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REASONABLE STUDY ON CTD AND eCTD FOR USFDA AND HEALTH CANADA FILING PROCEDURE

K. Ashok Kumar*, D. Nagarjuna Reddy, M. V. Nagabhushanam, Brahmaiah Bonthagarala and G. Ramakrishna

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

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***Corresponding Author**
K. Ashok Kumar
Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

ABSTRACT

The aim of work is to know the Active Substance Master Filing process in US and CANADA & their comparison. To know the DMF involvement in e-CTD and also the drug substance filing process comparison between Food Drug Administration (USA) and Health Canada (CANADA) and DMF involvement in the modules of eCTD and it's filling. The international agreement to assemble all Quality, Safety and Efficacy information for a drug or biologic product into a common format (called the CTD - Common Technical Document) has improved the speed and efficiency for companies working in global development programs and clarified expectations by regulatory bodies. Reformatting for multiple submissions is substantially limited. The CTD has improved the regulatory review processes and enabled implementation of good review practices. The eCTD has increased efficiency for reviewers and improved submission times. This article will provide you with an in-depth review of the content and format requirements of the CTD/eCTD. Hands-on activities will include organizing specific study reports and other documents into the CTD, using tools for the project management of the CTD preparation, and pre-publishing an eCTD.

KEYWORDS: Master Filing process, Drug Master Filling (DMF), eCTD, CTD, Food Drug Administration (USA) and Health Canada (CANADA).

1. INT0RDUCTION

Regulatory Affairs

Regulatory Affairs is a profession within regulated industries namely-pharmaceuticals, medical devices, energy and banking. It has specific meaning within healthcare industries namely- pharmaceuticals, medical devices, biologics and functional foods.(In this blog I am going to deal about Regulatory Affairs related to pharmaceuticals meant for human use).[1]

Regulatory Affairs in the pharma industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world."

Origin of Regulatory Affairs

- Elixir Sufanilamide, prepared using DEG (a poison) as solvent resulted in the death of more than 100 people in the USA in 1937. This incident led to the passing of the 1938 Federal Food, Drug and Cosmetic act in USA.

- Thalidomide use by pregnant women for treating morning sickness was linked to the cause of birth deformities in more than 10,000 children in late 1950s and early 1960s. This incident led to the Kefauver-Harris Amendment in USA-it is a 1962 amendment to the Federal Food, Drug and cosmetic act.

Similarly, other tragic incidents led to various acts/amendments.

Introduction to USFDA

Up until the 20th century, there were few federal laws regulating the contents and sale of domestically produced food and pharmaceuticals, with one exception being the short-lived Vaccine Act of 1813. A patchwork of state laws provided varying degrees of protection against unethical sales practices, such as misrepresenting the ingredients of food products or therapeutic substances. The history of the FDA can be traced to the latter part of the 19th century and the U.S. Department of Agriculture's Division of Chemistry (later Bureau of Chemistry). Under Harvey Washington Wiley, appointed chief chemist in 1883, the Division began conducting research into the adulteration and misbranding of food and drugs on the American market.[2-4]

DMF in US

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

Beginning on May 5, 2018, new DMFs, as well as all documents submitted to existing DMFs, must be submitted using the Electronic Common Technical Document (eCTD). DMF submissions that are not submitted in eCTD format after this date will be rejected.[5-7]

Introduction to Health Canada

Canada's publicly funded health care system is dynamic--reforms have been made over the past four decades and will continue in response to changes within medicine and throughout society. The basics, however, remain the same--universal coverage for medically necessary health care services provided on the basis of need, rather than the ability to pay.

The organization of Canada's health care system is largely determined by the Canadian Constitution, in which roles and responsibilities are divided between the federal, and provincial and territorial governments. The provincial and territorial governments have most of the responsibility for delivering health and other social services. The federal government is also responsible for some delivery of services for certain groups of people.

DMF in Canada[8,9]

A Master File (MF) is a reference that provides information about specific processes or components used in the manufacturing, processing, or packaging of a drug. The MF is a useful vehicle for providing information to Health Canada, where that information is of a proprietary nature [that is (i.e.), confidential business information] and is not available to the manufacturer of the dosage form or to the sponsors of a drug submission or clinical trial application (hereafter referred to as the applicants).

Type I ASMFs and Type IV Dosage Form Master Files are divided in two parts: the "Restricted Part" and the "Applicant's Part" which is provided to the Applicant and is usually included as part of the applicants drug submission or clinical trial application (CTA), with the accompanying Letter of Access (LOA).

For Type I ASMFs, the Applicant's Part contains the information that the ASMF Holder regards as non-confidential to the applicant, whereas the Restricted Part contains the information that the ASMF Holder regards as confidential. An MF will not be considered complete if both parts have not been provided to Health Canada.

The LOA is signed by the MF Holder and grants Health Canada permission to assess the information provided in the MF during the assessment of the applicant's drug submission or CTA. The Restricted Parts are filed by the MF Holder to Health Canada directly. An MF is submitted by the MF Holder only in cases where the company does not wish to disclose confidential business information (CBI) to the applicant of the drug submission or CTA.

Drug Master Files[9,10]

Drug Master File or DMF is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market.

The document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

2. CONTENTS OF DMF IN US.[11,12]

1. INTRODUCTION
2. DEFINITIONS
3. TYPES OF DRUG MASTER FILES
4. SUBMISSIONS TO DRUG MASTER FILES

A. Transmittal Letters

1. Original Submissions
2. Amendments

B. Administrative Information

1. Original Submissions
2. Amendments

C. Drug Master File Contents

1. Types of Drug Master Files

a. Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel

b. Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

c. Type III: Packaging Material

d. Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

e. Type V: FDA Accepted Reference Information

2. General Information and Suggestions

A. Environmental Assessment

B. Stability

C. Format, Assembly, and Delivery

V. Authorization to refer to a drug master file

A. Letter of Authorization to FDA

B. Copy to Applicant, Sponsor, or Other Holder

Vi. Processing and reviewing policies

A. Policies Related to Processing Drug Master Files

B. Drug Master File Review

Vii. Holder obligations

A. Notice Required for Changes to a Drug Master File

B. Listing of Persons Authorized To Refer to a Drug Master File

C. Annual Update

D. Appointment of an Agent

E. Transfer of Ownership

Viii. Closure of a drug master file

3. CONTENTS OF MF IN CANADA[13,14]

1. INTRODUCTION

1.1 Policy Objective

1.2 Policy Statements

1.3 Scope and Application

2.4.1.1 Transfer of Ownership and Company Name Changes

Master Files (MFs): Health Canada

Procedures and Administrative Requirements Guidance Document iv Revised Date: 2016/02/05; Effective Date: 2017/05/01

2.4.1.2 Change of the Authorized Master File Agent

2.5 Withdrawal of Letters of Access

2.6 Master File Closures

3. CONTACT INFORMATION

4. REFERENCES

4.1 Health Canada Documents

4.2 International Council on Harmonisation Guidelines

4.3 International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Documents.

5. APPENDICES

APPENDIX 1: RELEVANT ADDRESSES

APPENDIX 2: SAMPLE - LETTER OF ACCESS

APPENDIX 3: SAMPLE - AGENT AUTHORIZATION

APPENDIX 4: SAMPLE - CEP ATTESTATION LETTER

4. COMMON TECHNICAL DOCUMENT (CTD)

OBJECTIVE OF THE GUIDELINE[14]

This guideline presents the agreed upon common format for the preparation of a well structured Common Technical Document for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources needed 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 between Regulatory Authorities will be simplified.

BACKGROUND

Through the ICH process, considerable harmonisation has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use.

However, until now, there has been no harmonisation of the organisation of the registration documents. Each region has its own requirements for the organisation 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 organises 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. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the Common Technical Document that will be acceptable in all three regions.

SCOPE OF THE GUIDELINE

This guideline primarily addresses the organisation of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products). This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organisation of the Common Technical Document as outlined in the guideline. However, in the Nonclinical and Clinical Summaries, applicants can modify individual formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

GENERAL PRINCIPLES

Throughout the Common Technical Document, the display of information should be unambiguous and transparent, in order 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 by the method of 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. Every page should be numbered, according to the granularity document. 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 for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE) 1.

ORGANISATION OF THE COMMON TECHNICAL DOCUMENT[15,16]

The Common Technical Document is 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 this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

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.

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

The organisation of these summaries is described in Guidelines for M4Q, M4S, and M4E.

Module 3: Quality

Information on Quality should be presented in the structured format described in Guideline M4Q.

Module 4: Nonclinical Study Reports

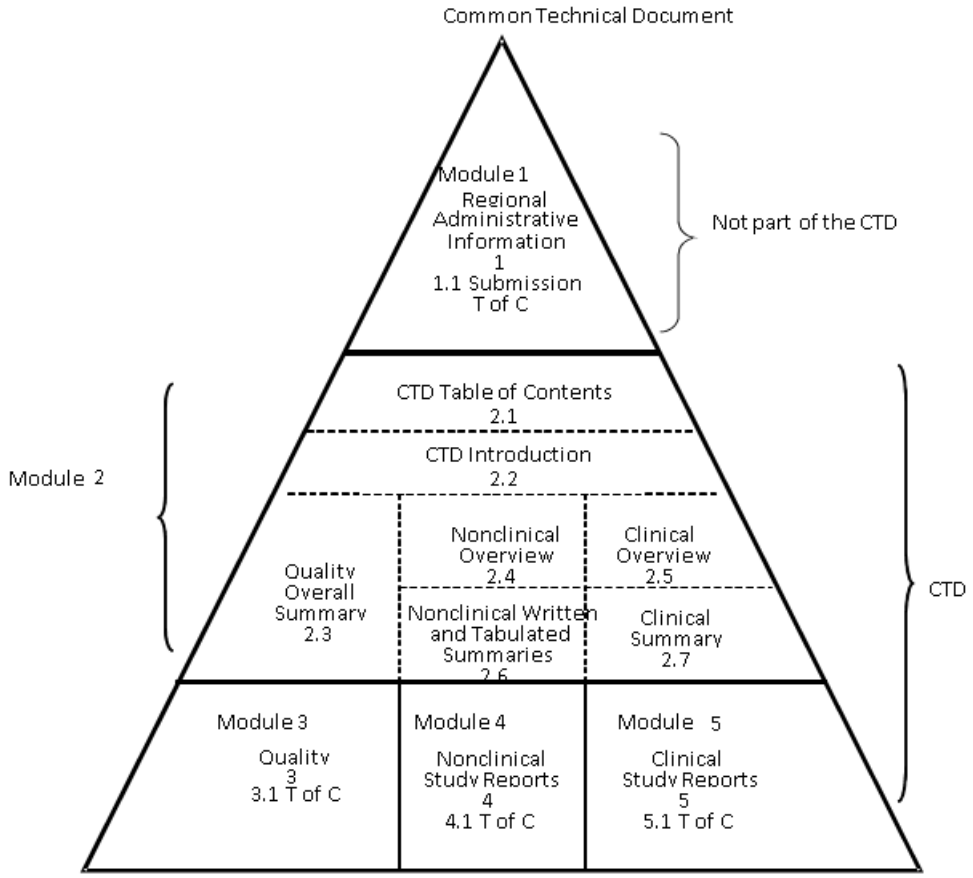
The nonclinical study reports should be presented in the order described in Guideline M4S.

Module 5: Clinical Study Reports

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

The overall organisation of the Common Technical Document is presented on the following pages.

CTD Triangle



MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.3: QUALITY OVERALL SUMMARY (QOS)

INTRODUCTION

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterisation (name, manufacturer)

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards or Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.3 Manufacture (name, dosage form)

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.6 Reference Standards or Materials (name, dosage form)

2.3.P.7 Container Closure System (name, dosage form)

2.3.P.8 Stability (name, dosage form)

2.3. A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form and manufacturer)

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

MODULE 3: QUALITY

3.1. TABLE OF CONTENTS OF MODULE 3

3.2. BODY OF DATA

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

3.2.S.1.2 Structure (name, manufacturer)

3.2.S.1.3 General Properties (name, manufacturer)

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

3.2.S.2.3 Control of Materials (name, manufacturer)

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

3.2.S.3.2 Impurities (name, manufacturer)

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

3.2.S.4.2 Analytical Procedures (name, manufacturer)

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

3.2.S.4.4 Batch Analyses (name, manufacturer)

3.2.S.4.5 Justification of Specification (name, manufacturer)

3.2.S.5 Reference Standards or Materials (name, manufacturer)

3.2.S.6 Container Closure System (name, manufacturer)

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

3.2.S.7.3 Stability Data (name, manufacturer)

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

3.2.P.2 Pharmaceutical Development (name, dosage form)

3.2.P.2.1 Components of the Drug Product (name, dosage form)

3.2.P.2.1.1 Drug Substance (name, dosage form)

3.2.P.2.1.2 Excipients (name, dosage form)

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development (name, dosage form)

3.2.P.2.2.2 Overages (name, dosage form)

3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

3.2.P.2.4 Container Closure System (name, dosage form)

3.2.P.2.5 Microbiological Attributes (name, dosage form)

3.2.P.2.6 Compatibility (name, dosage form)

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

3.2.P.3.2 Batch Formula (name, dosage form)

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

3.2.P.4.2 Analytical Procedures (name, dosage form)

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.4.4 Justification of Specifications (name, dosage form)

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

3.2.P.4.6 Novel Excipients (name, dosage form)

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

3.2.P.5.2 Analytical Procedures (name, dosage form)

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.5.4 Batch Analyses (name, dosage form)

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

3.2.P.6 Reference Standards or Materials (name, dosage form).

3.2.P.7 Container Closure System (name, dosage form)

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment(name, dosage form)

3.2.P.8.3 Stability Data (name, dosage form)

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

MODULE 4: NONCLINICAL STUDY REPORTS

4.1 Table of Contents of Module 4

4.2 Study Reports

4.3 Literature References

APPENDIX A

Examples of Tables and Figures for Written Summaries

APPENDIX B

The Nonclinical Tabulated Summaries - Templates

APPENDIX C

The Nonclinical Tabulated Summaries – Examples

MODULE 5 Clinical Study Reports

5. Ectd[15, 16]

I. INTRODUCTION

II. BACKGROUND

III. REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE2

A. Types of Submissions That Must Adhere to the Electronic Submission Requirement Described in This Guidance Document
B. Timetable for Implementation of Electronic Submission Requirements
C. Types of Submissions That Are Exempted From the Electronic Submission Requirement Described in This Guidance Document
D. D. The eCTD Specifications
E. E. Pre-Submission Considerations
F. F. Submission Structure: Granularity, Files, and Folders
G. G. File Formats and Versions
H. H. Document Lifecycle
I. Summary of Clinical Efficacy and Summary of Clinical Safety
J. Datasets and Study Information
K. Transmitting Electronic Submissions
L. FDA Forms
M. Restrictions on Submission of Paper Copies
N. Receipt Date

6. CONCLUSION

Besides Health Canada's electronic DMF mandate, the US FDA's DMF eCTD submission mandate is also set to come into effect on May 5, 2017. As deadlines draw nearer, understanding both the agencies' DMF submission requirements would be challenging. To enable organizations easily understand mandate requirements, here we provide a table that will demystify DMF submissions for both Health Canada and US FDA.

Agency	Mandate Deadline	Submission Type	Requirements
Health Canada	January 1, 2016 March 31, 2016	Non-eCTD electronic only or eCTD	All existing DMFs in paper format must be replaced by a complete DMF conversion in [electronic] format
US FDA	May 5, 2017	eCTD	Resubmitting previously submitted information is not required when converting an existing DMF

With the information sourced, it seems that each agency's DMF submission mandate varies with that of the deadlines, submission formats, and conversion requirements. While navigating through these variations, what DMF holders shall really look for is their existing internal practices of information management to streamline paper to eCTD conversions.

With Health Canada's mandate already in effect and US FDA's mandate just 17 months away, lack of knowledge on paper to eCTD conversions and eCTD submissions may put your DMF submission compliance efforts at risk and may prove costly too.

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