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).

CTD-Safety Questions and Answers

		Questions	Answers
1		**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	New	**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		**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		**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-Efficacy Questions and Answers

		Questions	Answers
General			
1		Clinical study reports contained in Module 5 are cited in the Clinical Overview and/or the Clinical Summary in Module 2. Each clinical study report may be given a unique short name when cited. **Does the method of citing and naming have to be uniform throughout all modules?**	We recommend that each study have a unique short identifier that is used consistently throughout the application. The applicant can select the identifier. The full title of the study is provided in the Tabular Listing of All Clinical Studies (Section 5.2).
2	**New**	**Definitions/Terminology** What is the definition of 'Common Adverse Events' as used in the CTD?	Guidance is provided by ICH E3 Guideline.
3	**New**	**Section Numbering/Title (in Module 5)** In the module 5 of the CTD, is it necessary to have a section number for each clinical study report in a certain section, or is it enough just to mention the title: 5.3.5 Reports of Efficacy... 5.3.5.1 Study Reports.... 5.3.5.1.1 Placebo Controlled.... Study XXX	See ICH Granularity document.
Section 2.7			
4		**How many pages should a Clinical Summary be for an application that contains multiple indications?**	The estimated size of this document is 50-400 pages, assuming one indication. Applications that include multiple indications will be larger, reflecting the submission of multiple efficacy sections.

Questions			Answers
Section 2.7 (cont.)			
5		**Section "2.7.3.3" Comparisons and Analyses of Results Across Studies** The Guideline provides "This section should also cross-reference important evidence from Section 2, such as data that supports the dosage and administration section of the labeling." However, this Guideline also provides a Section, "2.7.3.4. Analysis of Clinical Information Relevant to Recommended Dose." Please specify how to differentiate the two sections "2.7.3.3" and "2.7.3.4".	Section 2.7.3.3 summarizes the data across all studies that characterize efficacy of the drug; Section 2.7.3.4 provides an integrated summary of the dose-response or blood concentration-response relationships of effectiveness. In both cases, supportive data from Section 2.7.2 can also be incorporated.
6		**Overall Extent of Exposure** In the Guideline, a table is required to be generated to present the overall extent of drug exposure in all phases of the clinical development. Should the table include "patients alone" or "patients and healthy subjects"?	The table should refer to all subjects exposed to at least one dose of the drug product. Appropriate subsets of subjects relevant to the proposed indications should also be identified and considered.
7		**Summary of Clinical Safety** Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region?	Summaries of any bridging studies using clinical endpoints (i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)) should be included in Section 2.7.3.2. Where appropriate, such information should also be described in the summarization of safety data as related to intrinsic and extrinsic ethnic factors (ICH E5), in Sections 2.7.4.5.1 and 2.7.4.5.2. Finally, some applications might include in Section 5.3.5.3 a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information. Such information should be included in that detailed analysis of bridging.

Questions			Answers
Module 5			
8	**New**	**Bioavailability/Bioequivalence Study Data** Where should the information on bioequivalence studies for a generic application be included?	Bioavailability study reports should be included in Module 5 (Clinical documentation), under section 5.3.1 "Reports of Biopharmaceutical Studies". More specifically, reports of comparative Bioavailability/Bioequivalence studies should go under section 5.3.1.2.
9	**New**	**Tabular Listing of Clinical Studies in Paper CTD** In module 5, 5.2 is denoted as the 'Tabular Listing of all Clinical Studies'. Is this section for a summary listing of all clinical studies in the submission, or it is for the listings of the individual study reports? In other words, should the listings from the appendices of the individual study reports be included here, rather than as an appendix to the CSR, or are these only listings that summarize all studies?	The tabular listing described in section 5.2 is a listing of all clinical studies in the submission. An example of such a listing is given in Table 5.1.

Questions			Answers
5		**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.	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.
6		**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?	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.
7	**New**	**Nonclinical Tabulated Summaries Templates** Are the templates for the nonclinical tabulated summaries (module 2.6) a suggested or a required format?	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.
8	**New**	**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?	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.

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.