Guidance for Industry

M4: Organization of the CTD

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)

August 2001
ICH

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Copies of this Guidance are available from:

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Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
Internet: http://www.fda.gov/cder/guidance/index.htm.

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
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Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
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M4: The Organization of the CTD

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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 presents the agreed upon common format for the preparation of a well-structured harmonized application that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources used to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information among regulatory authorities will be simplified.

Guidance for industry on preparing the CTD has been divided into four guidance documents on (1) the organization of the CTD, (2) the quality section (3) the efficacy section (4) the safety section. For specific information on the quality, efficacy, and/or safety sections of the CTD, see the individual guidances for industry that discuss those parts of the CTD. For general information about submitting a marketing application in the CTD format in the U.S. region, as

[1] This guidance was developed by 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 was endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000. 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.

well as specific information about Module 1 (U.S. administrative information), see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format.*[2] The CTD guidances are intended to be used together with other ICH and Agency guidances. Please refer to those guidances for detailed information about the *contents* of an application.

BACKGROUND

The CTD

Through the ICH process, considerable harmonization has been achieved among the three regions (Japan, Europe, and the United States) in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of a submission. Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the *GAIYO*, which organizes and presents a summary of the technical information. In Europe, expert reports and tabulated summaries are required, and written summaries are recommended. The U.S. FDA has guidance regarding the format and content of the new drug application submission. To avoid generating and compiling different registration dossiers, this guidance describes a harmonized format for the CTD that will be acceptable in all three regions.

Preparing and Organizing the CTD

This guidance addresses the general organization of the information to be presented in the CTD application for new pharmaceuticals (including biotechnology-derived products). Guidance documents also are available that discuss the Quality, Efficacy, and Safety sections of the CTD. These guidances are not intended to indicate what studies are required. The guidances merely indicate an appropriate *format* for the data that have been acquired. Applicants should not modify the overall organization of the CTD. However, in the Nonclinical and Clinical Summaries sections of the CTD, applicants can modify individual formats to provide the best possible presentation of the technical information to facilitate the understanding and evaluation of the results.

Throughout the CTD, the display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured through binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the *Uniform Requirements*

[2] A draft version of the General Considerations guidance is currently available. Once it has been finalized, it will represent the Agency's thinking on this topic.

for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE).[3]

The CTD should be organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with the CTD guidances should help ensure that these four modules are provided in a format acceptable to the regulatory authorities (see the figure and overall outline on the following pages).

Module 1. Administrative Information and Prescribing Information
This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities. For information about this module see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format*.

Module 2. Common Technical Document Summaries
Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page.

Module 2 should contain 7 sections in the following order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary.

Because Module 2 contains information from the Quality, Efficacy, and Safety sections of the CTD, the organization of the individual Module 2 summaries is discussed in three separate documents:

- *M4Q: The CTD — Quality*
- *M4S: The CTD — Safety*
- *M4E: The CTD — Efficacy*.

Module 3. Quality
Information on Quality should be presented in the structured format described in the guidance, M4Q.

Module 4. Nonclinical Study Reports

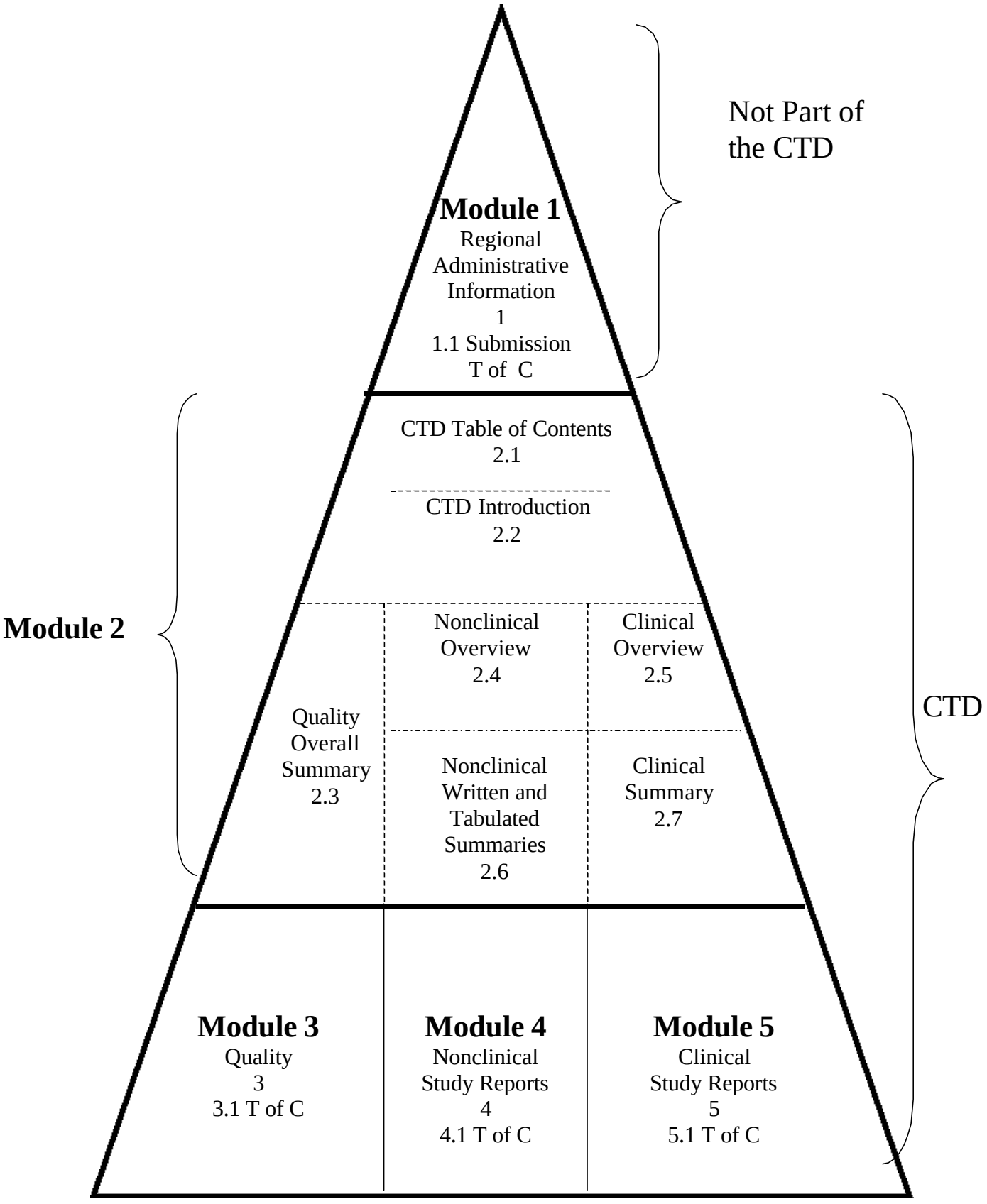
[3] The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

The Nonclinical Study Reports should be presented in the order described in the guidance M4S.

Module 5. Clinical Study Reports

The human study reports and related information should be presented in the order described in the guidance M4E .

Diagrammatic Representation of the ICH Common Technical Document



The CTD should be organized according to the following general outline.

Module 1: Administrative Information and Prescribing Information

1.1 Table of Contents of the Submission Including Module 1
1.2 Documents Specific to Each Region (for example, application forms, prescribing information)

Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents
2.2 CTD Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summary
Pharmacology
Pharmacokinetics
Toxicology
2.7 Clinical Summary
Biopharmaceutics and Associated Analytical Methods
Clinical Pharmacology Studies
Clinical Efficacy
Clinical Safety
Synopses of Individual Studies

Module 3: Quality

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References

Module 5: Clinical Study Reports

5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

Organization and Format of the ICH Guidances for Industry

The CTD is organized by modules. However, the guidances for industry that provide recommendations for applicants on preparing the CTD have been organized by topic: Quality, Safety, and Efficacy. The three guidances are organized as follows:

- Guidance on the Quality section of the CTD (Module 2, Quality Overall Summary (QOS), and Module 3) can be found in the guidance for industry *M4Q: The CTD — Quality*.

- Guidance on the Safety section of the CTD (Module 2, the Nonclinical Overview and the Nonclinical Written and Tabulated Summaries, and Module 4) can be found in the guidance for industry *M4S: The CTD — Safety*

- Guidance on the Efficacy section of the CTD (Module 2, the Clinical Overview and the Clinical Summary, and Module 5) can be found in the guidance for industry *M4E: The CTD — Efficacy*.

Because Module 2 contains information from Modules 3, 4, and 5, specific guidance on Module 2 is divided among the three guidances.

Numbering

In the guidances for industry on the Quality, Safety, and Efficacy sections of the CTD, Arabic numbers have been assigned to designate those specific sections that should be included in the CTD. The Arabic numbers used in the guidances also should be used when assembling the CTD for submission. For specific information on numbering the pages and volumes of the submission, see the guidance for industry *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format*. Sections in the guidance documents that are not numbered provide guidance on how to prepare those sections.

It is possible that information for more than one drug substance, drug product, or indication will be submitted. In such cases, please continue the use of Arabic numbers by repeating the specific section's numbering, making it clear that the data are for an additional drug substance, drug product, or indication. For example, for an additional indication, repeat section 2.7.3, including the name of the additional indication (e.g., 2.7.3 pneumonia, 2.7.3 URI). The same approach should be used in the Quality section of the application for additional drug substances (2.3.S) and drug products (2.3.P).