1.13

ICH M4 Guideline

Common Technical Document for the Registration of Pharmaceuticals for Human use Organisation CTD

ICH M4Q Guideline

Common Technical Document for the Registration of Pharmaceuticals for Human use Quality

Comments for its application

ICH M4
Organization of the Common Technical Document CTD

Objective of the guideline

- ❒ Harmonized format for the CTD that will be acceptable in all three regions
- ❒ Guidance indicates an appropriate format for the data that have been acquired but not what studies are required.
- ❒ Applicants should not modify individual formats.
- ❒ Information should be unambiguous and transparent to facilitate the review and help a reviewer to become quickly orientated.
- ❒ Text and tables should be prepared using margins that allow the document to be printed on A4 paper (EU and Japan) and 8.5x11" paper (USA)
- ❒ Times New Roman, 12-point font is recommended for narrative text

Organisation of the Common Technical Document CTD

The CTD is organized into five modules

❒ **Module 1. Administrative Information and Prescribing Information**

- This module contains documents specific for each region specified by the relevant regulatory authorities.
  - Application forms
  - Proposed label for use in this region

❒ **Module 2. Common Technical Document Summaries**

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

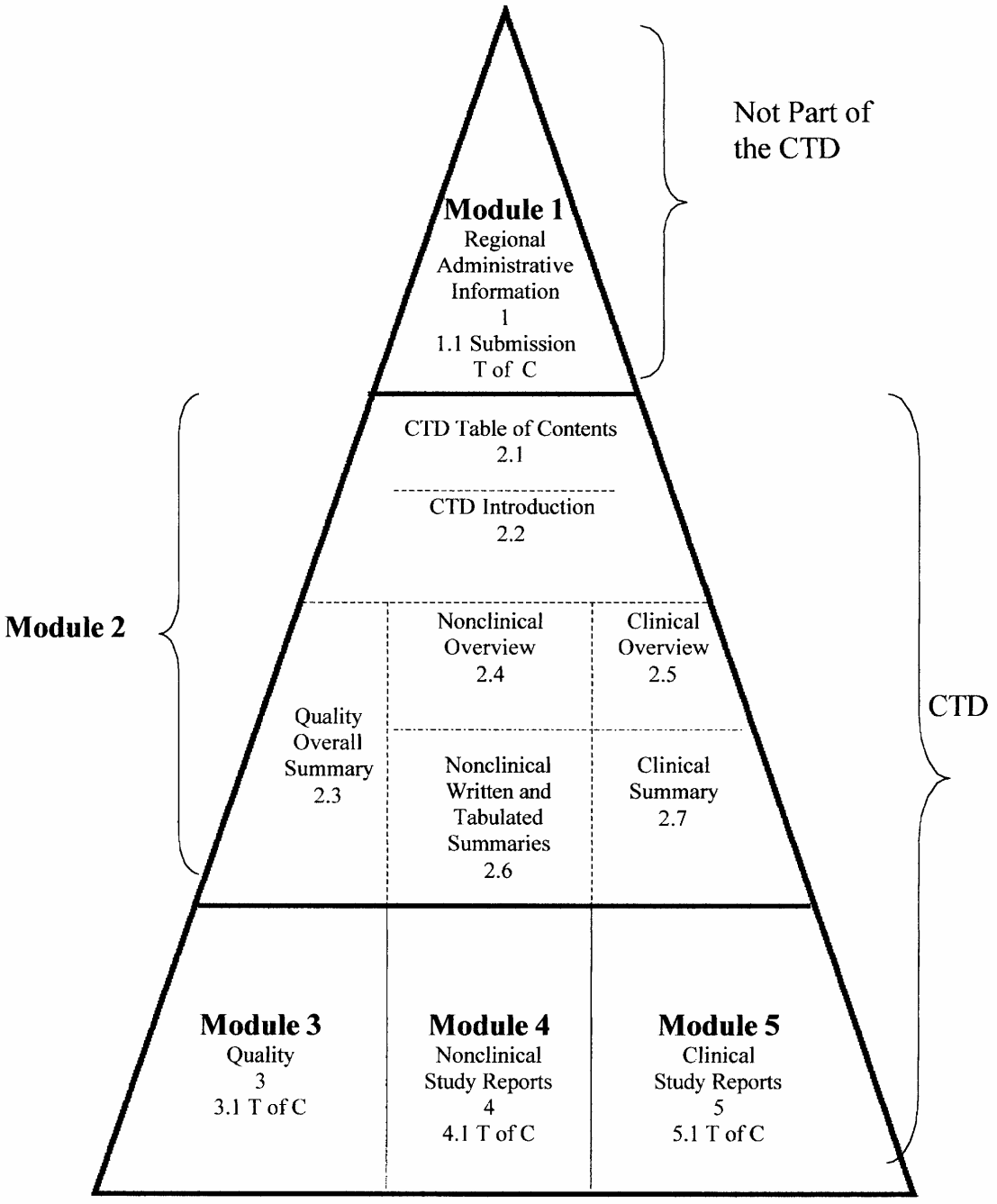
❒ **Module 3. Quality**
Information on quality should be presented in the structured format described in the guidance, M4Q

❒ **Module 4. Nonclinical Study Reports**
The Nonclinical Study Reports should be presented in the order described in the guidance M4S

❒ **Module 5. Clinical Study Reports**

The human study reports and related information should be presented in the order described in the guidance M4E

Diagrammatic Representation of the ICH Common Technical Document



❒ Implementation Dates of CTD

- Optional July 2001: EU, FDA, MHLW (Canada, Switzerland)
- Mandatory July 2003: EU, MHLW (Canada, Switzerland
- Highly recommended July 2003: FDA

❒ Scope of CTD

Type of Drug Product	EU	FDA	MHLW
New chemical entities	included	Included	included
New biologic	Included	Included	included
New indication	Included	Included	included
New dosage form	Included	Included	included
New route of administration	Included	Included	included
Generics	Included	Included	not included
OTC	Included	Included	not included

ICH M4Q Quality

Module 2 Quality Overall Summary

- QOS is a summary that follows scope and outline of Body of Data in Module 3
- QOS should not include information, data or justification that was not already included in Module 3
- QOS should include sufficient information to provide the reviewer with an overview of Module 3
- QOS should emphasise critical key parameters and justification in cases guidelines were not followed.
- QOS should include discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. Quality of impurities via toxicological studies)
- QOS should not exceed 40 pages of text, excluding tables and figures
- Most of the information in the QOS can be imported directly from Module 3

2.3 Introduction to the Quality Overall Summary

Introduction should include:

- Proprietary name
- Nonproprietary name or common name of the drug substance
- Company name
- Dosage forms
- Strengths
- Route of administration
- Proposed indications

Number	Subject	Data from Module 3
2.3.S	Drug Substance	
2.3.S.1	General Information	3.2.S.1
2.3.S.2	Manufacture	3.2.S.*2,* 3.2.*2.2,* 3.2.2.3, 3.2.2.4, 3.2.2.5, 3.2.2.6
2.3.S.3	Characterisation	3.2.S.3.1, 3.2.S.*3.2*
2.3.S.4	Control of Drug Substance	3.2.S.4.1, 3.2.S.4.4
2.3.S.5	Reference standards or Materials	3.2.S.5
2.3.S.6	Container Closure System	3.2.S.6

2.3.S.7	Stability	3.2.S.7.1, 3.2.S.7.2, 3.2.S.7.*3*
2.3.P 2.3.P.1	Drug Product Description and Composition of the Drug Product	3.2.P.1
2.3.P.2	Pharmaceutical Development	3.2.P.2
2.3.P.3	Manufacture	3.2.P.3, 3.2.P.3.3, 3.2.P.3.5
2.3.P.4	Control of Excipients	3.2.P.4
2.3.P.5	Control of Drug Product	3.2.P.5.1, 3.2.P.5.4
2.3.P.6	Reference Standards or Materials	3.2.P.6
2.3.P.7	Container Closure System	3.2.P.7
2.3.P.8	Stability	3.2.P 8.3, 3.2.P.8.2
2.3.R	Regional Information	Brief description

Module 3: Format of the Quality Section of the CTD

- This section provides guidance on the format of a registration application for drug substances and drug products.
- The content should include relevant information described in existing ICH guidances.
- The body of data section merely indicates where the information should be located. Neither the type nor extend of specific supporting data has been addressed .

3.1 Module 3 Table of Contents

A Table of Contents or the filed application should be provided

3.2 Body of Data

3.2.S Drug Substance

Number	Subject	Reference ICH
3.2.S	**Drug Substance**	
3.2.S.1	**General Information**	
3.2.S.1.1	Nomenclature	
3.2.S.1.2	Structure	
3.2.S.1.3	General Properties	Q6Q
3.2.S.2	**Manufacture**	
3.2.S.2.1	Manufacturer(s)	
3.2.S.2.2	Description of Manufacturing Process And Process Controls	
3.2.S.2.3	Control of Materials	Q6A

3.2.S.2.4	Controls of Critical Steps and Intermediates	Q6A
3.2.S.2.5	Process Validation and/or Evaluation	
3.2.S.2.6	Manufacturing Process Development	Q3A(R)
3.2.S.3	**Characterisation**	
3.2.S.3.1	Elucidation of structure and other Characteristics	Q6A
3.2.S.3.2	Impurities	Q3A(R),Q3C,Q6A
3.2.S.4	**Control of Drug Substance**	
3.2.S.4.1	Specification	Q6A
3.2.S.4.2	Analytical Procedures	Q2A,Q6A
3.2.S.4.3	Validation of Analytical Procedures	Q2A,Q2B,Q6B
3.2.S.4.4	Batch Analyses	Q3A(R),Q3C,Q6A
S 4.5	Justification of Specification	Q3A(R),Q3C,Q6A
3.2.S.5	**Reference Standards of Materials**	**Q6A**
3.2.S.6	**Container Closure System**	
3.2.S.7	**Stability**	
3.2.S.7.1	Stability Summary and Conclusions	Q1A(R2),A1B
3.2.S.7.2	Post-Approval stability Protocol and Stability Commitment	Q1A(R2)
3.2.S.7.3	Stability Data	Q1A(R2),Q1B,Q2A, A2B

3.2. P Drug Product

Number	Subject	Reference ICH
3.2.P.1	**Description and Composition of the Drug Product**	Q6A
3.2.P.2	**Pharmaceutical Development**	Q6A
3.2.P.2.1	Components of the Drug Product	
3.2.P.2.1.1	Drug Substance	
3.2.P.2.1.2	Excipients	
3.2.2.2	Drug Product	
3.2.P.2.2.1	Formulation Development	
3.2.P.2.2.2	Overages	
3.2.P.2.2.3	Physicochemical and Biological Properties	
3.2.P.2.3	Manufacturing Process Development	
3.2.P.2.4	Container Closure System	
3.2.P.2.5	Microbiological Attributes	
3.2.P.2.6	Compatibility	

3.2.P.3	**Manufacture**	
3.2.P.3.1	Manufacturer(s)	
3.2.P.3.2	Batch Formula	
3.2.P.3.3	Description of Manufacturing Process and Process Controls	
3.2.P.3.4	Controls of Critical Steps and Intermediates	Q2A, Q2B, Q6A
3.2.P.3.5	Process Validation and/or Evaluation	
3.2.P.4	**Control of Excipients**	
3.2.P.4.1	Specifications	Q6A
3.2.P.4.2	Analytical Procedures	Q2A,Q6A
3.2.P.4.3	Validation of Analytical Procedures	Q2A, Q2B
3.2.P.4.4	**Justification of Specifications**	Q3C
3.2.P. 4.5	Excipients of Human or Animal Origin	Q6B
3.2.P.4.6	Novel Excipients	
3.2.P.5	**Control of Drug Product**	
3.2.P.5.1	Specification(s)	Q3B(B),Q6A
3.2.P.5.2	Analytical Procedures	Q2A,Q6A
3.2.P.5.3	Validation of Analytical Procedures	Q2A,Q2B
3.2.P.5.4	Batch Analyses	Q3C,Q6A
3.2.P.5.5	Characterization of Impurities	Q6A
3.2.P.5.6	Justification of Specification(s)	Q6A
3.2.P.6	**Reference Standards or Materials**	Q6A
3.2.P.7	**Container Closure System**	
3.2.P.8	**Stability**	
3.2.P.8.1	Stability Summary and Conclusion	Q1A(R2),Q1B, Q1E, Q6A
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment	Q1A(R2)
3.2.P.8.3	Stability Data	Q1A(R2),Q1B, Q1E, Q2A, A2B
3.2.R	Regional information	
3.3	Literature References	

Module 3 Drug Substance

3.2.S. 7 Stability

3.2.S.7.1 Stability Summary and Conclusions

❒ **Summarized should be**

- Types of studies conducted,
- Protocols used,
- Results of studies

❒ **Summary should include**

- Results from forced degradation studies and stress conditions
- Results from primary stability investigation
- Conclusions regarding
  - Storage conditions
  - Retest date or shelf life.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

❒ **Post-approval stability protocol and stability commitment should be provided**

3.2.S.7.3 Stability Data

❒ **Results of stability studies in appropriate form**

- Tabular or
- Graphical or
- Narrative

❒ **Information on analytical procedure**

❒ **Validation of these Procedures**

ICH Guidelines: Q1A(R2), Q1E, Q1F, Q2A, Q1B, Q2B

Module 2 QOS Drug Substance

2.3.S.7 Stability

- ❒ **Summary of studies undertaken**
  - Conditions
  - Batches
  - Analytical procedures
- ❒ **Brief discussion of**
  - Results and conclusions
  - Proposed storage conditions
  - Retest date or shelf life

  as described in 3.2.S.7.1
- ❒ **Post-approval stability protocol**
  as described in 3.2.S.7.2
- ❒ **Tabulated summary of stability results with graphical representation, where appropriate**
  as described in 3.2.S.7.3

Module 3 Drug Product

3.2.S.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

- ❒ **Summarized should be**
  - Types of studies conducted,
  - Protocols used,
  - Results of studies
- ❒ **Summary should include**
  - Conclusions regarding
    - Storage conditions
    - Shelf life
    - In-use storage conditions if applicable

  ICH Guidelines: Q1A(R2), Q1E, Q1F, Q1B, Q3B(R), Q6A

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

- ❒ **Post-approval stability protocol and stability commitment should be provided**
  ICH Guidelines: Q1A(R2)

3.2.P.8.3 Stability Data

- ❒ **Results of stability studies in appropriate form**
  - Tabular or
  - Graphical or
  - Narrative

- ❒ **Information on analytical procedure**
- ❒ **Validation of these Procedures**

ICH Guidelines: Q1A(R2), Q1B, Q1E, Q1F, Q2A, Q2B

Module 2 QOS Drug Product

2.3.P.8 Stability

- ❒ **Summary of studies undertaken**
  - Conditions
  - Batches
  - Analytical procedures

- ❒ **Brief discussion of**
  - Results and conclusions of stability studies,
  - analysis of data.
  - Conclusions concerning
    - storage conditions
    - shelf life
    - in-use storage conditions and shelf life

    Information from P 8.1

- ❒ **Post-approval stability protocol as described in P 8.2**

- ❒ **Tabulated summary of stability results from P 8.3 with graphical representation**