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

M4 Implementation Working Group
Questions & Answers (R3)

Current version
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In order to facilitate the implementation of the CTD General (M4) guideline, the ICH Experts have developed a series of Q&As:

M4 Q&As
Document History

First Codification	History	Date	New Codification **November 2005**
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)

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines is more logical, consistent and clearer. Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1).

For better comprehension of the M4 references within the text, please see below the document change history for M4 guideline.

M4 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)

CTD General (M4) Questions and Answers (R3)

	Date of Approval	Questions	Answers
1	Sept. 2002	**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	Sept. 2002	**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	Sept. 2002	**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	Sept. 2002	**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).

CTD General (M4) Questions and Answers (R3)

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5	**Sept. 2002**	**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	**Sept. 2002**	**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	*Rev **Nov. 2003**	**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 many cases too long to indicate in a cross string.)	Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross string while maintaining the ease of use, it is recommended to include only the section number in the cross string and write the text so the

* Rev. = Revised

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			reader will also know the section content. For example, "…as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text "…no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.
8	**Sept. 2002**	**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	**Sept. 2002**	**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.

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10	Sept. 2002	**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.
11	June 2003	**Font style** On the basis of corporate identity we use the font style "Arial" for all of our documents. Can we use the font style "Arial" for CTD´s, or do we have to use "Times New Roman" style to match the recommendation for narrative texts according to the Guidance for Industry "Organisation of the CTD"?	"Times New Roman 12 point" is recommended for use in the CTD. This corresponds to MS Mincho, 10.5 point for the text written in Japanese.
12	June 2003	**Language** Can the CTD be in any language (e.g. Japanese, German, French, English)? Is it limited to a single language?	The CTD does not address this issue. Please refer to regional guidance.
13	June 2003	**Changes of numbering and section headers** With regard to the changes regarding numbering and section headers (September 11-12,2002), are the details in brackets (e.g. name, manufacturer or name, dosage form) only for use in eCTD format or for paper files also?	These changes in recommendation apply to all CTD/eCTD submissions.

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		Headers and page numbering What is your guidance for externally produced documents e.g. chromatograms, CTD format DMF, regarding page numbering and appropriate headers? Are there allowances regarding these documents with regard to pagination and headers i.e. are we allowed to submit them in the relevant document without a header or page number? **Tab** Do Tabs have to be printed? Do we have to use the full title with the number string on the tab? This is very difficult if the title is long.	Please refer to the CTD General Q&As No. 5 on the ICH Web site. Tabs should be printed for a paper submission. Tab abbreviations are acceptable.
14	**July 2003**	Is there a difference in the level of analysis in the non-clinical overview and the clinical overview in Module 2? Is there a difference between "critical analysis" (non-clinical overview) and "critical assessment" (clinical overview).	Please refer to the general guidance for both the non-clinical and clinical overviews. The level of analysis does not differ between these two overviews. The guidance describes the information that should be included in the "critical and integral" assessment/analysis in both overviews.
15	**July 2003**	Is the term, "section", defined in the CTD? Is there a different use of the term in Module 2 and 3? Do the ICH regions define sections differently?	Each section in the CTD is identified by a number and a heading Please refer to the Granularity Document Annex for a description documents to be provided in each section. The annex delineates when multiple documents per heading may be provided. Also, refer to regional guidance as to when one or multiple documents should be provided per heading.
16	**July 2003**	Does the deadline for mandatory submission of the CTD in Japan, the EU and the US (highly recommended in the US) also refer to the eCTD? Has ICH considered planning a seminar to help with CTD and eCTD submissions?	The deadline does not refer to the eCTD although the regulatory authorities are accepting eCTD submissions. Please refer to regional guidance for specific guidance on eCTD submissions. Currently the ICH is not planning to conduct a CTD seminar. However, the ICH6 Conference, November 2003 in Osaka Japan, will focus on the CTD and eCTD.

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17	**July 2003**	Has the DTD reached its final stage of approval in the ICH process?	The eCTD DTD has reached step 5 in the ICH process, which is the implementation step.
18	**July 2003**	Is there a definition of which attachments should be included in the CTD?	It is not suggested that additional attachments be included in the CTD.
19	**Nov. 2003**	**CTD training** Does ICH recommend any particular comprehensive training course on the implementation of the CTD?	No, there are no general ICH recommendations for training on CTD implementation.
20	**Nov. 2003**	**Applicant's Logo** Is it allowed to add the Applicant's Logo either on top of the CTD, or in the titles of CTD sections.	The applicant is free to put his logo on top of the CTD. However, logos are not acceptable in CTD sections' titles. (The latter have been harmonized internationally; therefore applicants are not allowed to modify them.)
21	**Nov. 2003**	**Herbal CTD** Will a Herbal Products version of the CTD be published and how much will it vary from the pharmaceutical CTD.	ICH does not plan to issue any specific version of the CTD for Herbal Products.
22	**Nov. 2003**	**Granularity: section headings and numbers, documents location/hierarchy, documents pagination** 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?	Please refer to the Annex of the Organisation of the Common Technical Document: "Granularity Document".

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23	**June 2004**	**Amendments and variations in CTD format** Is there a separate format for amendments/variations submitted in CTD format or should applicants use the CTD format as it is now? If used as it is now, is it enough to simply indicate whatever modules are not used?	The CTD structure is suitable for amendments and variations (refer to regional guidance for applicabilities). The applicant should not submit the modules that are not used i.e. it is unnecessary to include “not applicable” pages against unused CTD headings.