ABSTRACT

New drug development process is highly regulated. Every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality. A dossier containing detailed information about the drug and results of the studies carried out in its development process has to be submitted to the regulating bodies for getting marketing authorization. CTD (Common Technical Document) is critical for dossier submissions. Literature on CTD, its structure and modules and details of information to be included in CTD and eCTD submissions are reviewed in this article.

KEYWORDS: New Drug Approval Process, Dossier, CTD, eCTD.

INTRODUCTION

New Drug Approval Process

Developing a new drug requires great amount of research work in chemistry, molecular biology, biochemistry, preformulation and formulation development, process development and manufacturing, quality control, preclinical and clinical studies. Drug regulatory agencies globally bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. Different countries have different regulatory requirements for approval of new drug. For IND, NDA or marketing authorization application (MAA) a single regulatory approach applicable to various countries is almost a difficult task, not available at present. Hence it is necessary to have knowledge about regulatory requirements for drug approval process of each country.
The new drug approval process consists of two stages, the first stage is for IND and the second stage is for NDA and marketing authorization of drug. Firstly, non-clinical studies of drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of respective country. In next step, clinical trials are carried out in four phases i.e. phase 1 to phase 4 study. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is verified by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug is found to be safe and effective with desired therapeutic effect.

**Dossier**

The dossier is a complete file containing detailed information about the product for the registration of pharmaceutical products in various countries. The dossier should be prepared as per CTD format.

**COMMON TECHNICAL DOCUMENT (CTD)**

The document that contains the quality, safety and efficacy data in a common format for a new drug to be submitted to various regulatory authorities for its approval is called a common technical document. It helps in presentation of the information in an organized manner. ICH had proposed the development of a common technical document with a view to harmonize the format of the application to be submitted to various health authorities for approval of a new drug. Such a format helps in saving the time that is required for preparing NDAs in different formats for submission to different authorities.

The CTD was developed by the efforts of the European Medicine Agency (EMEA), the US Food and Drugs Administration (US FDA) and the Ministry of Health and Labour, Japan and is applicable across these three nations i.e., Europe, The United States and Japan. It is maintained by ICH. The format and organization of the CTD should not be altered by the applicants. However they can alter the format of clinical and non clinical summaries to help in better understanding and evaluation of results.

**ORGANISATION OF CTD**

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. The structure of CTD is shown in Fig. 1.

**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.

1. CTD Table of Contents
2. CTD Introduction
3. Quality Overall Summary
4. Nonclinical Overview
5. Clinical Overview
6. Nonclinical Written and Tabulated Summaries
7. Clinical Summary

The organization 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.
Fig.1: Structure of CTD.

Module 1: Administrative Information and Prescribing Information

1.0 Cover Letter
1.1 Comprehensive Table of Content
1.2 Application Form
1.3 Product Information
  1.3.1 SPC’s, Labeling and Packaging
  1.3.2 Mock-Up
  1.3.3 Specimen
  1.3.4 Consultation with target patient group
  1.3.5 SPC’s already approved in the Member states
  1.3.6 Braille
1.4 Information about the Experts
1.5 Specific Requirements for different types of applications
1.6 Environmental Risk Assessment
1.7 Information relating to Orphan Market Exclusivity
1.8 Information relating to Pharmacovigilance
1.9 Information relating to Clinical Trials
1.10 Information relating to Pediatrics
1.11 Response to Queries
1.12 Additional Data
Module 2: CTD Summary

2.1 Table of Content (Comprehensive)

2.2 Introduction (general introduction to the pharmaceutical, including its pharmacology class, mode of action, and proposed clinical use)

2.3 Quality Overall Summary

2.4 Non-clinical Overview

2.5 Clinical Overview

2.6 Non-clinical Written and Tabulated Summaries

2.7 Clinical summary

2.4 Non-clinical Overview

2.4.1 General Aspects

2.4.2 Content and Structural Format

2.5 Clinical Overview

2.5.1 Product Development of Content Rationale

2.5.2 Overview of Biopharmaceutics

2.5.3 Overview of Clinical Pharmacology

2.5.4 Overview of Efficacy

2.5.5 Overview of Safety

2.5.6 Benefits and Risks Conclusions

2.5.7 Literature References

2.6 Non-clinical Written and Tabulated Summaries

2.6.1 Pharmacology

2.6.2 Pharmacokinetics

2.6.3 Toxicology

2.7 Clinical summary

2.7.1 Biopharmaceutic Studies and Associated Analytical Methods

2.7.2 Clinical Pharmacology Studies

2.7.3 Clinical Efficacy

2.7.4 Clinical Safety

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

Module 3: Quality

3.1 Table of Contents
3.2 Body of Data
3.2. S Drug Substance
3.2. S.1 General Information
3.2. S.1.1 Nomenclature
3.2. S.1.2 Structure
3.2. S.1.3 General Properties
3.2. S.2 Manufacture
3.2. S.2.1 Manufacturer Details
3.2. S.2.2 Description of Manufacturing Process and Process Controls
3.2. S.2.3 Control of Materials
3.2. S.2.4 Controls of Critical Steps and Intermediates
3.2. S.2.5 Process Validation and/or Evaluation
3.2. S.2.6 Manufacturing Process Development
3.2. S.3 Characterization
3.2. S.3.1 Elucidation of structure and other Characteristics
3.2. S.3.2 Impurities
3.2. S.4 Control of Drug Substance
3.2. S.4.1 Specification of Drug Substance
3.2. S.4.2 Analytical Procedures
3.2. S.4.3 Validation of Analytical Procedures
3.2. S.4.4 Batch Analyses
3.2. S.4.5 Justification of Specification
3.2. S.5 Reference Standards or Materials
3.2. S.6 Container Closure System
3.2. S.7 Stability
3.2. S.7.1 Stability Summary and Conclusions
3.2. S.7.2 Post-approval Stability Protocol and Stability Commitment
3.2. S.7.3 Stability Data
3.2. P Drug Product
3.2. P.1 Description and Composition of the Drug Product
3.2. P.2 Pharmaceutical Development
3.2. P.2.1 Components of Drug Product
3.2. P.2.2 Drug Product
3.2. P.2.3 Manufacturing Process Development
3.2. P.2.4 Container Closure System
3.2. P.2.5 Microbiological Attributes
3.2. P.2.6 Compatibility
3.2. P.3 Manufacture
3.2. P.3.1 Manufacturer
3.2. P.3.2 Batch Formula
3.2. P.3.3 Description of Manufacturing Process and Process Controls
3.2. P.3.4 Controls of Critical Steps and Intermediates
3.2. P.3.5 Process Validation and/or Evaluation
3.2. P.4 Control of Excipients
3.2. P.3.2 P.4.1 Specifications
3.2. P.4.2 Analytical Procedures
3.2. P.4.3 Validation of Analytical Procedures
3.2. P.4.4 Justification of Specifications
3.2. P.4.5 Excipients of Human or Animal Origin
3.2. P.4.6 Novel Excipients
3.2. P.4.7 Control of Drug Product
3.2. P.5.1 Specification of Drug Product
3.2. P.5.2 Analytical Procedures
3.2. P.5.3 Validation of Analytical Procedures
3.2. P.5.4 Batch Analyses
3.2. P.5.5 Characterization of Impurities
3.2. P.5.6 Justification of Specification
3.2. P.6 Reference Standards or Materials
3.2. P.7 Container Closure System
3.2. P.8 Stability
3.2. P.8.1 Stability Summary and Conclusions
3.2. P.8.2 Post-approval Stability Protocol and Stability Commitment
3.2. P.8.3 Stability Data
3.2. A Appendices
3.2. A.1 Facilities and Equipment
3.2. A.2 Adventitious Agents Safety Evaluation
3.2. A.3 Novel Excipients
3.2. R Regional Information/ Requirements
3.2. R.1 Process Validation and or Evaluation
3.2. R.2 Medical Device
3.2. R.3 Restricted part of DMF
3.2. R.4 Medicinal products containing or using in the manufacturing process materials of animal and/or human origin.
3.3 List of Literature References

**Module 4: Non-clinical Study Reports**
4.1 Table of contents
4.2 Study Reports
4.2.1 Pharmacology
4.2.1 Primary Pharmacodynamic
4.2.2 Secondary Pharmacodynamic
4.2.3 Safety pharmacology
4.2.4 Pharmacodynamic drug Interactions
4.2.2 Pharmacokinetics
4.2.2.1 Analytical Methods and validation Reports
4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4.2.2.5 Excretion
4.2.2.6 Pharmacokinetic Drug Interactions
4.2.2.7 Other Pharmacokinetic studies
4.2.3 Toxicology
4.2.3.1 Single-dose toxicity
4.2.3.2 Repeat-dose toxicity
4.2.3.3 Genotoxicity
4.2.3.4 Carcinogenicity
4.2.3.5 Reproductive and developmental toxicity
4.2.3.6 Local tolerance
4.2.3.7 Other toxicity studies
4.3 Literature References
Module 5: Clinical Study Reports

5.1 Table of Contents

5.2 Tabular Listings of All Clinical Studies

5.3 Clinical Study Reports

5.3.1.1 Bioavailability (BA) study Reports

5.3.1.2 Comparative BA and Bioequivalence study reports

5.3.1.3 In-vitro In-vivo Correlation study reports

5.3.1.4 Reports of Bioanalytical and Analytical methods

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using human Biomaterials

5.3.3.1 Healthy Subject PK and Initial Tolerability study reports

5.3.3.2 Patient PK and Initial Tolerability study reports

5.3.3.3 Intrinsic Factor PK study reports

5.3.3.4 Extrinsic Factor PK study reports

5.3.3.5 Population PK study reports

5.3.4.1 Healthy subject PD and PK/PD study reports

5.3.4.2 Patient PD and PK/PD study reports

5.3.5.1 Study reports of controlled clinical studies

5.3.5.2 Study reports of Uncontrolled clinical studies

5.3.5.3 Reports of Analyses of data from more than one study

5.3.5.4 Other clinical study reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case report forms and Individual patient listings

5.4 List of Key Literature References

eCTD

The eCTD is the electronic submission equivalent to the CTD. The eCTD is an interface between industry and agency for transfer of regulatory information, taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission. The eCTD submissions contain all the information of CTD. The backbone of eCTD is an XML file (Extensible Markup Language) representing the structure of the submission. It includes links to files and other metadata such as check sum information. The scheme for the XML is very rigid. Once a submission is sent in eCTD format all future
submissions for the application should be in eCTD format. Lifecycle Management of the submission is easier with eCTD.

**BIBLIOGRAPHY**

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