The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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ICH M4
GENERAL QUESTIONS AND ANSWERS
COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Step 5

GENERAL QUESTIONS AND ANSWERS
(CPMP/ICH/2887/99)

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CTD General Questions and Answers

Questions			Answers
1	**New**	**Format or Content?** Will a dossier using the CTD format (Modules 2 to 5) be identical for all regions?	Not necessarily. The CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions. However, the CTD does not address the content of submissions. There are many regional requirements, as well as applicants' preferences, that could affect the contents of dossiers submitted in each region.
2	**New**	**Expert Reports** Are expert reports still required for submissions under the CTD format?	No. Expert Reports are replaced by Module 2. (N.B. For specific European requirements regarding experts' signatures, please refer to the European Commission Web Site.)
3	**New**	**Tables of Contents and Pagination** For a paper CTD submission, the guideline states that, for the comprehensive Table of Contents in module 1, no page numbers should be used. Does this apply only to the TOC in module 1, or for all TOCs in every module? Also, besides the volume numbers and tab identifiers, should the module numbers also be included? For modules 3, 4, and 5, should the volume number be part of the Table of Contents?	There are no specific guidelines for the page numbers of the TOC. Module numbers, volume numbers, and tab dividers should be part of all TOC's.
4	**New**	**How to paginate Literature References** When provided, how should literature references be paginated in a paper CTD? Should each reference start with page 1, or should the page number from the source (journal, abstract, etc) be the only page number included?	Literature References should be paginated according to the page numbering of the source (journal, abstract, etc).

Questions			Answers
5	**New**	**Sub-Heading Numbering, or Numbering Within Sections** How should sub-numbering within a document be organised? Some documents can be up to 50 pages in length with no defined CTD guideline heading, and potentially therefore no TOC entries or bookmarks (in the electronic version). Some guidance would be welcome to avoid regional interpretations on what is considered acceptable.	Within the document, the applicant can use section numbers at a lower level than those specified in the CTD guideline. However, there should be no other headings appearing in the overall TOC going below the numbering given in the CTD guideline. *For example, for section 3.2.P.3.3 it would be possible to use subsequent numbers (3.2.P.3.3.1, 3.2.P.3.3.2, etc.) to provide further navigation within the document. These should not appear in the overall TOC but can be included as bookmarks within the PDF files.*
6	**New**	**Titles of Documents Within Sections (e.g. reports etc.)** In the header or footer of each document in a dossier the appropriate TOC title entry should be included. In case of e.g. a clinical report the TOC entry is the title of the report and this can be really long. Would the use of the report number (alone) be considered sufficient? In other words, can the layout of the pages throughout the dossier be different: one page layout for reports and another one for Quality sections?	It is recommended that a distinct identifier be put in headers/footers on every page. However, it does not need to be the full title. An abbreviation would suffice.
7	**New**	**Cross references / Cross Strings (in Paper Submissions)** It is stated in the CTD that the section should be indicated in cross strings. What is meant here: The section number, or the section number and section name? (The section name is in a lot of cases way too long to indicate in a cross string.)	For the sake of clarity and ease for the reader/reviewer it is recommended that in paper submissions both the title and the section number be indicated in cross-references (or cross-strings). (However, it does not need to be the full title. An abbreviation would suffice.)

Questions			Answers
8	**New**	**General Glossary of Terms** Will there be a general glossary of recommended terminology for use in the CTD?	No glossary of terms is planned at this time.
9	**New**	**Location of the Information on Biological Comparability** A combined comparability section might be beneficial to the review process. Is it possible to consider a modification to the CTD to provide for such a section for Biological products? *N.B. Currently, comparability data should be included under 2.3.S.2/3; preclinically as proposed; and clinically under 2.5.2 and 2.5.6. Each part should summarise briefly the conclusions from the other sections.* - *in the clinical summary, antigenicity should go under either 2.7.4.3 or 2.7.4.4* - *in the clinical summary, "AEs of special interest" and "Mortality and Hospital Re-admission" should go under 2.7.4.2.1.4 (Other significant AEs).*	No, for the moment the CTD does not foresee any separate section combining all the comparability data.
10	**New**	**Information for Generic Drug Applications** Should the preclinical and clinical summary sections of the CTD be included in applications for generic drug approvals? More specifically, are Module 4 and 5 of the CTD applicable to Abbreviated New Drug Applications (ANDA) in the US and Abridged Marketing Authorization applications in the EU? Both categories of applications apply to generic drug applications, which ordinarily provide preclinical and clinical data based on available literature.	The CTD provides a format for the submission of information to regulatory authorities. It does not define content. Please refer to region-specific requirements to determine content requirements for the specific submission type.