ICH
harmonisation for better health

ICH M4Q(R2): The Common Technical Document for the Registration of Pharmaceuticals for Human Use

Step 2 document – to be released for comments

Date 18 June 2025

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

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Background

- **ICH M4Q(R2) was signed off as a *Step 2* document on 13 May 2025 to be issued for public consultation**
- **This set of slides were developed to facilitate the public consultation**

Outline

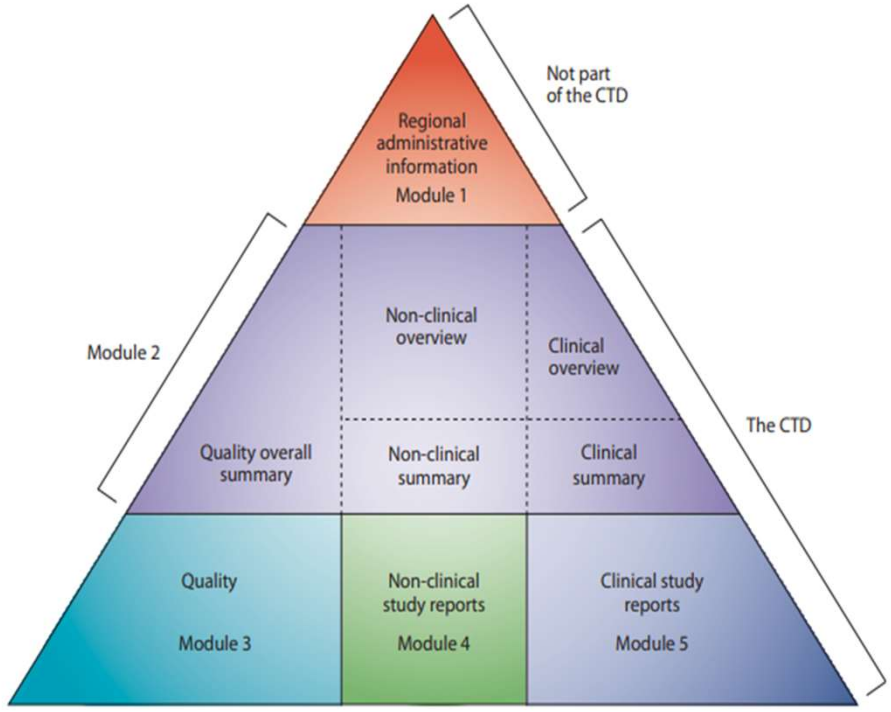
- Introduction
- Objectives and Benefits
- M4Q(R2) Design
- Comparison of M4Q(R2) and M4Q(R1)
- Looking Ahead
- Recommendations for Providing Feedback
- Additional Reference Information

Introduction

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



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

ICH's Effort to Shape the Future

STEP 1

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

STEP 2

ICH M16 (SPQS) will define Structured Product Quality Submissions

Cloud computing

Big data analytics

Knowledge management

Artificial Intelligence

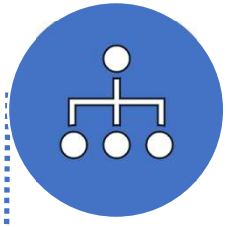
Objectives and Benefits

M4Q(R2) Objectives

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

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

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



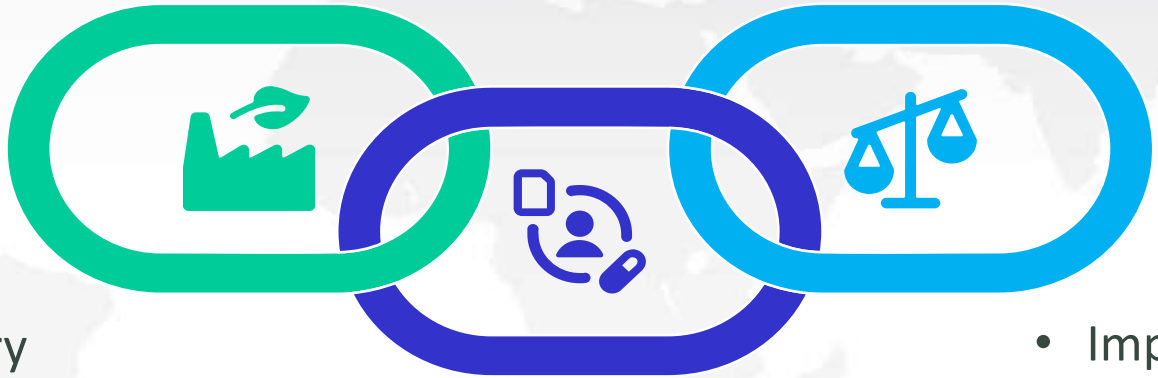
Expand the scope of M4Q(R1) guideline to include all pharmaceutical drug substances and products (both chemical and biological)

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

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

ICH M4Q-R2 Concept paper

ICH M4Q(R2) Benefits



Industry

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

Patients

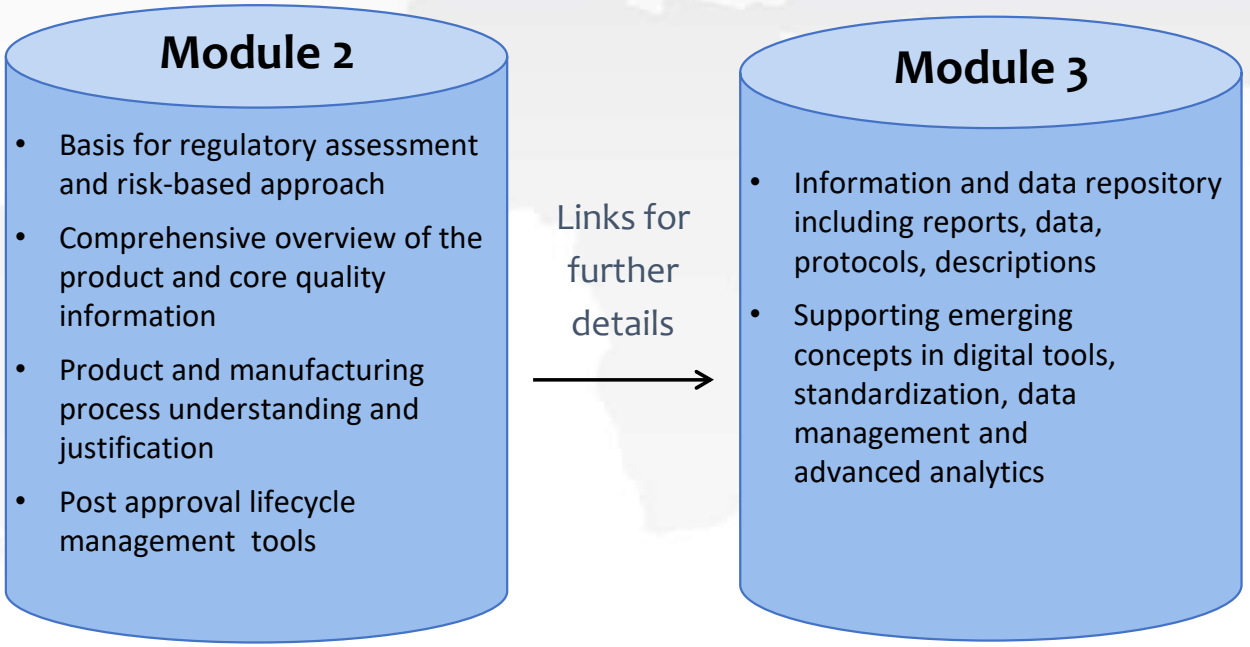
- Accelerated access to new medicines
- Improved lifecycle management reducing supply issues

Regulators

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

M4Q(R2) Design

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

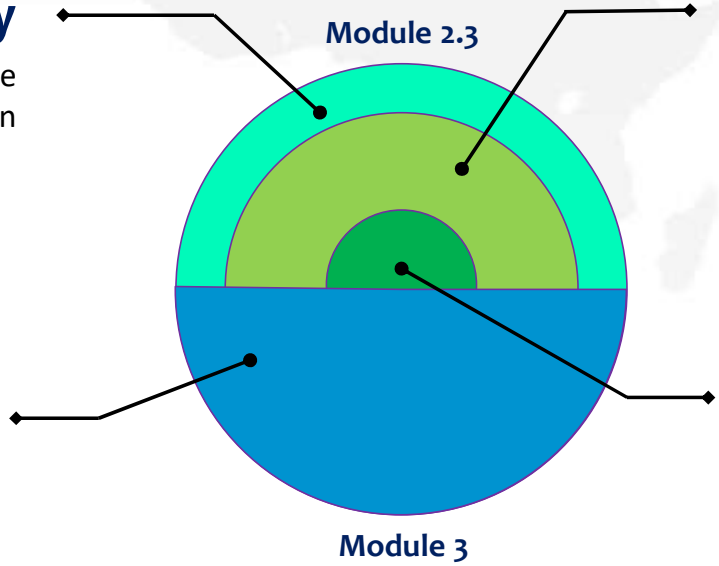
M4Q(R2) Design

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



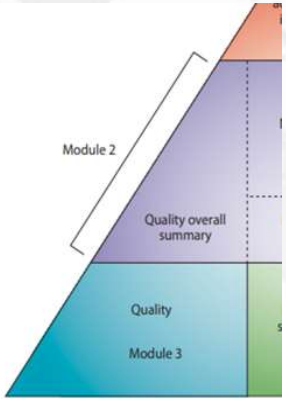
Body of Data

Offers additional in-depth information to support the submission

Core Quality Information

Focuses on the essential quality aspects of the product

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

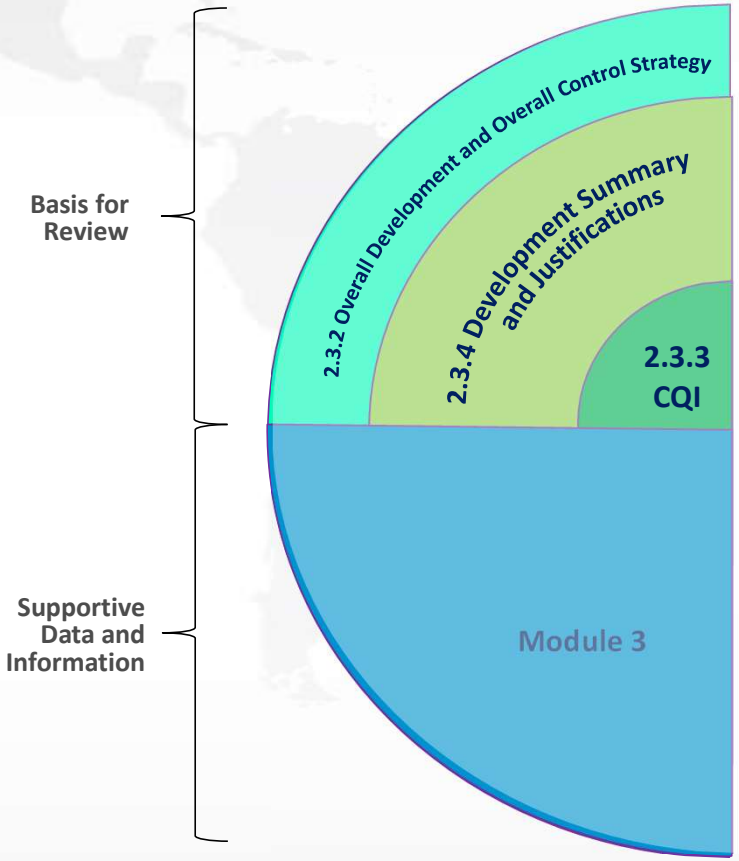
2.3.5 Product Lifecycle Management (PLCM)
- Strategy for managing post-approval changes, including a summary of changes, the PLCM, and any associated protocols or commitments

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



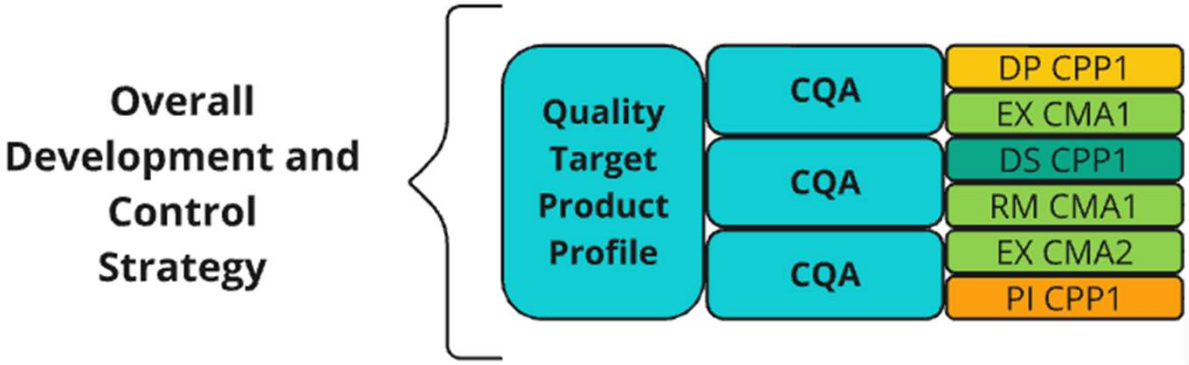
	Function During Initial Marketing Authorisation	Function During Lifecycle Management
Basis for Review	Facilitates overall understanding and supports an efficient assessment	The integrated Module 2.3 sections and Development Summary and Justifications are supportive and may be supplemented or amended due to a Post-approval change
Basis for Review	Describes how the product and manufacturing process were developed, including science- and risk-based justifications	
Basis for Review	Information considered necessary to support a science- and risk-based regulatory assessment	The content of Core Quality Information (CQI) should be maintained throughout the product lifecycle to ensure that product quality information remains current.
Supportive Data and Information	Repository for detailed descriptions of methods, data, and other assessment-relevant quality information	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

- Essential product details such as names, dosage forms, strengths, administration routes, packaging, medical devices and maximum daily dose.

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

- Overall development strategy provides a concise overview of the development rationale, highlighting the pivotal decisions made to achieve intended quality
- Overall control strategy (OCS) is not a new concept, covered in ICH Q10 and other guidelines
- OCS provides a placeholder within the CTD to present 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



CMA: Critical Material Attribute
CPP: Critical Process Parameter
CQA: Critical Quality Attribute
DP: Drug Product
EX: Excipients
DS: Drug Substances
RM: Raw Materials
PI: Product Intermediates

M4Q(R2) Structure:
2.3.3 Core Quality Information

- Core Quality Information (CQI) supports a science- and risk-based regulatory assessment to enable marketing authorization and facilitate lifecycle management
- This 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 Established Conditions (ECs) per Q12 are approved, lifecycle activities should follow the approved PLCM in 2.3.5.2
- However, the identification of ECs should not result in a reduction of information submitted in the marketing authorisation application

M4Q(R2) Structure:
2.3.4 Development Summary and Justification

- Should describe how the drug substance and product, their components (if applicable), and manufacturing process were developed, including the main choices made throughout the development
- Should discuss all scientific and risk-based justifications, including discussion of the proposed commercial process and control strategy, and justification of ECs and reporting categories when ICH Q12 is applied
- The content of the DSJ is supportive. The applicant may amend or supplement it due to post-approval changes.
- Sections under 2.3.4.IN include justifications of topics when a holistic discussion across several parts of the dossier is advantageous (e.g., extractables and leachables, adventitious agents, products without a defined and/or isolated drug substance, equivalency, similarity or sameness with a reference product)
- Corresponding CQI should be provided in relevant subsections of 2.3.3 and the data and supportive information in Module 3.

M4Q(R2) Structure:
2.3.5 Product Lifecycle Management

- Should include a change summary and justification for post-approval change submissions
  - A summary of the proposed change and background
  - A table with present and proposed content, including listing of the updated CTD sections with cross-referencing
  - The justification for the proposed update(s) which may be provided here or by cross-referencing to updated section(s) of 2.3.4 with cross-reference to section 2.3.3 and 3.2
- May also use this section to capture use of ICH Q12 tools (as applicable) and regulatory commitments

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

- PQBR allows sponsors to contextualize quality risks in relation to patient risks, which can be particularly beneficial in situations such as accelerated development pathways
- Is expected to support the overall benefit risk assessment by cross-referencing section 2.5 Clinical Overview
- Includes a summary that explains the rationale regarding mitigations of quality risks, concluding how the anticipated patient centric benefits outweigh the residual risks and assessing the impact on safety and/or effectiveness of the product's usage

** It is outside the scope of the EWG to dictate how different authorities will utilize this information*

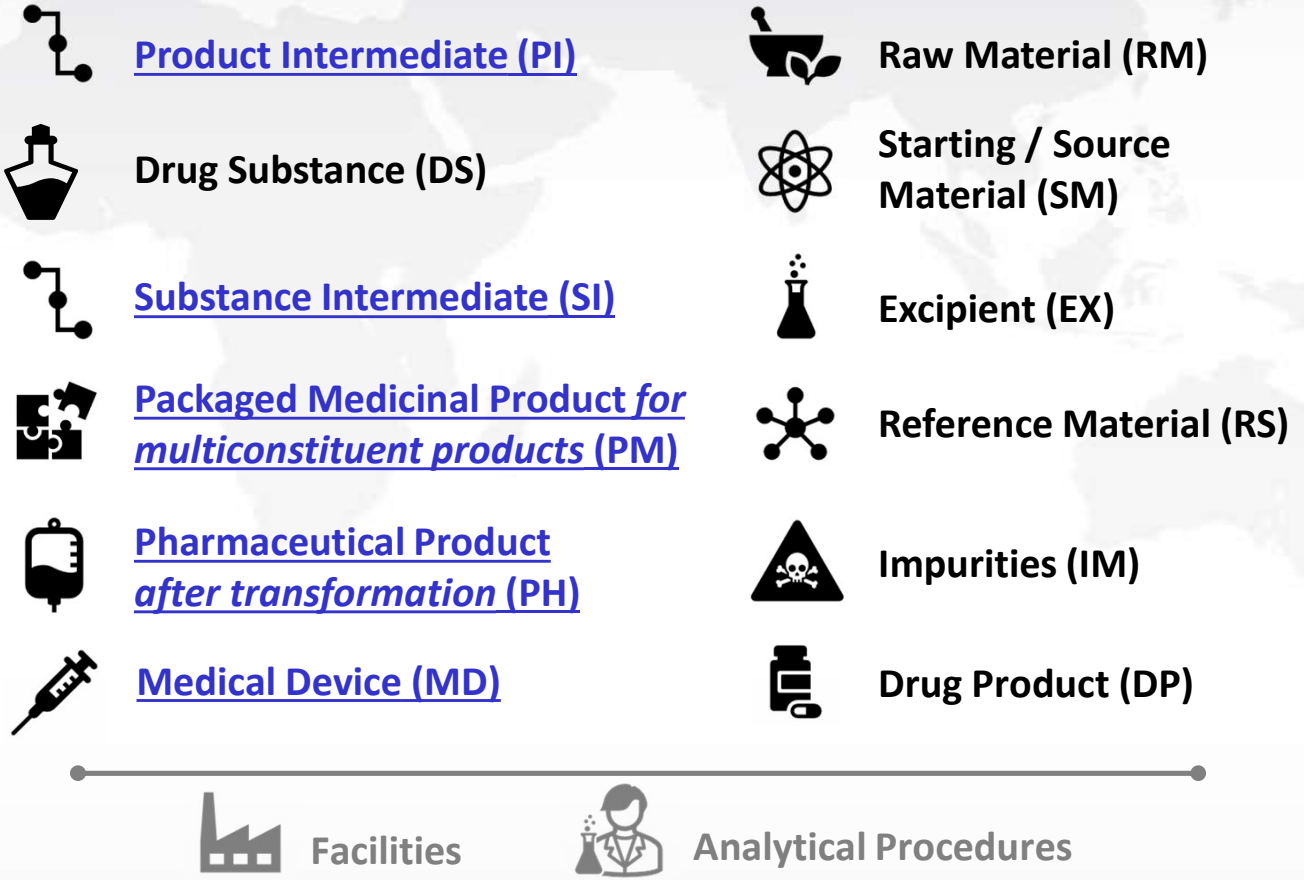
M4Q(R2) Structure: Module 3

- 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



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

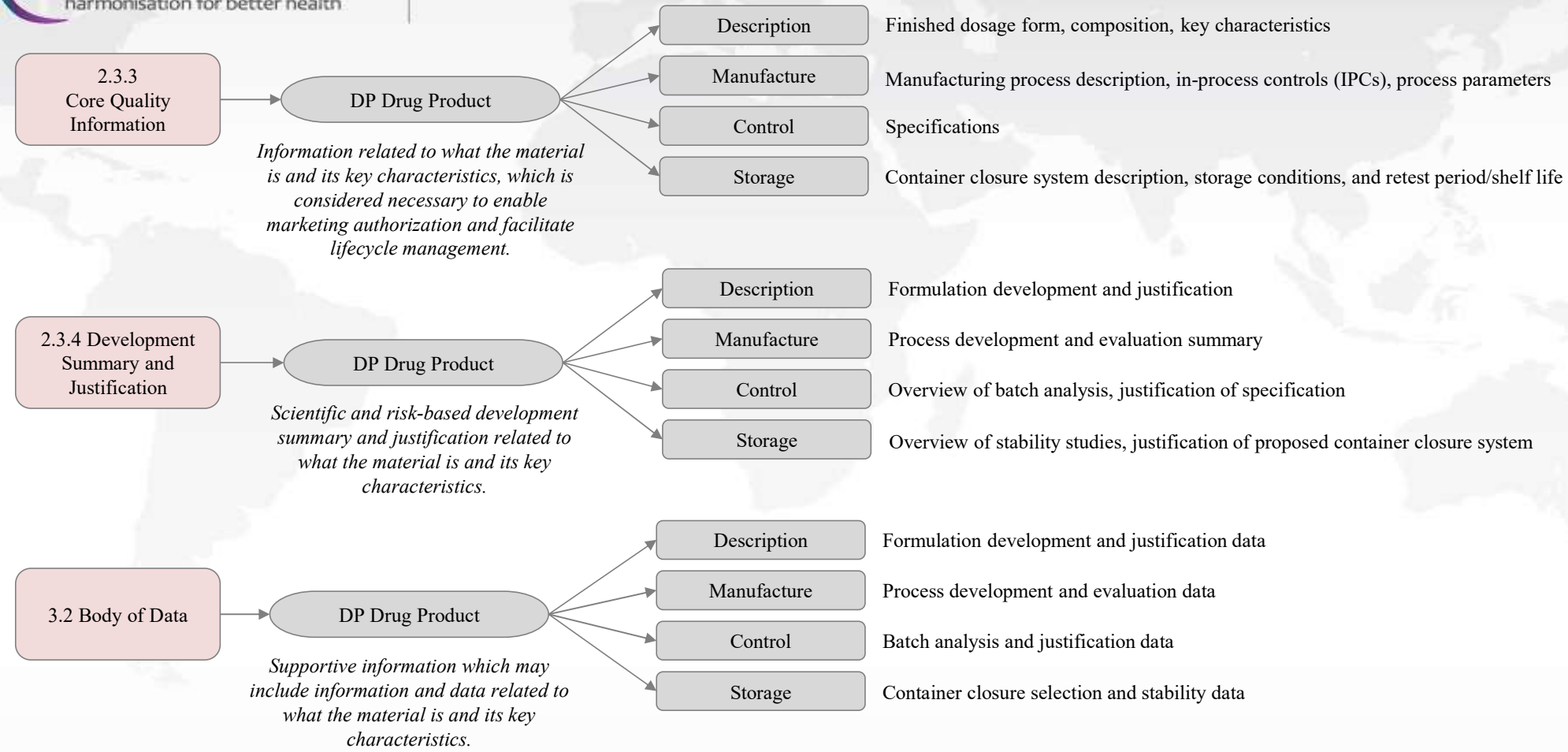


Figure 1: Illustration of relationships among sections 2.3.3 Core Quality Information, 2.3.4 Development Summary and Justifications, and Module 3.2 Body of Data in the context of DMCS Model used for materials.

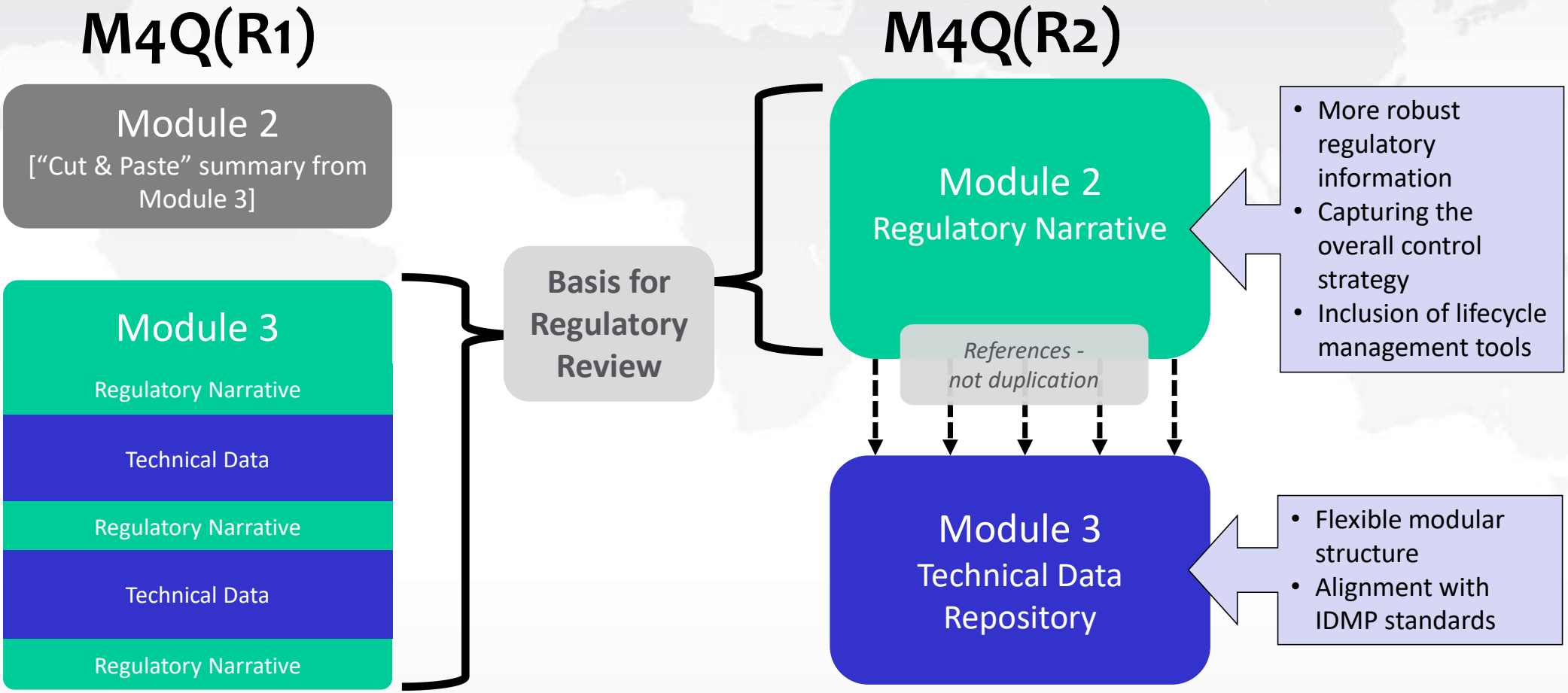
Regional Information

- 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
- As an example, batch records should be provided in section 3.2.DP.M.1 when required as per regional regulations, as they would be considered as supportive information related to the description of manufacturing process

Comparison of M4Q(R2) and M4Q(R1)

Current vs Future Framework

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



M4Q(R1) to M4Q(R2) Comparison

Aspect	M4Q(R1)	M4Q(R2)
Format	Based on a linear, section-by-section format	Modular approach – organized into consistent and reuseable components to support digitalization
Content Focus	Comprehensive data presentation without clear distinction between core and supportive information.	Clear separation of core information (CQI) vs. supportive content.
Risk-Based Principles	Limited use of Quality Risk Management (QRM) and lack of well-defined location.	Explicit integration of QRM throughout the dossier. Encourages justification-based content.
Data Redundancy	Repetitive presentation of information across modules.	Minimized duplication by using a modular and structured format.

M4Q(R1) to M4Q(R2) Comparison (cont.)

Aspect	M4Q(R1)	M4Q(R2)
Terminology and Definitions	Some ambiguity and regional variation in interpretation.	Updated terminology aligned with IDMP and improved definitions for global clarity and consistency.
Submission and Assessment Efficiency	Manual, repetitive, and time-consuming. Assessors must manually search for information dispersed across documents.	Structured elements promote efficient data entry and reuse, improve navigation, and allow faster retrieval of critical information for assessment.
Lifecycle Considerations	Limited integration of lifecycle and post-approval change management concepts.	Enables science- and risk-based lifecycle management. Facilitates clear documentation of PACs and aligns with ICH Q12 tools.
Implementation and Flexibility	Static template, limited flexibility.	Promotes flexibility and innovation, aligned with modern regulatory and scientific practices.
Digital Compatibility	Designed for paper-based submission. Not optimized for digital automation.	Designed to be compatible with eCTD v4.0 and structured data formats, enabling automation.

Looking Ahead

ICH M4Q(R2) Work Plan

	Expected completion date	Milestone
☑	***Mar. 2025***	*ICH interim meeting in Budapest, Hungary – discuss comments received during formal consultation*
☑	***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*
	2025 - 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*

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…

Recommendations for Providing Feedback

Recommendations for Commenting

Please do not provide duplicate comments through multiple organizations.

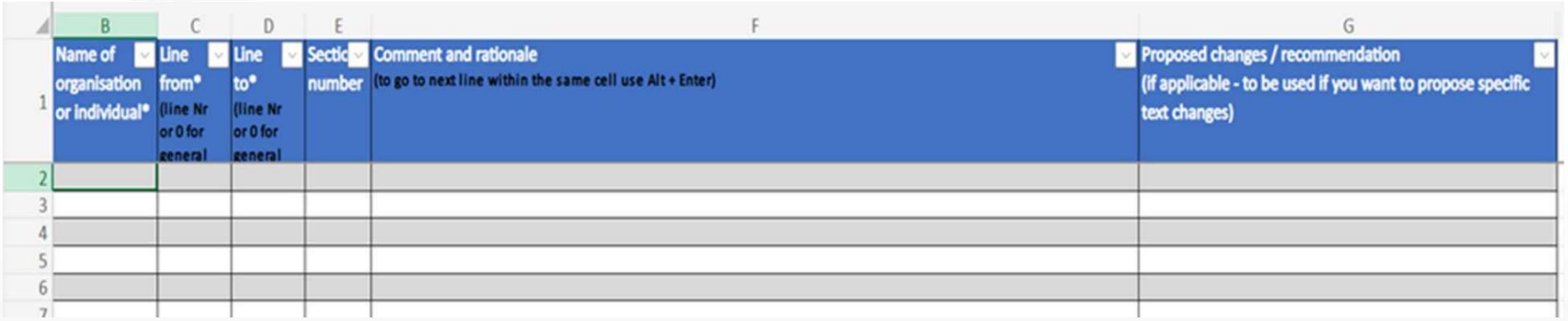
If a comment is considered critical, please indicate this within the comment (Column F of the comments template) and provide a rationale.

Please include recommendations for training material where a concern is too specific for the guideline or where further explanation is needed.

Commenting Process

The reviewer should follow the commenting process either per the ICH site or the regional authority they are sending their comments through.

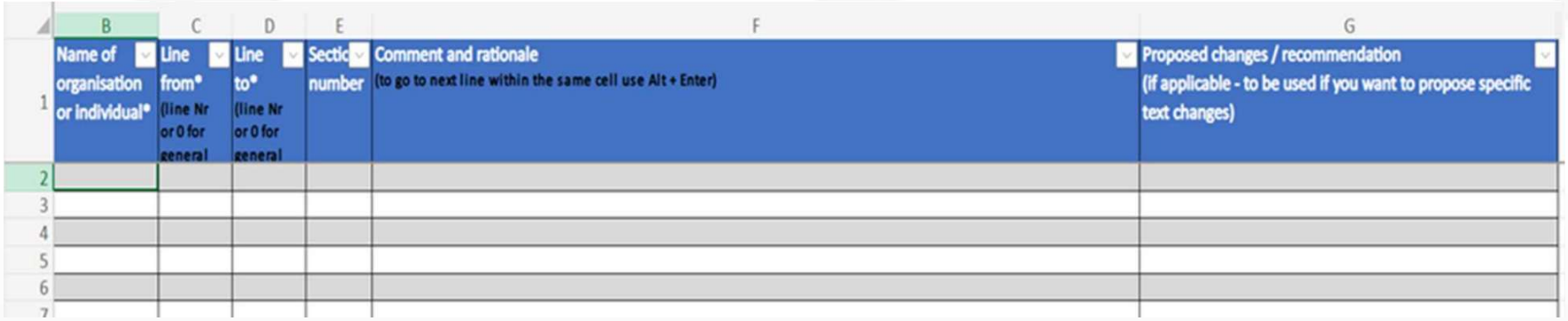
- **Column B "Name of organisation or individual*": this is set up as free text and is mandatory**
- **Column C "Line from*": this is set up to allow numbers only. If you want to submit a general comment, please enter 0 (zero). This field is mandatory**
- **Column D "Line to*": If your comment applies to a single line, repeat the number of column C. This field is mandatory.**



	B	C	D	E	F	G
1	Name of organisation or individual*	Line from* (line Nr or 0 for general	Line to* (line Nr or 0 for general	Sectic number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
2						
3						
4						
5						
6						

Commenting Process

- **Column E “section number”: this is set up to allow numbers only. This is not mandatory but strongly encouraged.**
- **Column F “Comment and rationale”: It is not possible to fill in this column if columns B, C and/or D are not filled in. An error message will appear if B, C and/or D are empty. This column has been set up as wide as possible to allow long comments (up to 32,767 characters).**
- **Column G “Proposed changes/recommendation (if applicable)”: See column F.**



	B	C	D	E	F	G
1	Name of organisation or individual*	Line from* (line Nr or 0 for general	Line to* (line Nr or 0 for general	Sectic number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
2						
3						
4						
5						
6						

Contact

For any questions please contact the ICH Secretariat: admin@ich.org

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) Concept Paper:

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
harmonisation for better health

Thank you!

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

Additional Reference Information

Substance and Product Intermediates

Substance Intermediate

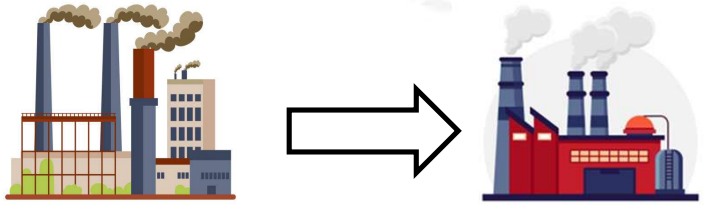
- Part of end-to-end DS Manufacturing
- May have specifications, IPC, extended hold times
- Part of CQI but not expected to have a separate DSJ with DMCS

Same manufacturer of DS and SI

→ Provide integrated manufacturing process description in 2.3.3.DS.M

Separate manufacturer of SI, or SI for complex biological substances

DS Manufacture



→ Provide SI manufacturing process description in separate 2.3.3.SI.M section

2.3.3. Product Intermediate (PI)

Concept of product intermediate, bulk product and drug product for the purpose of modular approach

2.3.3.PI section has been introduced as placeholder for situations where e.g., a product intermediate has established specifications, and/or is supplied by a separate manufacturer

These are the definitions:*

- Product intermediate: A material that is produced as part of the drug product manufacturing process after the defined drug substance(s) and subject to further processing before the finished dosage form ***(e.g., tablet core)***
- Bulk product: Bulk finished dosage form, that has completed all processing stages before immediate packaging ***(e.g., film-coated tablet)***
- Drug product: The Finished Dosage Form in the final immediate packaging intended for sale or supply ***(e.g., film-coated tablet in blister)***

**There may be regional differences regarding the definitions for product intermediates/ bulk product.*

2.3.3. PI section as new section in R2 format – Illustrative example of flexible use of PI section

Product Intermediates

Bulk drug product

Drug product

2.3.3. PI section (Description Control Storage DCS structure only)

2.3.3. PI section (DMCS structure)

Immediate release granules

Sustained release pellets purchased from a different manufacturer

Mixture of both intermediates with further Excipients

Filling of capsules

Hard Capsules as bulk product

Packaging of capsules

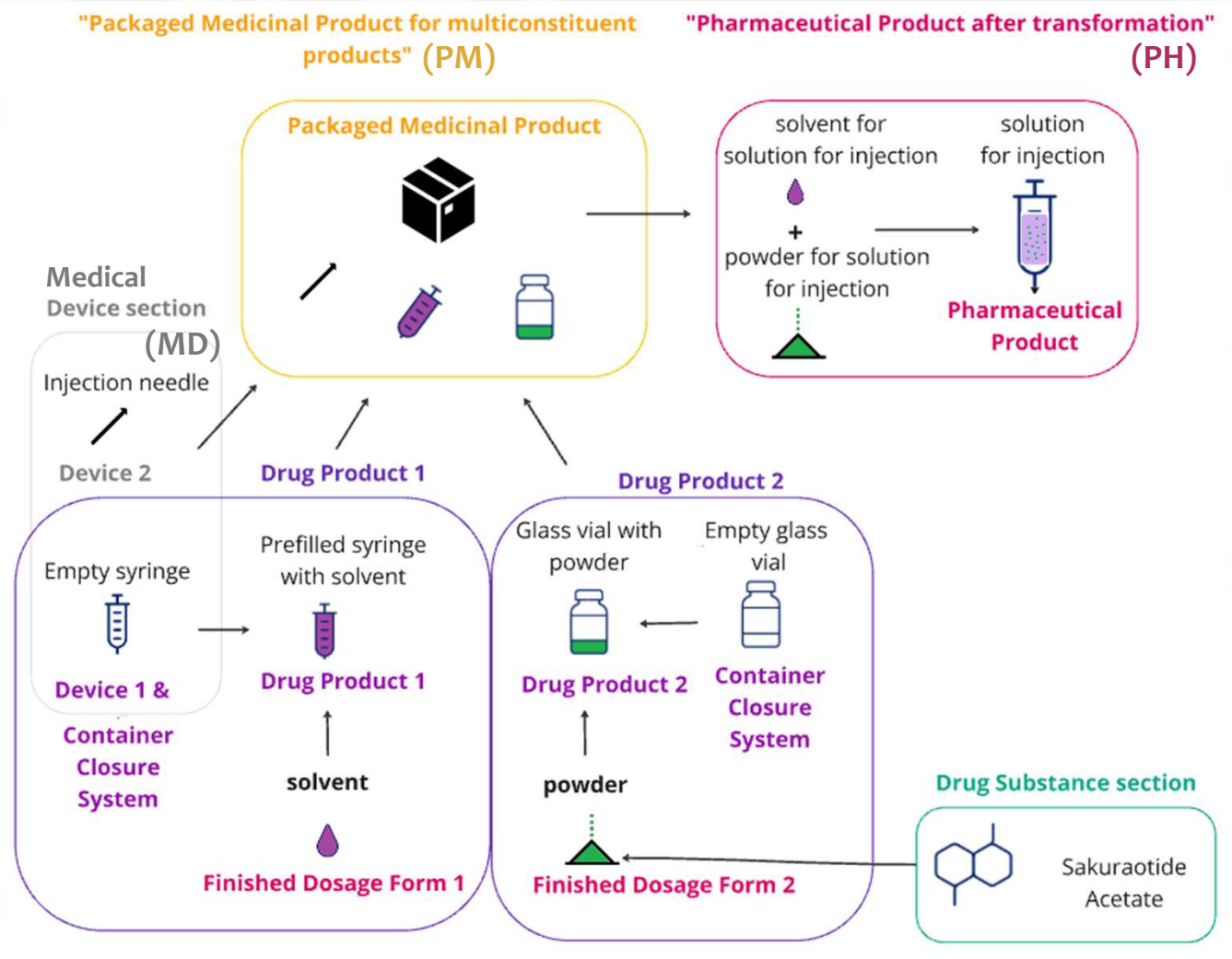
Hard Capsules in bottles

2.3.3.DP section (M only) for
1) immediate release granules
2.3.3.DP section (DMCS) for:
2) mixture with further excipients + granules + pellets (no established specification)
3) filling of capsules and storage of "bulk product" filled capsules
4) primary packaging process (if no functional secondary packaging is used)

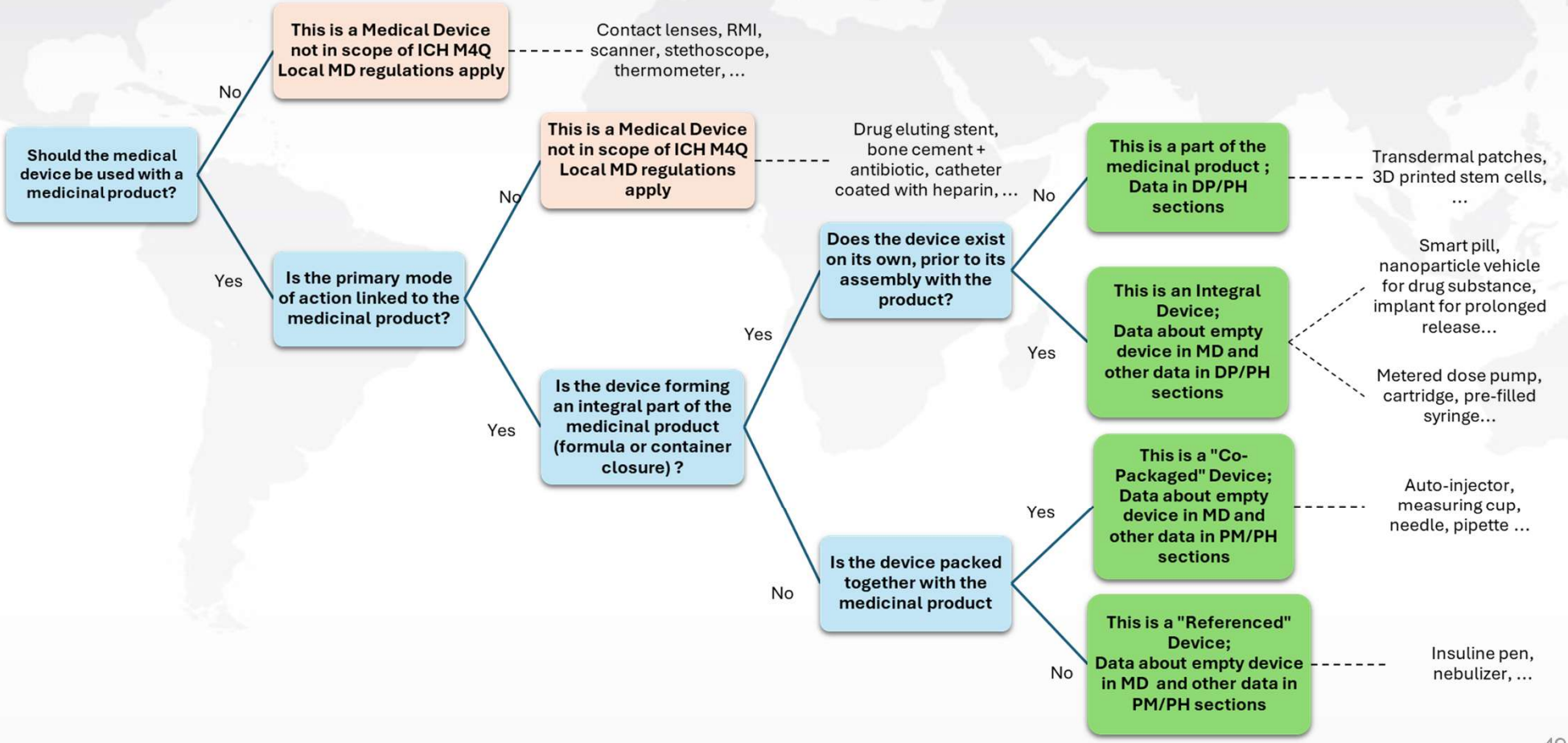
Drug Product (DP), Packaged Medicinal Product for multiconstituent products (PM), Pharmaceutical Product after transformation (PH), and Medical Device (MD)

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



Medical Device Information Location Decision Tree



Conventions used in M4Q(R2)

Keywords

Conventions used in M4Q(R2):

Parentheses ( )
standard keywords

Square Brackets [ ]
optional keywords

Keywords help clearly identify sections by naming the described object or distinguishing between duplicates (e.g., a product with two Drug Substances).

Benefits of using keywords:

- Flexibility to combine sections when content is minimal and harmonized (e.g., a shared 2.3.4.EX section with a table listing excipients)
- Option to split into sub-sections for detailed or distinct information (e.g., 2.3.4.EX [Novel Excipient 1] for a novel excipient requiring detailed, distinct documentation)
- Aids in document organization
- May serve as metadata to support different views