Guidance for Industry

Granularity Document

Annex to
M4: Organization of the CTD

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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Contains Nonbinding Recommendations

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INTRODUCTION

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). This annex to the M4 guidance on the organization of the CTD was developed by ICH in response to requests for additional information after the harmonized CTD guidance documents were finalized in November 2000. The annex is intended to clarify what constitutes a document in the paper CTD and in the eCTD, and includes the following information for modules 2 through 5:

- location and hierararchy of headings within the modules
- document pagination and segregation
- section numbering within documents
- formatting of the table of contents

The information provided here reflects the consensus of the ICH parties. The annex will be incorporated in FDA's next revision of the M4 guidance.

[1] This guidance was developed within the M4 CTD and M2 eCTD Implementation Working Groups of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process in September 2002. A revision was signed off by ICH in November 2003, and the annex was corrected in Janaury 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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?

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. 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.