Guidance for Industry

M4: The CTD — Efficacy 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

Revision 2

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TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
M4: CTD — Efficacy
Questions and Answers

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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 efficacy. Other question and answer (Q &A) guidances are under development to address general questions as well as questions related to quality and safety. The questions and answers provided here reflect the consensus of the ICH parties.

This guidance is being revised to include additional questions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was developed within the M4 CTD-Efficacy 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, November 11, 2003. 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.

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) M4: The CTD — Quality, (3) M4: The CTD — Efficacy, and (4) M4: The CTD — Safety. Since implementation of these 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: 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?

A1: 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)

Q2: Definitions/Terminology

What is the definition of* Common Adverse Events *as used in the CTD?

A2: Guidance is provided by ICH E3 Guideline.

Q3: Section Numbering/Title (in Module 5)

In 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 Report of Efficacy….
5.3.5.1 Study Reports….
5.3.5.1.1 Placebo Controlled….
Study XXX

A3: See ICH granularity document.

Q4: How many pages should a Clinical Summary be for an application that contains multiple indications?

A4: 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.

Q5: 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".

A5: 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.

Q6: 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"?

A6: That 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.

Q7: Summary of Clinical Safety

Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region?

A7: 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.

Q8: Bioavailability/Bioequivalence Study Data

Where should the information on bioequivalence studies for a generic application be included?

A8: 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.

Q9: 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 listing 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?

A9: 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.

Q10 Integrated Summary of Safety and Effectiveness

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)?

A10: 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 guidance *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, 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.

Q11: 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?

A11: 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.

Q12: Clinical Variation

For a clinical variation application, is it mandatory to submit a clinical overview and a clinical summary, or is it acceptable to submit either only an overview or only a summary? What are the parameters/conditions to be taken into account for choosing one or the other approach?

A12: Since variation is a term from the EU regulations, the answer should be provided by the EMEA.

Q13: Integrated Analysis of Efficacy (ISE) Section 2.7 – Clinical Summary – Statistical Listings

What approach should applicants take for the formatting and presentation of their integrated analyses when they have large amounts of statistical output to present (several thousands of pages)?

A13: As stated in section Reports of Analyses From More Than One Study 5.3.5.3, where the details of the analysis are too extensive to be reported in a summary document (for example, section Clinical Summary 2.7), they should be presented in a separate report. Such report should be placed in section 5.3.5.3.

Q14: 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 many cases too long to indicate in a cross string.)

A14: Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross string while maintaining the ease of use, it is recommended to include only the section number in the cross string and write the text so the reader will also know the section content. For example, "…as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text "…no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.

Q15: Limitations of the Safety Database and Potential Implications

Section 2.5 Clinical Overview and section 2.5.5 Overview of Safety both refer to an assessment of the limitations of the safety database but give few details on how to describe them. How should these limitations be described? In addition, there is no specific reference to any postmarketing steps the applicant can take to remedy those limitations. Where should a discussion of any postmarketing pharmacovigilance and other postmarketing study plans go?

A15: A fuller discussion of how to describe in the CTD the limitations of the safety database and the potential implications for the safety of the drug when marketed is as follows:

- Nonclinical toxicology and safety pharmacology concerns, such as those arising from reproductive / developmental toxicity, carcinogenicity, hepatic injury, central nervous system injury, or effects on cardiac repolarization that are not fully resolved by available human data, or that arise from incomplete testing.

- Limitations of human safety database, such as:
  - Patient selection criteria that excluded people who are likely to be candidates for treatment in medical practice.
  - Evaluations that were deficient for certain purposes (e.g., many drugs with sedative properties are not evaluated for effects on cognitive function in the elderly).
  - Limited exposure of demographic or other subgroups, such as children, women, the elderly, or patients with abnormal hepatic or renal function.

- Identified adverse events and potential adverse events that require further characterization or evaluation with respect to frequency and/or seriousness in the general population or in specific subgroups.

- Important potential risks (e.g., known risks of pharmacologically related drugs) that require further evaluation.

- Drug-drug interactions that have not been assessed adequately.

Such information should be described and discussed in section 2.5.5 Overview of Safety, with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections.

A discussion of any planned postmarketing activity or study to address the limitations of the premarketing safety database should also be included in section 2.5.5 Overview of Safety, with any protocols for specific studies provided in section5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

An ICH guideline (E2E Pharmacovigilance Planning) is being developed to further address the question of how to describe the safety data and its limitations and how to describe planned postmarketing activities and studies.

Q16: Multiple Indications

When submitting one dossier for multiple indications, how should the applicant present them in the clinical part of the registration dossier, for example sections 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy, and 5.3.5 Reports of Efficacy and Safety Studies?

A16: One section 2.5 Clinical Overview is recommended for multiple indications to be registered along with development rationale and cross-referencing to the corresponding 2.7.3 and 5.3.5 sections; the "benefit/risk" conclusions should support corresponding claimed indications.

For section 2.7.3 Summary of Clinical Efficacy, in the case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indication, for example:

2.7.3.UTI Summary of Clinical Efficacy
2.7.3.1.UTI Background
2.7.3.2. UTI Summary of Results of individual studies
2.7.3.3. UTI comparison and analysis
2.7.3.3.1. UTI study population
2.7.3.3.2. UTI Comparison of efficacy results
2.7.3. Pneumonia Summary of Clinical Efficacy
2.7.3.1. Pneumonia Background

Other sections follow the same organization where applicable.

For section 5.3.5 Reports of Efficacy and Safety Studies, in case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indications, for example:
5.3.5.UTI
5.3.5.1. UTI Controlled studies
5.3.5.2. UTI Uncontrolled studies
5.3.5. Pneumonia
5.3.5.1. Pneumonia Controlled studies
5.3.5.2. Pneumonia Uncontrolled studies
Other sections follow the same organization, where applicable.

Q17: Narrative Descriptions

The CTD guidance for Section Overall Safety Evaluation Plan and Narratives of Safety Studies 2.7.4.1.1 states that narrative descriptions for studies that contributed both efficacy and safety should be included in Section Summary of Results of Individual Studies 2.7.3.2 and only referenced in the safety section. Please clarify whether the narrative to be included in 2.7.3.2 should include the safety results as well as "enough detail to allow the reviewer to understand the exposure… and how safety data were collected" or whether the results should be included in Section 2.7.4.1.1.

A17: In general, safety results should be described in section 2.7.4.1.1, because section Summary of Clinical Efficacy 2.7.3 is devoted to efficacy. To avoid the need to describe the same study twice, section 2.7.3.2 asks for a reasonably complete description of studies pertinent to both safety and efficacy, including, in study narratives, information about the extent of exposure of study subjects to the test drug and how safety data were collected. This approach is confirmed in section 2.7.4.1.1, which notes that narratives for studies contributing both safety and efficacy data should be included in section 2.7.3.2. As noted in section Background and Overview of Clinical Efficacy 2.7.3.1, however, any results of these studies that are pertinent to evaluation of safety should be discussed in section Summary of Clinical Safety 2.7.4.