

CTD General Questions and Answers

Date of Approval		Questions	Answers
1	Sept. 2002	<p>Format or Content? Will a dossier using the CTD format (Modules 2 to 5) be identical for all regions?</p>	<p>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.</p>
2	Sept. 2002	<p>Expert Reports Are expert reports still required for submissions under the CTD format?</p>	<p>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.)</p>
3	Sept. 2002	<p>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?</p>	<p>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.</p>
4	Sept. 2002	<p>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?</p>	<p>Literature References should be paginated according to the page numbering of the source (journal, abstract, etc).</p>

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5	Sept. 2002	<p>Sub-Heading Numbering, or Numbering Within Sections</p> <p>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.</p>	<p>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.</p> <p><i>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.</i></p>
6	Sept. 2002	<p>Titles of Documents Within Sections (e.g. reports etc.)</p> <p>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?</p>	<p>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.</p>
7	Sept. 2002	<p>Cross references / Cross Strings (in Paper Submissions)</p> <p>It is stated in the CTD that the section should be indicated in cross strings.</p> <p>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.)</p>	<p>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).</p> <p>(However, it does not need to be the full title. An abbreviation would suffice.)</p>

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8	Sept. 2002	<p>General Glossary of Terms Will there be a general glossary of recommended terminology for use in the CTD?</p>	No glossary of terms is planned at this time.
9	Sept. 2002	<p>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?</p> <p><i>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.</i></p> <ul style="list-style-type: none"> - 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	Sept. 2002	<p>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.</p>	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.

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11	June 2003	<p>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"?</p>	<p>“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.</p>
12	June 2003	<p>Language Can the CTD be in any language (e.g. Japanese, German, French, English)? Is it limited to a single language?</p>	<p>The CTD does not address this issue. Please refer to regional guidance.</p>
13	June 2003	<p>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?</p> <p>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?</p> <p>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.</p>	<p>These changes in recommendation apply to all CTD/eCTD submissions.</p> <p>Please refer to the CTD General Q&As No. 5 on the ICH Web site.</p> <p>Tabs should be printed for a paper submission. Tab abbreviations are acceptable.</p>

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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 of 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.
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.

CTD-Safety Questions and Answers		
Date of Approval	Questions	Answers
1 May 2001	Kinetics in Pregnant Animals and Neonates Kinetics in pregnant animals and neonates are included in the PK section. Is it expected that these data will come from PK studies, or can they be from kinetics in the Segment 2 studies?	The CTD-S guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.
2 Sept 2002	Conduct/Non-Conduct of Specific Studies If a particular category of toxicology studies (e.g. carcinogenicity) is not conducted for a drug because of the nature of the drug (e.g. oncology agent), should the section heading be maintained in the CTD document with an explanation provided as to why these studies were not conducted, or should the heading section be deleted and subsequent sections renumbered?	Section headings should be maintained in the CTD document and a brief explanation provided as to why these studies were not conducted.
3 Sept 2002	Pivotal Studies Would a 3-month toxicity study that was needed to support clinical studies of 3-month's duration, that was later replaced with a 9-month toxicity study, be considered "pivotal" and tabulated as in Table 2.6.7.7?	Yes. There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.
4 Sept 2002	Tabulated Summary Are only toxicologically significant changes, as considered by applicants, to be tabulated in CTD?	Only noteworthy findings should be tabulated in CTD. These might include statistically significant differences from controls, as well as noteworthy findings that are not statistically significant.

CTD-Safety Questions and Answers		
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5	<p>Sept 2002</p> <p>Impurity Data Table in CTD-Safety – 1 Generally speaking, it is unlikely to have the finalized specification for related substances and their analytical method throughout drug development. Therefore, direct comparison of related-substance data between different stages of development would be very difficult, because of analytical method changes.</p>	<p>One purpose of the "Drug Substance" table is to facilitate a review of the qualification of the specified impurities. If the analytical methods have changed, information on early batches may not be applicable for qualification of impurities. In this case, it is recommended to use footnotes in the "Drug Substance" table to identify the batches that are relevant to qualification of impurities.</p>
6	<p>Sept 2002</p> <p>Impurity Data Table in CTD-Safety – 2 Should impurity-specification test results of test articles used in early-stage toxicology studies be included in CTD tables? Do test articles of non-GLP studies in the CTD need to have specification test data?</p>	<p>There is no requirement to analyze the drug substance used in non-GLP studies. However, if such analyses have been conducted, the results should be included in the "Drug Substance" table.</p>
7	<p>Sept 2002</p> <p>Nonclinical Tabulated Summaries Templates Are the templates for the nonclinical tabulated summaries (module 2.6) a suggested or a required format?</p>	<p>It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.</p>
8	<p>Sept 2002</p> <p>List of References A section for list of references of the nonclinical summary (2.6.8 or 2.6.2.8 plus 2.6.4.11 plus 2.6.6.11) is not covered in the guidance, unlike for the clinical summary and both nonclinical and clinical overview. Could you please provide clarity where in these summaries lists of references should be included?</p>	<p>Applicants can place the list of references in the most appropriate location and create new subsection numbers as far as it facilitates the best possible understanding by the regulatory reviewers.</p>

CTD-Safety Questions and Answers

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9	Feb 2003	<p>Nonclinical pharmacokinetics</p> <p>A number of studies in nonclinical pharmacokinetics could appear more than one place in this section. Should we add nonclinical pharmacokinetic studies to all Pharmacokinetics sections?</p>	<p>In such a case, the sponsor could either put that study report in the first place in the CTD module (i.e., Absorption section) and then cross reference to this study report in the remaining sections, or place the full study report in each adequate section.</p> <p>If submitting an e-CTD, a sponsor needs not submit multiple files are not required. References to the one file should be provided.</p>
10	Feb 2003	<p>Microbiology information</p> <p>The microbiology data will include both in vitro studies (e.g. mechanism of action, mechanism of resistance for anti-infectives, etc.) as well as in vivo studies (animal models, PK/PD, etc).</p> <p>Where should the microbiology summary, overview, and study reports be included?</p>	<p>The microbiology data from both in vitro and in vivo studies should be included in the pharmacology section. The pharmacological and toxicological effects of the pharmaceuticals should be discussed with the pharmaco- and toxico-kinetic data in each summary section.</p> <p>Any correlations within the Quality, Safety and Efficacy studies should also be discussed in the Nonclinical Overview. The study reports of the pharmacology should be arranged in the pharmacology section</p>
11	July 2003	<p>The template for local tolerances (2.6.7.16) in M4S does not provide an example of a tabulated summary of a local tolerance. Is there one available?</p>	<p>The template for 2.6.7.16 is the same as the template for 2.6.7.17. Therefore for an example of 2.6.7.16, please refer to the example of 2.6.7.17.</p>

<p>12</p>	<p>July 2003</p>	<p>In the development of human monoclonal antibodies, part of the nonclinical development is to perform 2 cross reactivity studies; 1) animal species cross reactivity study and 2) human tissue cross reactivity study.</p> <p>The animal species cross reactivity test is not really a toxicity study, and the human tissue cross reactivity study is not a study generally performed. We are in doubt where to place these in module 4. Where should these studies be placed in module 4? Under 4.2.3.7 Other toxicity studies?</p>	<p>Applicants can place such studies in the most appropriate location in Module 4 in order to facilitate the best possible understanding by the regulatory reviewers. (<i>This can be the similar answer to the Question #8</i>)</p>
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