INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE
M4

Current *Step 4* version
dated June 15, 2016

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, USA, Canada and Switzerland.

M4(R3)
Document History

First Codification	History	Date	New Codification **November 2005**
M4	Approval by the Steering Committee under *Step 2* and release for public consultation.	20 July 2000	M4
M4	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	8 November 2000	M4
M4	Approval by the Steering Committee of Numbering and Section Headers changes for consistency directly under *Step 4* without further public consultation. Inclusion of the Granularity Document as Annex.	12 September 2002	M4(R1)
M4	Approval by the Steering Committee of the Revision of the Annex: Granularity Document.	11 November 2003	M4(R2)
M4	Approval by the Steering Committee of the corrections given on the Revised Annex: Granularity Document.	13 January 2004	M4(R3)

Current *Step 4* version

M4	Approval by the Assembly of the corrections given on the Revised Annex: Granularity Document.	15 June 2016	M4(R4)

In order to facilitate the implementation of the M4 guideline, the ICH Experts have developed a series of Q&As which can be downloaded from the ICH web site: http://www.ich.org

M4 Questions & Answers History

M4 Q&As	Approval by the Steering Committee.	12 September 2002	M4 Q&As
M4 Q&As	Approval by the Steering Committee of the newly added questions.	18 July 2003	M4 Q&As (R1)
M4 Q&As	Approval by the Steering Committee of the newly added questions.	11 November 2003	M4 Q&As (R2)

Current M4 Questions & Answers posted on the web site

M4 Q&As	Approval by the Steering Committee of the newly added questions.	10 June 2004	M4 Q&As (R3)

ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Harmonised Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on November 8, 2000, this guideline is recommended for adoption to the three regulatory parties to ICH

(Numbering and Section Headers have been edited for consistency and use in e-CTD as agreed at the Washington DC Meeting, September 11-12, 2002)

(The Annex : Granularity Document has been revised at the Steering Committee held in Osaka, November 11, 2003 and has been corrected on January 13, 2004 : The table for Module 2 has a row for 2.3.S.7 added)

(The Annex: Granularity Document has been adopted at the Assembly meeting on June 15, 2016 to add Module 2 and 3 tables and Appendices for eCTD v4, as well as, corrections to Module 2 and 3 tables for eCTD v3.2.2)

OBJECTIVE OF THE GUIDELINE

This guideline presents the agreed upon common format for the preparation of a well-structured Common Technical Document for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified.

BACKGROUND

Through the ICH process, considerable harmonisation has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonisation of the organisation of the registration documents. Each region has its own requirements for the organisation of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the GAIYO, which organises and presents a summary of the technical information. In Europe, Expert Reports and tabulated summaries are required, and written summaries are recommended. The U.S. FDA has guidance regarding the format and content of the New Drug Application. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the Common Technical Document that will be acceptable in all three regions.

SCOPE OF THE GUIDELINE

This guideline primarily addresses the organisation of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products).

This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organisation of the Common Technical Document as outlined in the guideline. However, in the Nonclinical and Clinical Summaries, applicants can modify individual

formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

GENERAL PRINCIPLES

Throughout the Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE)[1].

ORGANISATION OF THE COMMON TECHNICAL DOCUMENT

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

Module 1. Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module 2. Common Technical Document Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

Module 2 should contain 7 sections in the following order :

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

The organisation of these summaries is described in Guidelines for M4Q, M4S, and M4E.

[1] The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

Module 3. Quality

Information on Quality should be presented in the structured format described in Guideline M4Q.

Module 4. Nonclinical Study Reports

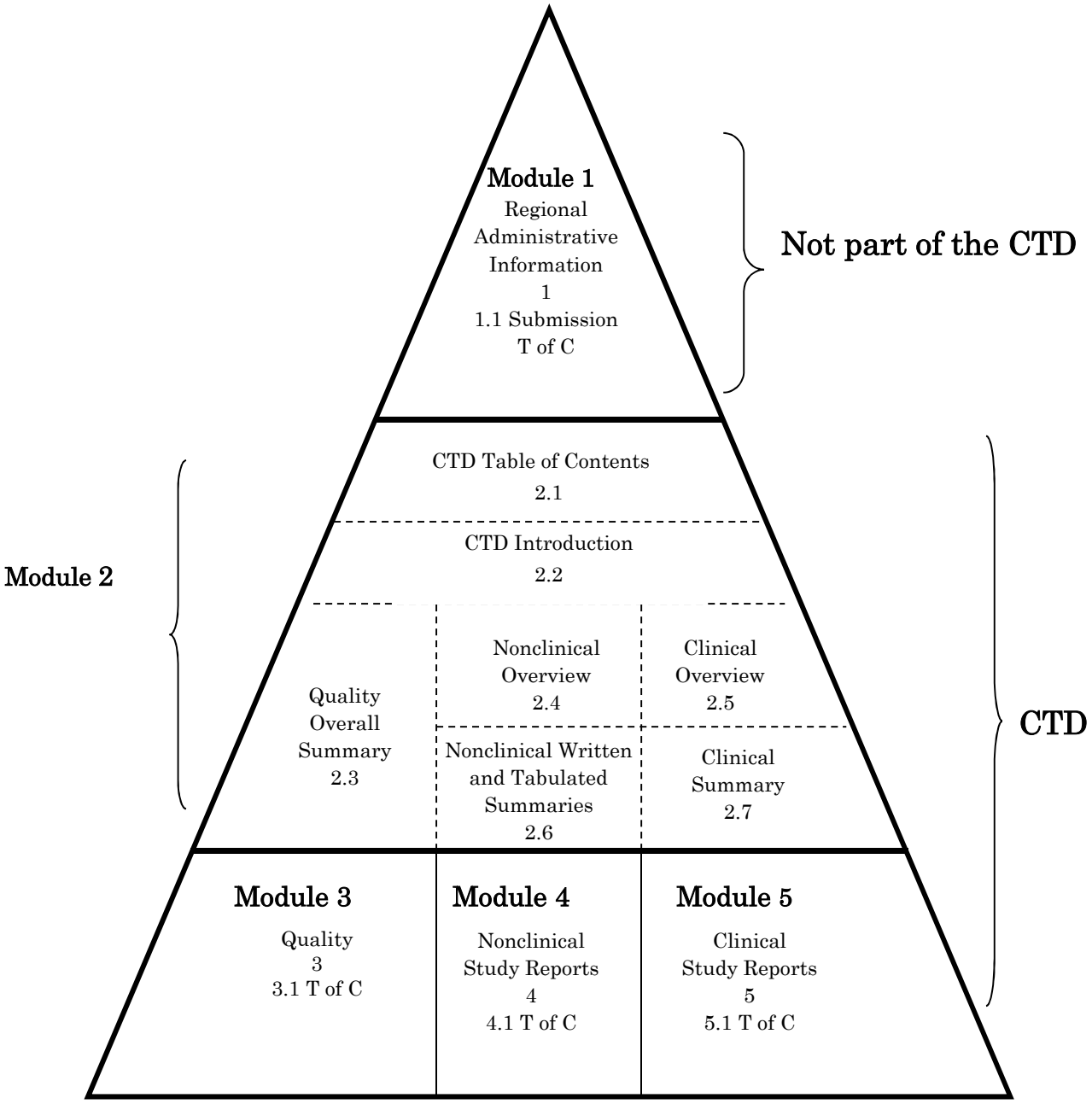
The nonclinical study reports should be presented in the order described in Guideline M4S.

Module 5. Clinical Study Reports

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

The overall organisation of the Common Technical Document is presented on the following pages.

Diagrammatic Representation of the Organization of the ICH CTD
Common Technical Document



ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information

- 1.1 Table of Contents of the Submission Including Module 1
- 1.2 Documents Specific to Each Region (for example, application forms, prescribing information)

Module 2: Common Technical Document Summaries

- 2.1 Common Technical Document Table of Contents (Modules 2-5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview
- 2.6 Nonclinical Written and Tabulated Summaries
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- 2.7 Clinical Summary
  - Biopharmaceutic Studies and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Literature References
  - Synopses of Individual Studies

Module 3: Quality

- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- 3.3 Literature References

Module 4: Nonclinical Study Reports

- 4.1 Table of Contents of Module 4
- 4.2 Study Reports
- 4.3 Literature References

Module 5: Clinical Study Reports

- 5.1 Table of Contents of Module 5
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

ANNEX : Granularity Document

The CTD specifies many section headings and numbers. Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents? Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy?

As a consequence of this definition could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include?

Definition of a Document

A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab (see Document Pagination and Segregation section of this Annex). A document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent, although if a paper submission is updated to be an electronic submission, some changes in granularity could be introduced to facilitate on-going lifecycle management. In an electronic submission, a new file starts at the same point at which in a paper submission, a tab divides the documents.

In deciding whether one or more documents or files are appropriate, it should be considered that **once a particular approach has been adopted, the same approach should be used throughout the life of the dossier** since it is the intention that replacement documents/files be provided when information is changed.

The following tables describe the levels in the CTD/eCTD hierarchy at which documents/files should be placed and whether single or multiple documents are appropriate at each point. This describes all sections of a CTD/eCTD but for individual submissions all sections might not be applicable.

For modules 2.3 and 3, the recommended granularity depends on the version of the eCTD standard that is used to prepare the submission, whereas the same Module 4 and 5 granularity applies to all eCTD standards.

For submissions filed using eCTD v3.2.2: Refer to Tables 1, 2, 5 and 6, as well as the additional guidance provided in separate ICH eCTD Q&As.

For submissions filed using eCTD v4: Refer to Tables 3, 4, 5 and 6, as well as the additional guidance provided in Appendices A-F.

For paper CTD submissions: Refer to Tables 1, 2, 5 and 6 OR Tables 3, 4, 5 and 6. (Additionally, see regional guidance.)

TABLE 1: Module 2 (paper and eCTD v3.2.2 submissions)

Module 2	2.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD	
	2.2		
	2.3 Note 1	Introduction	
		2.3.S Note 2	2.3.S.1
			2.3.S.2
			2.3.S.3
			2.3.S.4
			2.3.S.5
			2.3.S.6
			2.3.S.7
		2.3.P Note 3	2.3.P.1
			2.3.P.2
			2.3.P.3
			2.3.P.4
			2.3.P.5
			2.3.P.6
			2.3.P.7
			2.3.P.8
		2.3.A	2.3.A.1
			2.3.A.2
			2.3.A.3
		2.3.R	
	2.4		
	2.5		
	2.6	2.6.1	
		2.6.2	
		2.6.3	
		2.6.4	
		2.6.5	
		2.6.6	
		2.6.7	
	2.7	2.7.1	
		2.7.2	
		2.7.3 Note 4	
		2.7.4	
		2.7.5	
		2.7.6	

Key
Documents rolled up to this level are not considered appropriate
One document may be submitted at this level
One or multiple documents can be submitted at this level
Documents may not be submitted at this level for eCTD submissions (documents may be written at this level but must be submitted at the higher level)

Note 1: Optionality of granularity for the Quality Overall Summary is provided in order to accommodate different levels of complexity of products. The applicant can choose the level at which the QOS is managed.

Note 2: One document should be submitted for each drug substance

Note 3: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part “P” document

Note 4: One document for each indication should be submitted, although closely related indications can be within a single document.

TABLE 2: Module 3 (paper and eCTD v3.2.2 submissions)

Once a granularity option is chosen, continue with that option during the application's lifecycle.

Module 3 Note 1	3.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	3.2	3.2.S Note 2	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4 Note 3	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7	3.2.S.7.1
				3.2.S.7.2
				3.2.S.7.3
		3.2.P Note 4	3.2.P.1	
			3.2.P.2	3.2.P.2.1 Note 5
				3.2.P.2.2 Note 5
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3
				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5 Note 3	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5

Key
Documents rolled up to this level are not considered appropriate
One or multiple documents can be submitted at this level
Documents may not be submitted at this level for eCTD submissions (documents may be written at this level but must be submitted at the higher level)

Note 1: In choosing the level of granularity for this Module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD.

Note 2: For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

Note 3: One or more control strategy summary documents may optionally be placed here.

Note 4: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P", as appropriate.

Note 5: The lower level of each heading included in CTD-Q at this point is unlikely to contain individual documents or files.

				3.2.P.5.6
			3.2.P.6	
			3.2.P.7	
			3.2.P.8	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3
		3.2.A	3.2.A.1	
			3.2.A.2	
			3.2.A.3	
		3.2.R	Note 6	
	3.3	One file per reference Note 7		

Note 6: Refer to regional guidances.

Note 7: Literature References should be listed in the tables of contents.

TABLE 3: Module 2 (paper and eCTD v4 submissions)

Module 2	2.1	A TOC is not applicable for eCTD.	
	2.2		
	2.3 Note 1, Note 2	Introduction	
		2.3.S Note 1, Note 3	
		2.3.P Note 1, Note 4	
		2.3.A	2.3.A.1 Note 1, Note 5
			2.3.A.2 Note 1, Note 6
			2.3.A.3 Note 1
		2.3.R Note 1	
	2.4		
	2.5		
	2.6	2.6.1	
		2.6.2	
		2.6.3	
		2.6.4	
		2.6.5	
		2.6.6	
		2.6.7	
	2.7	2.7.1	
		2.7.2	
		2.7.3 Note 7	
		2.7.4	
		2.7.5	
		2.7.6	

Key
Documents rolled up to this level are not considered appropriate
One document may be submitted at this level
One or multiple documents can be submitted at this level

Note 1: Granularity options for the Quality Overall Summary are available to accommodate varying complexity of products. An applicant can submit a single 2.3 document OR write document(s) as 2.3 Introduction, 2.3.S (or 2.3.S.x), 2.3.P (or 2.3.P.x), 2.3.A.x, and 2.3.R, and submit at the 2.3.x or 2.3.x.n levels as shown in the table. Refer to Appendix A for keyword guidance for drug substance and drug product.

Note 2: A document may be split for technical reasons (e.g., if exceeding the maximum PDF size limit).

Note 3: For a drug product containing >1 drug substance, separate document(s) may be provided for each drug substance (by using the substance keyword). Typically, separate documents are not provided for each manufacturer. Refer to Appendix A for keyword guidance.

Note 4: For drug product supplied with reconstitution diluent(s), separate document(s) may be provided for the diluent(s) (by using the product keyword). If there is >1 dosage form, then separate document(s) may be provided for each (by using the dosage form keyword). Refer to Appendix A for keyword guidance.

Note 5: If multiple facilities are presented, one document may be provided for each facility by using the facility keyword. Refer to Appendix F for keyword guidance.

Note 6: For multiple components or for combination products (e.g., for vaccines), one document may be provided for each component by using the component keyword. Refer to Appendix F for keyword guidance.

Note 7: One document for each indication should be submitted, although closely related indications can be within a single document.

TABLE 4: Module 3 (paper and eCTD v4 submissions)

Once a granularity option is chosen, continue with that option during the application's lifecycle.

Module 3 Note 1	3.1	A TOC is not applicable for eCTD.		
	3.2	3.2.S Note 2, Note 3	3.2.S.1 Note 4	
			3.2.S.2 Note 2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3 Note 2	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4 Note 2	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7 Note 2	3.2.S.7.1
				3.2.S.7.2
				3.2.S.7.3 Note 5
		3.2.P Note 2, Note 6	3.2.P.1	
			3.2.P.2 Note 7	3.2.P.2.1 Note 4
				3.2.P.2.2 Note 4
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3 Note 2	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3
				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4 Note 8	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5 Note 2	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5
				3.2.P.5.6
			3.2.P.6	

Key
Documents rolled up to this level are not considered appropriate and no document is to be present at this level
One or multiple documents can be submitted at this level
One or multiple documents can be submitted at this level, but its content is not rolled up from lower levels

Note 1: In choosing the level of granularity for Module 3, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: Document(s) may be present at this level in addition to having document(s) at lower level(s); refer to Appendix B.

Note 3: For a drug product containing more than one drug substance, the "S" information should be provided in its entirety for each drug substance. Refer to Appendix A. Refer to health authority for guidance if a drug substance is already approved.

Note 4: The lower level of each heading included in CTD-Q at this point is unlikely to contain individual documents or files.

Note 5: For stability, the information may be provided in its entirety or per manufacturer, stability study protocol, and/or any other distinguishing information. Refer to Appendix C.

Note 6: For a drug product supplied with reconstitution diluent(s), the "P" information on the diluent(s) should be provided in its entirety as separate drug product(s), as appropriate. Refer

			3.2.P.7 Note 9	
			3.2.P.8 Note 2	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3 Note 10
		3.2.A Note 2	3.2.A.1 Note 11	
			3.2.A.2 Note 12	
			3.2.A.3 Note 13	
		3.2.R Note 14		
	3.3	One file per reference		

to Appendix A.

Note 7: For the P.2 content, use the 3.2.P.2 (i.e., roll up of P.2.1 to P.2.6) OR 3.2.P.2.x level. Additionally, a Control Strategy Summary may be placed at 3.2.P.2. A single 3.2.P.2 document is not recommended for Quality by Design or large molecule applications.

Note 8: For excipient guidance on when to use the 3.2.P.4 and/or 3.2.P.4.x level, refer to Appendix D.

Note 9: For a drug product containing >1 container closure system, the information may be provided in its entirety or per system or per other distinguishing information. Refer to Appendix E.

Note 10: For stability, the information may be provided in its entirety or per container closure system, manufacturer, strength, stability study protocol, and/or any other distinguishing information. Refer to Appendix C.

Note 11: If >1 facility is provided, document(s) may be provided per facility. Refer to Appendix F.

Note 12: Typically only one 3.2.A.2 document is provided, but if there is >1 component (e.g., multiple component vaccines or combination products), then document(s) may be provided per component. Refer to Appendix F.

Note 13: If >1 excipient is provided, document(s) may be provided per excipient.

Note 14: Use 3.2.R OR its sub-sections, if applicable; refer to regional guidance.

TABLE 5: Module 4 (paper and eCTD submissions)

Module 4	4.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD			
	4.2	4.2.1	4.2.1.1	Studies Note 1	
			4.2.1.2	Studies Note 1	
			4.2.1.3	Studies Note 1	
			4.2.1.4	Studies Note 1	
		4.2.2	4.2.2.1	Studies Note 1	
			4.2.2.2	Studies Note 1	
			4.2.2.3	Studies Note 1	
			4.2.2.4	Studies Note 1	
			4.2.2.5	Studies Note 1	
			4.2.2.6	Studies Note 1	
			4.2.2.7	Studies Note 1	
		4.2.3	4.2.3.1	Studies Note 1	
			4.2.3.2	Studies Note 1	
			4.2.3.3	4.2.3.3.1	Studies Note 1
				4.2.3.3.2	Studies Note 1
			4.2.3.4	4.2.3.4.1	Studies Note 1
				4.2.3.4.2	Studies Note 1
				4.2.3.4.3	Studies Note 1
			4.2.3.5	4.2.3.5.1	Studies Note 1
				4.2.3.5.2	Studies Note 1
				4.2.3.5.3	Studies Note 1
				4.2.3.5.4	Studies Note 1
			4.2.3.6	Studies Note 1	
			4.2.3.7	4.2.3.7.1	Studies Note 1
				4.2.3.7.2	Studies Note 1
				4.2.3.7.3	Studies Note 1
				4.2.3.7.4	Studies Note 1
				4.2.3.7.5	Studies Note 1
				4.2.3.7.6	Studies Note 1
				4.2.3.7.7	Studies Note 1
	4.3	One file per reference Note 2			

Key
Documents rolled up to this level are not considered appropriate
One or multiple documents can be submitted at this level

Note 1: Typically, a single document should be provided for each study report included in Module 4. However, where the study report is large, (e.g., a carcinogenicity study), the applicant can choose to submit the report as more than one document. In this case, the text portion of the report should be one document and the appendices can be one or more documents. In choosing the level of granularity for these reports, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: Literature References should be listed in the tables of contents.

TABLE 6: Module 5 (paper and eCTD submissions)

Module 5	5.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	5.2			
	5.3	5.3.1	5.3.1.1	Studies Note 1
			5.3.1.2	Studies Note 1
			5.3.1.3	Studies Note 1
			5.3.1.4	Studies Note 1
		5.3.2	5.3.2.1	Studies Note 1
			5.3.2.2	Studies Note 1
			5.3.2.3	Studies Note 1
		5.3.3	5.3.3.1	Studies Note 1
			5.3.3.2	Studies Note 1
			5.3.3.3	Studies Note 1
			5.3.3.4	Studies Note 1
			5.3.3.5	Studies Note 1
		5.3.4	5.3.4.1	Studies Note 1
			5.3.4.2	Studies Note 1
		5.3.5 Note 2	5.3.5.1	Studies Note 1
			5.3.5.2	Studies Note 1
			5.3.5.3	Studies Note 1
			5.3.5.4	Studies Note 1
		5.3.6		
		5.3.7	Studies Note 1	
	5.4	One file per reference Note 3		

Key
Documents rolled up to this level are not considered appropriate
One document can be submitted at this level
One or multiple documents can be submitted at this level

Note 1: The applicants should ordinarily provide the study reports as multiple documents (a synopsis, a main body of the study report and appropriate appendices). Appendices should be organized in accordance with the ICH E3 guideline, which describes the content and format of the clinical study report. In choosing the level of granularity for reports the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: For applications in support of more than one indication, this section should be repeated for each indication.

Note 3: Literature References should be listed in the tables of content.

Document Pagination and Segregation

Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient. Applicants need not display the number as "1 of n" where n is the total number of pages in the document.

Additionally, all pages of a document should include a unique header or footer that briefly identifies its subject matter. In a paper-based drug submission, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier. An abbreviation of the full section number and title can be used.

If a section contains more than one document, a specific Table of Contents for that section can be included to identify the chronology and titles of the documents contained therein, e.g.

- Tab with "3.2.S.4.2 Analytical Procedures"
    - Table of Contents, listing the title of Procedure A, Procedure B, Procedure C
- Tab with "3.2.S.4.2 Procedure A";
    - Procedure A (i.e. document, page 1-n)
- Tab with "3.2.S.4.2 Procedure B";
    - Procedure B (i.e. document, page 1-n)
- Tab with "3.2.S.4.2 Procedure C";
    - Procedure C (i.e. document, page 1-n)

If a section contains only a single document (e.g. 3.2.S.1.1 Nomenclature), only a tab identified by "3.2.S.1.1 Nomenclature" should precede the document.

Section Numbering within Documents

In order to avoid 5th, 6th etc. level subheading numbering (e.g. 2.6.6.3.2.1) within a document, the applicant can use a shortened numbering string. In this case, the document number and the name (e.g. 2.6.6 Toxicology Written Summary) should appear in page headers or footers and then section numbering within the document can be used, for example, 1, 1.1, 2, 3, 3.1, 3.2 etc. Use of the full numbering string (e.g. 2.6.6.3.2.1) is also considered acceptable.

Table of Contents Formatting

Module 2

The 2.1 CTD Table of Contents should go down to the third (e.g. 2.3.S) or fourth (e.g. 2.3.S.1) level, depending on how a document is defined for the Quality Overall Summary. (See **Definition of a document for Module 2**.)

Module 3

The Table of Contents provided under 3.1 should cover the high-level section numbering, the associated section heading and the Volume number in the order that they appear in the drug submission. This Table of Contents would be used to identify the contents of Module 3 as defined in the M4Q guideline. It should go down to the fifth level only (e.g. 3.2.P.2.1). Note that additional subsections and subheadings are defined in the M4Q guideline beyond this level (e.g. under 3.2.P.2) and this formatting should be used within the dossier, despite not being included in the 3.1 Table of Contents. The lower level Table of Contents described

under **Document Pagination and Segregation** should be excluded from the 3.1 Table of Contents.

At the applicant's discretion, a Table of Contents can also be included for a particular section that contains multiple documents, in order to identify the chronology and the document subject matter. If there is a desire to introduce additional headers or subsection numbering beyond those which are defined in the M4Q guideline, these should only be included within a document and should be created neither as a separate document nor as a new subsection. In this case, a specific Table of Contents for that document can be included to identify the chronology and titles of the subsections contained therein. These documents and subsections should not appear in the 3.1 Table of Contents.

Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided. In this case, a cross-reference should be made within the relevant section to the attached or appended document. If there is a desire to append or attach additional information to a section that is comprised of only one document, this information should be incorporated within that document.

All Table of Contents title entries should either correspond to heading names and section numbering as defined in the M4Q guideline or to identifiers appearing on tabs (for a paper-based drug submission only), preferably by their full title, which should easily identify any abbreviated title that might be used on the corresponding tab. The Table of Contents should not specify any page numbers.

Literature References should be listed in a Table of Contents specific for this section.

Module 4

The Table of Contents for Module 4 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (for example, 4.2.3.5.1 Fertility and early embryonic development) and should continue down to at least the level of the study report. Thus each study report should be identified in the table of contents. The sections of a study report could be identified in the Module 4 Table of Contents of the dossier or only in the Table of Contents of the individual study report.

Illustration of part of the Module 4 Table of Contents

4.2.3.2 Repeat-Dose Toxicity

Study aa-aaa: 30 day repeat dose toxicity study with Drug C in rat

Study bb-bbb: 6 month repeat dose toxicity study with Drug C in rat

Study cc-ccc: 30 day repeat dose toxicity study with Drug C in dog

Study dd-ddd: 6 month repeat dose toxicity study with Drug C in dog

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

Study ee-eee: Ames test with Drug C

etc.

Module 5

The Table of Contents for Module 5 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (for example, 5.3.5.1.1 Placebo Controlled Trials) and should continue down to at least the level of the clinical study report. Thus each clinical study report should be identified in the table of contents. The sections of a clinical study report (E3) could be identified in the Module 5 Table of Contents of the dossier or only in the Table of Contents of the individual clinical study report.

Illustration of part of the Module 5 Table of Contents

5.3.5 Indication Z - Reports of Efficacy and Safety Studies

5.3.5.1 Indication Z - Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication

5.3.5.1.1 Indication Z - Placebo Controlled Trials

Study xx-xxx: A double blind, placebo-controlled trial of Drug A in Indication Z

Study yy-yyy: A double blind……

5.3.5.1.2 Indication Z - Active Controlled Trials

Study zz-zzz: A double blind, active controlled trial of Drug A vs. Drug C in Indication Z

5.3.5 Indication Q - Reports of Efficacy and Safety Studies

5.3.5.1 Indication Q - Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication etc.

Appendices for eCTD v4 Submissions

Appendix A: Guidance on Using the Substance, Manufacturer, Product, and Dosage Form Keywords

These keywords (called "attributes" in v3.2.2) are optional and should only be used when needed; to add value to the review, one or more keywords could be used to repeat a section and uniquely identify it. The applicant decides when and how to use these keywords.

In all cases, a short informative value is adequate per keyword, since the keyword is intended to be an aid to a viewer of the application (e.g., to differentiate different drug substance or drug product sections), and not for computerized data management. Alternatively, documents could be differentiated by using unique titles, or by explaining differences within one document (e.g., with a comparative table of the manufacturing processes).

The keywords used in Module 2.3 need not match those used in Module 3.

For Module 2.3, the least granular option is a document that covers all topics, in which case there are no keywords. If the applicant uses a finer level of granularity (e.g., 2.3.S) a document (or documents with unique titles) could be provided using separate values for "substance" and/or "manufacturer". In this case, 2.3.S and 3.2.S keyword values (if used) can be different.

The "substance" keyword was designed primarily to distinguish different drug substances found in drug products containing multiple drug substances or for different drug products that are co-packaged. An International Non-proprietary Name (INN) is recommended for this keyword. Long INN names may be shortened. Consider the inclusion of any moiety to distinguish between different salt-forms that can be used in different dosage forms. If an INN is not available, a company code will suffice.

The "manufacturer" keyword was designed to facilitate lifecycle management where there might be different manufacturers (e.g., using a different drug substance route of synthesis (chemical entity) or manufacturing process (biologic)). If the applicant determines that there is no need to have multiple 3.2.S or 3.2.P sections (e.g., where few 3.2.S.x topics have manufacturer/site/process-specific documents (either now or likely in the future)) then the use of this keyword is not recommended; there is no benefit of a general umbrella term such as "all" or "applicant" or "not specified". The value for the "manufacturer" keyword might be a firm's name, the first word or abbreviation of a long company name, a site name, or simply words that differentiate different routes or processes. Use a term that is less likely to change during the life of the application.

The value for the "product" keyword could be used to distinguish, for example, between an "active", "device", "placebo", and/or a "diluent" drug product section, if applicable. The value for the "product" keyword could also be utilized to distinguish between an "A-type" versus a "B-type" drug product preparation and/or it could include strength information (if a separate 3.2.P section for another strength(s) can be justified). Proprietary names such as trademarks are not recommended, since proposed trademarks are not always accepted by authorities (trademark acceptability may not be known until after the eCTD application has been submitted).

The value for the "dosage form" keyword might consist of short descriptive text such as "powder for suspension". Including details such as strength, concentration, or fill volume in the "dosage form" keyword is not recommended.

Appendix B: Further Explanation of "Blue" Granularity and Control Strategy Summaries

"Blue" granularity: As of ICH eCTD v4.0, a new "blue" granularity option was introduced to Module 3. Inclusion of documents at this level is not a new expectation, but documents can be useful in certain circumstances. Examples are:

- a cross-reference to a Drug Master File could be placed at the 3.2.S or 3.2.P level
- a cross-reference to a Certificate of Suitability could be placed at the 3.2.S.4 or 3.2.P.5 level
- a Note to the Reviewer could be placed at any "blue" (or "green") level
- an Overall Control Strategy Summary could be placed at several possible locations (see below).

These optional documents should have clear and informative titles.

Control strategy summaries: Currently there are no specific locations defined for control strategy summaries in Module 3, so the placement of overall control strategy summaries is at the applicant's discretion. For example, overall control strategy summaries may be placed at the level of 3.2.S.4 and 3.2.P.5, 3.2.S.2.6 and 3.2.P.2 (or 3.2.P.2.3), or 3.2.S.4.5 and 3.2.P.5.6. The applicant should state in Module 2.3 (e.g., 2.3 Introduction) where all the Module 3 control strategy summaries are located.

Appendix C: Stability Data Guidance

Applicants may choose a granularity that best suits their business needs and as appropriate for the application. The use of the "descriptor" keyword is optional and the applicant decides when and how to use it. Each "descriptor" keyword value generates a separate 3.2.S.7.3 and/or 3.2.P.8.3 section. All stability data can be organised using one or multiple documents and within one or multiple Stability Data sections.

If there are several documents within a section, some differentiation can be achieved by informative naming of the documents' titles. Examples of titles for documents assigned to 3.2.P.8.3 could be:

- "Blister – 10 mg – long term storage"
- "Blister – 10 mg – accelerated"
- "Accelerated – bottles – 10 mg, 25 mg"
- "Accelerated – blisters – 10 mg, 25 mg"
- "36 months – bottles – 10 mg, 25 mg"

When there are multiple documents under a section, the priority number assigned to each document determines the order in which the documents appear within the section.

Additional or other information may be provided either in the value for the "descriptor" keyword or in the document's title (e.g., storage condition, orientation of the container, and/or information such as "primary" vs. "supportive"). It is not recommended to use general umbrella terms such as "all strengths".

Appendix D: Excipient Guidance

Applicants may choose a granularity that best suits their business needs and as appropriate for the application. All excipient data can be organised using one or multiple documents and within one or multiple Excipient sections. The use of the "excipient" keyword is optional and the applicant decides when and how to use it. Each "excipient" keyword value generates a separate 3.2.P.4 and/or 3.2.A.3 section. The "excipient" keyword

does not have to be used (i.e., only one excipient section can be provided even if there is more than 1 excipient in the drug product). However if repeating 3.2.P.4 sections are used, then the "excipient" keyword should be used as it identifies and distinguishes the content of the section. General terms (e.g., "compendial", "coating agent", "non-compendial") and/or specifically-named excipient keyword values are acceptable.

One or multiple documents can be submitted covering each excipient, all excipients, each excipient topic (i.e., 3.2.P.4.1-3.2.P.4.6), or all excipient topics:

- **Option 1 (using a single 3.2.P.4 section without any lower level granularity):** This option is appropriate if the overall volume of information is small, such as when only compendial excipients are used. In this case, only a single document would typically be submitted at the 3.2.P.4 level, with or without an "excipient" keyword, and the document would cover all excipients used and all excipient topics (i.e., 3.2.P.4.x).
- **Option 2 (using multiple 3.2.P.4 sections without lower level granularity for 3.2.P.4.x):** One or multiple documents can be submitted at the 3.2.P.4 level (and not at a 3.2.P.4.x level) per excipient or grouping of excipients, covering relevant excipient topics. The "excipient" keyword is used to identify the name of a single or group of excipient(s) (e.g., "compendial"). A single document might be used to cover either all topics (3.2.P.4.x) or each topic separately.
- **Option 3 (using multiple 3.2.P.4 sections with 3.2.P.4.x granularity):** One or multiple documents can be submitted at the appropriate 3.2.P.4.x level per excipient CTD topic. Multiple documents at the same 3.2.P.4.x level (e.g., separate documents for each excipient or grouping of excipients covering each of the 3.2.P.4.x topics) can be distinguished using informative document titles and/or in combination with the use of the "excipient" keyword, if desired.

Options 2 and 3 might be combined in a sequence. For example, a single document covering all compendial excipients (i.e., a grouping with an excipient keyword of "compendial", for example, can be provided at a 3.2.P.4 level in one section (Option 2), but more granular documents can be provided in named or grouped (e.g., "coating agent") non-compendial excipient sections at the relevant 3.2.P.4.x levels (Option 3).

For all options, there is no ICH consensus on granularity if no human, animal, and/or novel excipients are used. Refer to regional guidance recognizing that an "excipient" keyword such as "Human-Animal-Novel" might be a possibility for a separate section used to discuss 3.2.P.4.5 and 3.2.P.4.6.

Considerations when choosing excipient granularity include the amount of information to be provided and future lifecycle potential, business processes for the generation and sources of global documentation, and the re-usability of information for worldwide markets.

Since the current use of the excipient keyword is intended to be an aid to the viewer of the application, and not for computerized data management, avoid multiple documents per compendial excipient where content is just a reference(s) to a compendial monograph(s).

Per ICH M4Q, all components of the dosage form should be listed in 3.2.P.1 (Description and Composition of the Drug Product), each with its function and reference to a quality standard (e.g., compendial monographs, manufacturer's specifications). Within section 3.2.P.4 (Control of Excipients), it is an ICH expectation to provide excipient specifications in 3.2.P.4.1 (Specifications). An optional re-listing of the excipients within 3.2.P.4 or a link back to the list in 3.2.P.1 might be helpful in some cases, but it is not an ICH expectation to repeat a list of excipients in 3.2.P.4.

If a non-compendial excipient becomes compendial

If the application has only one 3.2.P.4 section where either the excipient keyword is not used or the excipient keyword is used without "compendial" or "non-compendial" as its keyword value, then affected document (s) can be replaced or removed.

If the application contains more than one 3.2.P.4 section:

- If the excipient name was used as the keyword value and there is no other section for grouped compendial excipient(s) (e.g., "compendial" as its keyword value) then the affected document content needs to be updated (or a new document created). An option for the next sequence is to apply a status code value of "suspended" in the original section; then create a new 3.2.P.4 section with a new identifier and a new keyword value (e.g., "compendial") and apply the updated or new document to the new 3.2.P.4 section.
- If groupings of excipients were used with keyword values of "compendial" and "non-compendial", for example, then in the compendial section any affected document(s) is(are) replaced with the updated content. In the non-compendial section, the document(s) that now correspond to pharmacopoeial content have the status code value of "suspended" applied to them.

If extensive information was provided in 3.2.A.3 on the originally non-compendial excipient, apply the status code value of "suspended" if there is a desire to no longer maintain or lifecycle this information under 3.2.A.3.

If an excipient is renamed

As of ICH eCTD v4.0, it is possible to change the keyword value or display name.

For a novel excipient that is no longer regarded as being novel

If there is a desire to no longer maintain or lifecycle this information under 3.2.P.4.6 and/or 3.2.A.3, as applicable, then apply the status code value of "suspended" to the original section. Update 3.2.P.4 to acknowledge that the excipient is no longer regarded as novel.

Appendix E: Container Closure System Guidance

Applicants may choose granularity that best suits their business needs. All container closure information could be in one document or multiple documents and within one or multiple Container sections. The use of the "container" keyword is optional and the applicant decides when and how to use it. Each "container" keyword value generates a separate 3.2.P.7 section (e.g., for products supplied in more than one type of container closure system).

If there are several documents within a section, some differentiation can be achieved by informative naming of the documents' titles. Examples of titles of documents assigned to 3.2.P.7 could be:

- "Description – Blister"
- "Description – HDPE Bottle – 50 mL"
- "HDPE Bottle – 50 mL – Description"
- "HDPE Bottle – 50 mL – Manufacturers"
- "HDPE Bottle – 50 mL – Specification"

When there are multiple documents under a section, the priority number assigned to each document determines the order in which the documents appear within the section.

Additional or other information may be provided in the document title (e.g., packaging component information (Al lidding, PVC laminate)) to differentiate documents.

Alternatively, individual documents for each container closure system (e.g., bottles vs. blisters) could be provided.

Appendix F: Guidance on Using the "Facility" and "Component" Keywords

Applicants may choose granularity that best suits their business needs.

Facility: The use of the "facility" keyword is optional and the applicant decides when and how to use it. Each "facility" keyword value generates a separate 2.3.A.1 and/or 3.2.A.1 section. All facility information could be in one document or multiple documents and within one or multiple Facility sections.

The value for the "facility" keyword might be a town or a site's location (e.g., "East Park") or it might be more specific (e.g., "East Park Building 2"). Additional details may be used in the naming of the document titles appearing under the 2.3.A.1 and/or 3.2.A.1 section to further supplement the keyword value.

Although documents containing information that is applicable to more than one 3.2.A.1 section (e.g., room classifications) can be placed under each section, reviewer preference is to minimize the number of documents with identical content. If only a limited number of documents can be shared across sections, use less specific keyword values (resulting in fewer sections) instead of detailed values (that result in many sections). If a sufficient number of documents are common across facilities, only one 3.2.A.1 section can be provided (i.e., without a keyword) and combined with the use of distinctive document titles or comparative tables within the documents.

Component: The use of the "component" keyword is optional and the applicant decides when and how to use it. Each "component" keyword value generates a separate 2.3.A.2 and/or 3.2.A.2 section. All adventitious agent safety evaluation information could be in one document or multiple documents and within one or multiple adventitious agent safety evaluation sections (i.e., each section covering a different drug substance and/or drug product "component"). For products containing a single drug substance and requiring an adventitious agents safety evaluation, one 3.2.A.2 document covering both the 3.2.S and 3.2.P sections may be sufficient. The use of a "component" keyword is not necessary in this case.

For drug products containing multiple drug substances (e.g., multiple component vaccines or combination products), it may be appropriate to provide a separate adventitious agents safety evaluation for each drug substance component, in which case a unique "component" keyword may be used to identify and distinguish the information in repeated sections, with the combined use of one or multiple documents.

For some combination products, where an adventitious agents safety evaluation may need to be provided for each drug substance component as well as the combined product, the use of the "component" keyword may also be practical in combination with one or multiple documents.