Guidance for Industry

M4: The CTD — Safety Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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TABLE OF CONTENTS

Guidance for Industry[1]
M4: The CTD — Safety
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I. INTRODUCTION

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). This guidance provides answers to questions that have arisen since the finalization of the harmonized CTD guidance documents in November 2000. This guidance specifically addresses questions related to safety. Other question and answer (Q &A) guidances are under development to address general questions as well as questions related to quality and efficacy. The questions and answers provided here reflect the consensus of the ICH parties.

II. BACKGROUND

The guidance for industry issued in November 2000 on preparing the CTD was divided into four separate documents: (1) M4: Organization of the CTD, (2) M4Q: The CTD — Quality, (3) M4E: The CTD — Efficacy, and (4) M4S: The CTD — Safety. Since implementation of these

[1] This guidance was developed within the M4 CTD-Safety Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, September 12, 2002. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

guidances, a number of questions regarding the various CTD documents have been submitted to the various ICH regions. The ICH has developed a process for responding to questions submitted to the ICH Web site.

III. QUESTIONS AND ANSWERS

Q1: Kinetics in Pregnant Animals and Neonates

Kinetics in pregnant animals and neonates are included in the pharmacokenetics (PK) section. Is it expected that these data will come from PK studies, or can they be from kinetics in the Segment 2 studies?

A1: The CTD — Safety guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

Q2: Conduct/Nonconduct 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?

A2: Section headings should be maintained in the CTD and a brief explanation provided as to why these studies were not conducted.

Q3: Pivotal Studies

Would a 3-month toxicity study that was needed to support clinical studies of 3-months' duration, which was later replaced with a 9-month toxicity study, be considered "pivotal" and tabulated as in Table 2.6.7.7?

A3: Yes. There should be one table for each of the repeat-dose toxicity studies specified by the ICH guidance M3, as well as any other repeat dose toxicity studies that could be considered pivotal.

Q4: Tabulated Summary

Are only toxicologically significant changes, as considered by applicants, to be tabulated in CTD?

A4: Only noteworthy findings should be tabulated in the CTD. These might include statistically significant differences from controls, as well as noteworthy findings that are not statistically significant.

Q5: 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.

A5: 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 might not be applicable for qualification of impurities. In this case, it is recommended that you use footnotes in the "Drug Substance" table to identify the batches that are relevant to qualification of impurities.

Q6: 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 (good laboratory practice) studies in the CTD need to have specification test data?

A6: You need not 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.

Q7: Nonclinical Tabulated Summaries Templates

Are the templates for the nonclinical tabulated summaries (Module 2.6) a suggested or a required format?

A7: 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.

Q8: Granularity/Nonclinical Tabulated Summaries

Is it right that we need to correct the "Nonclinical Tabulated Summaries – Word Templates" (in Appendix B) lines "Location in the CTD" with* volume *and* section *instead of* volume *and* page*?

A8: Yes. Applicants should put *volume* and *section number* in the column of "Location in the CTD" within the Nonclinical Tabulated Summaries.

Q9: 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?

A9: 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.