Guidance for Industry
M4: The CTD — General Questions and Answers

Guidance for Industry

M4: The CTD — General Questions and Answers

Additional copies are available from:

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)

December 2004
ICH

Revision 3

TABLE OF CONTENTS

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

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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 addresses general questions about the CTD. Other question and answer (Q & A) guidances are under development to address questions related specifically to quality, safety, and efficacy. 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 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, June 10, 2004. 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) M4Q: The CTD — Quality, (3) M4E: The CTD — Efficacy, and (4) M4S: 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:   Format or Content?

Will a dossier using the CTD format (Modules 2 to 5) be identical for all regions?

A1:   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 submission. There are many regional requirements, as well as applicants' preferences, that could affect the contents of dossiers submitted in each region.

Q2:   Expert Reports

Are expert reports still required for submissions under the CTD format?

A2:   No. Expert reports are replaced by Module 2. For specific European requirements regarding experts' signatures, please refer to the European Commission Web Site.

Q3:   Tables of Contents and Pagination

For a paper CTD submission, the guidance states that for the comprehensive Table of Contents (TOC) 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?

A3:   There are no specific guidelines for the page numbers of the TOC. Module numbers, volume numbers, and tab dividers should be part of all TOCs.

Q4:   *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?

A4:   Literature references should be paginated according to the page numbering of the source (journal, abstract, etc.).

Q5:   *Subheading numbering, or numbering within sections*

How should subnumbering within a document be organized? Some documents can be up to 50 pages in length with no defined CTD guidance 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.

A5:   Within the document, the applicant can use section numbers at a lower level than those specified in the CTD guidance. However, there should be no other headings appearing in the overall TOC going below the numbering given in the CTD guidance.

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.

Q6:   *Titles of Documents Within Sections (e.g., Reports)*

In the header or footer of each document in a dossier, the appropriate TOC title entry should be included. In the case of, for example, a clinical report, the TOC entry is the title of the report and this can be very 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?

A6:   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.

Q7:   *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? (In many cases, the section name is way too long to indicate in a cross-string.)

A7:   (This answer was revised at the November 2003 ICH meeting.) 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.

Q8:   *General Glossary of Terms*

**   *Will there be a general glossary of recommended terminology for use in the CTD?***

A8:   No glossary of terms is planned at this time.

Q9:   *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?***

**   *Currently, comparability data should be included under 2.3.S32/3; preclinically as proposed; and clinically under 2.5.2 and 2.5.6. Each part should summarize 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).**

A9:   No, for the moment the ICH does not foresee a separate CTD section combining all the comparability data.

Q10:   *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 Modules 4 and 5 of the CTD applicable to abbreviated new drug applications (ANDAs) in the United States and Abridged Marketing Authorization applications in the European Union? Both categories of applications apply to generic drug applications, which ordinarily provide preclinical and clinical data based on available literature.***

A10: 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.

Q11: *Font Style and Size*

On the basis of corporate identity we use the font style Arial for all of our documents. Can we use the font style Arial for CTDs, or do we have to use Times New Roman style to match the recommendation for narrative texts according to the guidance for industry M4: Organization of the CTD?

A11: Times New Roman 12 point is recommended for use in the CTD. This corresponds to MS Mincho, 10.5 point for the text written in Japanese.

Q12: *Language*

Can the CTD be in any language (e.g., Japanese, German, French, English)? Is it limited to a single language?

A12: The CTD does not address this issue. Please refer to regional guidance.

Q13a: *Changes in Numbering and Section Headers*

With regard to the changes in numbering and section headers (September 11-12, 2002), are the details in brackets (e.g., name, manufacturer or name, dosage form) only for use in eCTD format or for paper files also?

A13a: These changes apply to all CTD/eCTD submissions.

Q13b: *Headers and Page Numbering*

What are your recommendations for externally produced documents (e.g., chromatograms, CTD format DMFs) regarding page numbering and appropriate headers? Are there allowances regarding these documents with regard to pagination and headers (i.e., are we allowed to submit them in the relevant document without a header or page number)?

A13b: Please refer to Q & A no. 5 above.

Q13c: Tabs

Do tabs have to be printed? Do we have to use the full title with the number string on the tab? This is very difficult if the title is long.

A13c: Tabs should be printed for a paper submission. Tab abbreviations are acceptable.

Q14: Is there a difference in the level of analysis in the nonclinical overview and the clinical overview in Module 2? Is there a difference between "critical analysis" (nonclinical overview) and "critical assessment" (clinical overview).

A14: Please refer to the general guidance for both the nonclinical and clinical overviews. The level of analysis does not differ between these two overviews. The guidance describes the information that should be included in the "critical and integral" assessment/analysis in both overviews.

*Q15: Is the term **section** defined in the CTD? Is there a different use of the term in Modules 2 and 3? Do the ICH regions define sections differently?*

A15: Each section in the CTD is identified by a number and a heading. Please refer to the Granularity Document Annex for a description documents to be provided in each section. The annex delineates when multiple documents per heading may be provided. Also, refer to regional guidance as to when one or multiple documents should be provided per heading.

Q16: Does the deadline for mandatory submission of the CTD in Japan, the EU, and the United States (highly recommended in the United States) also refer to the eCTD?

Has ICH considered planning a seminar to help with CTD and eCTD submissions?

A16: The deadline does not refer to the eCTD although the regulatory authorities are accepting eCTD submissions. Please refer to regional guidance for specific guidance on eCTD submissions.

Currently the ICH is not planning to conduct a CTD seminar. However, the ICH6 Conference, November 2003 in Osaka Japan, will focus on the CTD and eCTD.

Q17: Has the DTD reached its final stage of approval in the ICH process?

A17: The eCTD DTD has reached step 5 in the ICH process, which is the implementation step.

Q18: *Is there a definition of which attachments should be included in the CTD?*

A18:   It is not suggested that additional attachments be included in the CTD.

Q19: *CTD Training*

Does ICH recommend any particular comprehensive training course on the implementation of the CTD?

A19:   No, there are no general ICH recommendations for training on CTD implementation.

Q20: *Applicant's Logo*

Is it allowed to add the applicant's logo either on top of the CTD, or in the titles of CTD sections?

A20:   The applicant is free to put his logo on top of the CTD. However, logos are not acceptable in CTD sections' titles. (The latter have been harmonized internationally; therefore applicants are not allowed to modify them.)

Q21: *Herbal CTD*

Will a Herbal Products version of the CTD be published and how much will it vary from the pharmaceutical CTD?

A21:   ICH does not plan to issue any specific version of the CTD for herbal products.

Q22: *Granularity: Section Headings and Numbers, Documents Location/Hierarchy, Documents Pagination*

The CTD specifies many section headings and numbers. Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents? Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy?

As a consequence of this definition could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include?

A22:   Please refer to the Annex of the Organization of the Common Technical Document: "Granularity Document."

Q23: ***Is there a separate format for amendments and variations submitted in CTD format, or should applicants use the CTD format as it is now? If used as it is now, is it enough to simply indicate whatever modules are not used?***

A23: The CTD structure is suitable for amendments and variations (refer to regional guidance for applicabilities). The applicant should not submit the modules that are not used, i.e., it is unnecessary to include "not applicable" pages against unused CTD headings.