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.

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5	Sept 2002	**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	Sept 2002	**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	Sept 2002	**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	Sept 2002	**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.

CTD-Safety Questions and Answers

	Date of Approval	Questions	Answers
9	**Feb 2003**	**Nonclinical pharmacokinetics** 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?	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. If submitting an e-CTD, a sponsor needs not submit multiple files are not required. References to the one file should be provided.
10	**Feb 2003**	**Microbiology information** 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). Where should the microbiology summary, overview, and study reports be included?	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. 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

CTD-Efficacy Questions and Answers

	Date of Approval	Questions	Answers
General			
1	**Feb 2002**	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	**Sept 2002**	**Definitions/Terminology** What is the definition of 'Common Adverse Events' as used in the CTD?	Guidance is provided by ICH E3 Guideline.
3	**Sept 2002**	**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	**Feb 2002**	**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.

CTD-Efficacy Questions and Answers

	Date of Approval	Questions	Answers
Section 2.7 (cont.)			
5	**Feb 2002**	**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	**Feb 2002**	**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	**Feb 2002**	**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.

CTD-Efficacy Questions and Answers

Date of Approval		Questions	Answers
Module 5			
8	**Sept 2002**	**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	**Sept 2002**	**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.

CTD-Efficacy Questions and Answers

Date of Approval		Questions	Answers
Module 2			
10	**Feb 2003**	**ISS/ISE** Does the CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v, vi) calling for integrated summary of safety and effectiveness (ISS/ISE)?	The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDA's Guideline for the Format and Content of Clinical and Statistical Sections of Application gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries. The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (Structure and Content of Clinical Study Reports). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis. If, the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, then the CTD Module 2 section would fulfill the need for an ISS/ISE. In some cases it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5. Any questions about these matters can be raised with the reviewing division.