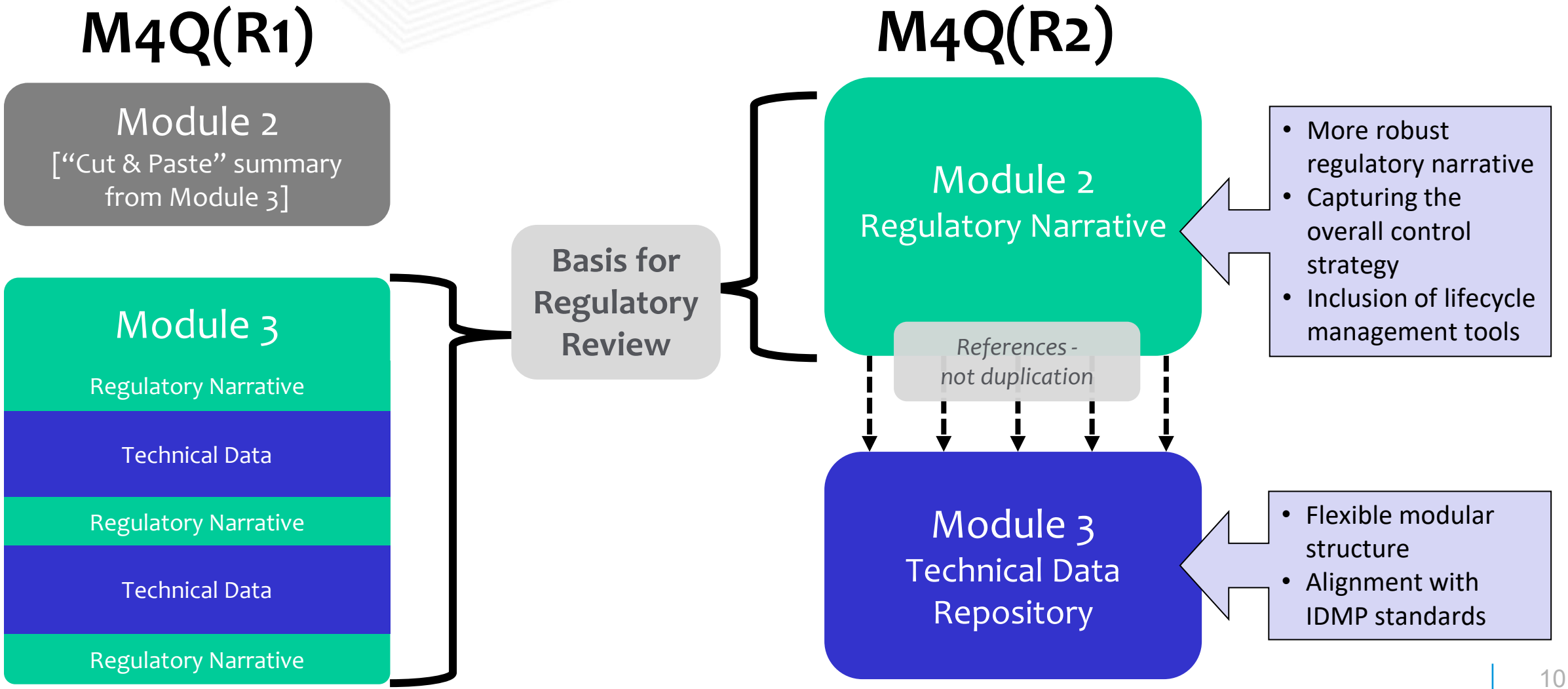
ICH elected a step-wise approach to modernise M4Q



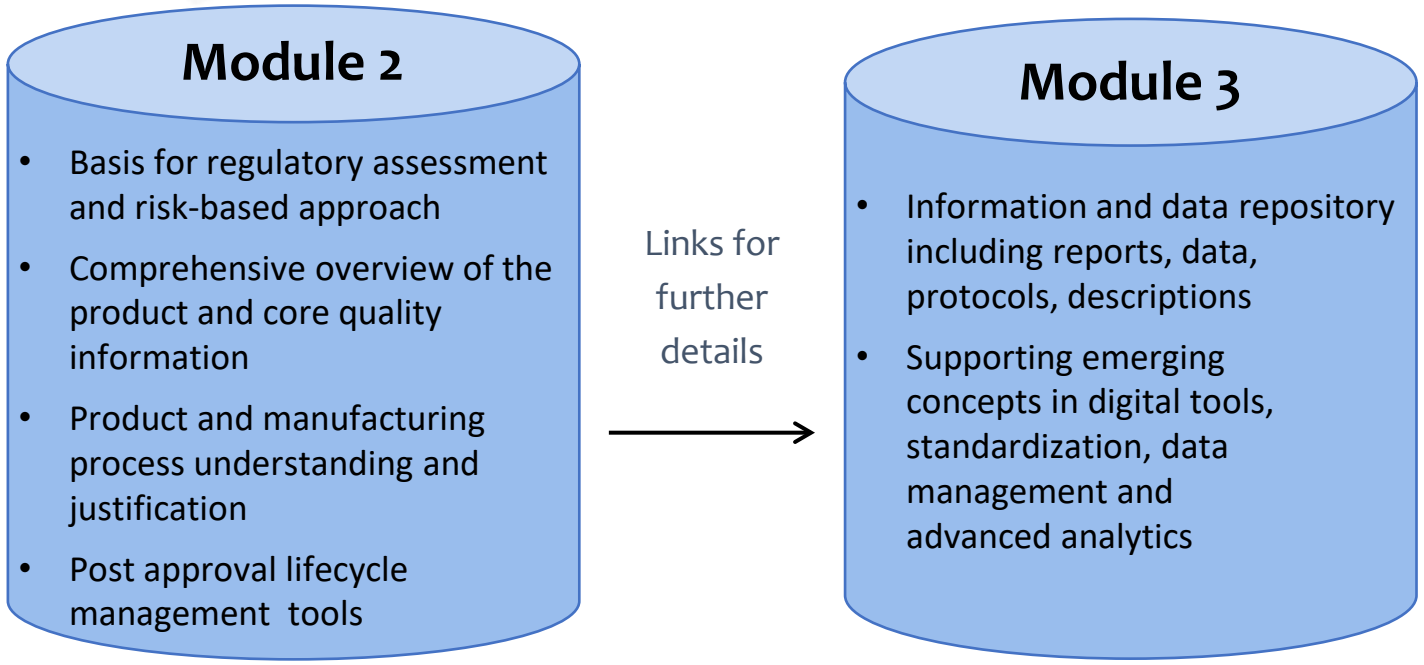
- When M4Q(R2) reaches step 2, the work on ICH M16 concept paper outline will start

Revision Overview: Current vs. Future Framework

Changes to the location of information, regulatory expectations are not changing



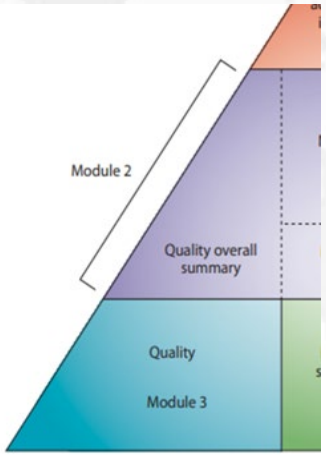
M4Q(R2) Establishes Module 2 as the Basis for Regulatory Assessment, Supported by Module 3



M4Q(R2) should enable and support

- efficient, effective, patient-centric and globally harmonised submissions, assessment and lifecycle management, and minimize dossier redundancies
- various types of submission and product modalities
- future move to structured product quality submissions (SPQS)

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 integrated control strategy**, including the QTPP, 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

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

Module 2.3 Quality Overview Key Principles
The Role of CQI (2.3.3) and its Relationship with other Sections

- **Module 2.3:**
  - The basis for regulatory assessment and lifecycle management

    → Does not supersede regional post approval change requirements
  - Sufficiently comprehensive overview applying science- and risk-based principles
  - Works complementary with Module 3

- **Core Quality Information (2.3.3):**
  - Should include all information subject to lifecycle management per regional post-approval change requirements to ensure product quality
  - Should be maintained throughout product lifecycle to ensure that product quality information remains current

- Information in 2.3.1, 2.3.2, 2.3.4, 2.3.6, and Module 3 is supportive

  → May be amend or supplemented for post-approval submissions

M4Q(R2) introduces specific subsections for materials/components

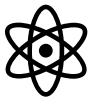
- Facilitates re-use of information/ minimises duplication
- Alignment with ISO IDMP standards
- Information organised in defined substructure (DMCS)

- 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.

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.

Illustration of relationships among Module 2.3 and Module 3 in the context of DMCS Model used for Materials

	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 development and justification data
Manufacture	Manufacturing process description, IPCs, critical process parameters	Process development and validation/evaluation summary	Process development and validation/evaluation data
Control	Specifications	Overview of batch analysis, justification of specifications	Batch analysis and justification data
Storage	Container closure system description, storage conditions, and retest period/shelf life	Overview of stability studies, justification of proposed container closure system	Container closure selection and stability data

Regional Information

- 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

Looking Ahead
ICH M4Q(R2) Work Plan

	Expected completion date	Milestone
☑	***May 2025***	*ICH meeting in Madrid, Spain - Step 1 Expert sign off*
☑	***May 2025***	*Step 2a Endorsement by Members of the Assembly* *Step 2b Endorsement by Regulatory Members of the Assembly* *Release for public consultation*
	October 2025	*4-month public consultation in the EU (ending 24 October 2025)*
	January 2026	*Public comment period to be completed in all regions*
	2025-2026	*Public workshops/presentations 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*

Looking Ahead
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

Useful Links

ICH M4Q(R2) Draft Guideline:

https://database.ich.org/sites/default/files/ICH%20M4Q%28R2%29_Draft_Guideline_2025_0514.docx

ICH M4Q(R2) Step 2 Presentation:

https://database.ich.org/sites/default/files/M4Q%28R2%29_Step%202_Slides%20to%20Accompany%20Consultation_2025_0624_SEC.pdf

ICH Public Consultations webpage:

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

ICH M4Q(R2) Concept Paper:

https://database.ich.org/sites/default/files/ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf

ICH M4Q(R2) Business Plan:

https://database.ich.org/sites/default/files/ICH_M4Q-R2_BusinessPlan_Endorsed_2021_1115.pdf

ICH M4Q(R2) Work Plan:

https://database.ich.org/sites/default/files/ICH_M4Q%28R2%29_EWG_WorkPlan_2025_0207.pdf

Thank you for your attention

For additional questions:

[ivica.malnar@halmed.hr]

Agency for Medicinal Products and Medical Devices
Ksaverska cesta 4, 10 000 Zagreb
Telephone: +385 1 4884 100 • Telefax: +385 1 4884 110
E-mail: halmed@halmed.hr
www.halmed.hr