European Medicines Agency

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ICH Topic M 4 S
Common Technical Document for the Registration of Pharmaceuticals for Human Use – Safety
Questions and Answers

Step 5

QUESTIONS AND ANSWERS
(CPMP/ICH/2887/99 - Safety)

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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		**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.

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		**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		**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
9		**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	**Rev Nov 03**	**Microbiology data** The microbiology data will include both in vitro and in vivo studies. Where should the microbiology summary, overview and study reports be included?	***Revision to the answer provided on February 2003.*** The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the Nonclinical sections as appropriate.
11		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?	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.
12		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. 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?	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. *(This can be the similar answer to the Question #8)*