INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

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

Current *Step 4* version
dated January 13, 2004

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 and USA.

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)

Current *Step 4* version

M4	Approval by the Steering Committee of the corrections given on the Revised Annex: Granularity Document.	13 January 2004	M4(R3)

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 Tripartite 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)

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

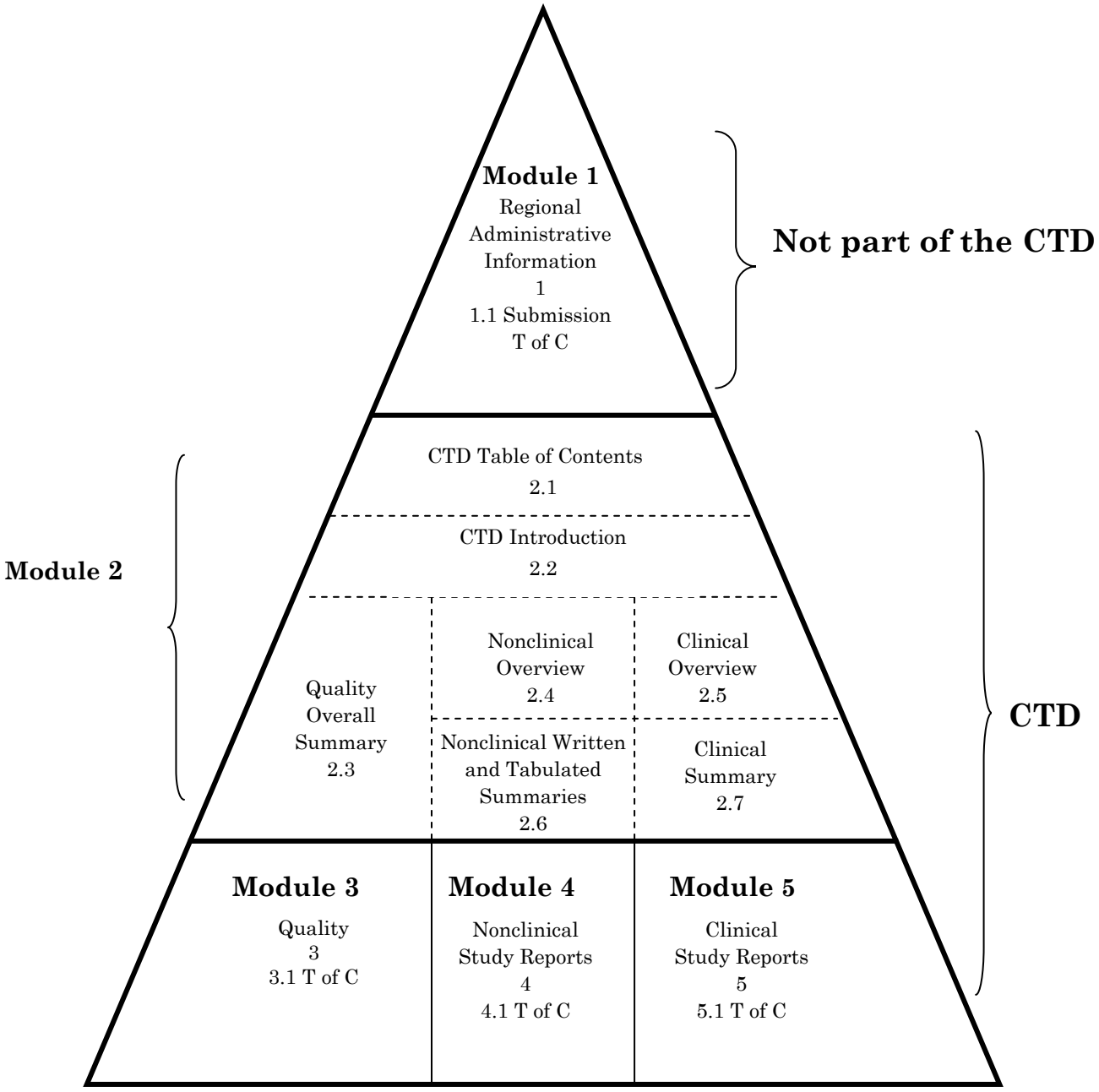
The nonclinical study reports should be presented in the order described in Guideline M4S.

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.

Module 2

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

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

Module 3

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	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 3	3.2.P.1	
			3.2.P.2	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	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	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	
			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 5	
	3.3	One file per reference Note 6		

Key
Documents rolled up to this level are not considered appropriate
One or multiple documents can be submitted at this 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 : 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 4 : The lower level of headings included in CTD-Q at this point are unlikely to be individual documents or files.

Note 5 : Refer to regional guidances.

Note 6 : Literature References should be listed in the tables of contents.

Module 4

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.

Module 5

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.