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Research

Planning and execution of dossier compilation of countries Germany, Canada and Australia

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Abstract

To prepare and compile the Dossier required for Registration of Pharmaceutical Products as per the requirements of each countries which shall be acceptable internationally to develop one regulatory approach. To avoid variation in the documents submitted in the form of dossier for registration of Pharmaceutical Products in the different countries of the world it's important to know the requirements of Regulatory Authorities of each countries in which the Dossier is filled for the smooth Registration. When submitting your drug benefit assessments to the German Authority or other (foreign) regulatory agencies, you need to provide your reports in a specific format. . Drug regulatory affairs in pharma industries have mandated two types of dossier namely CTD (Common Technical Dossier) and ACTD (Asean Common Technical Dossier). Regulated pharma markets (eg.USA, Europe) markets require submission of dossier in CTD format which has to provide clinical trial and bioequivalence studies. As against this, semi-regulated pharma markets (South East Asian) require ACTD format which does not require exhaustive details like CTD. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

Keywords: CTD, ACTD, Dossier

INTRODUCTION

Pharmaceutical Dossier

Pharmaceutical Dossier defines the collection of detailed documents containing information about a particular drug which require extensive data to be attached on the dossier for submission to Regulatory Authority for grant of Regulatory Approval in any country with which a Licensed Product must be registered or approved for the Manufacturing, Marketing, Use, Distribution or Sale of such Licensed Product in the Field. Commonly called as Marketing Authorization Application (MAA) for European Union and New Drug Application (NDA) for United Nation.

Dossier is required to prepare as per the internationally accepted format i.e. CTD & ACTD so as to reduce the time and extra working for registration of single Drug Product in Multiple countries. There is huge contribution of ICH in this for standardizing and bringing the concept of Internationally acceptable format

known as Common Technical Dossier (CTD) containing Five Modules and having importance of each module for justifying the Quality, Safety, Efficacy and Toxicity of the drug which is acceptable by all the main regulatory bodies i.e USA, EU and Japan for submission and accepting the documents as per the requirements of ICH Guideline and compilation of Dossier as per the format mentioned in ICH M4.

General Principles

In the ACTD and CTD, the information that is displayed shall be written unequivocal and easy to perceive, this will help the reviewer to read the data and quickly align the content of the application. The text and tables shall be prepared using margins that allow the document to be printed on either A4 or 8.5 x 11 papers. The left hand margin shall have that much space that the information mentioned on that paper shall not be conceal by doing binding. Font and size, (Times New Roman, 12-point font), for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Every page should be numbered, with the first page of each part designated as page 1. For a paper, Common Technical Acronyms and abbreviations should be defined the first time they are used in each part.[1,2]

Definition of a Document

A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab. A document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent, although if a paper submission is updated to be an electronic submission, some changes in granularity could be introduced to facilitate on-going lifecycle management. In an electronic submission, a new file starts at the same point at which in a paper submission, a tab divides the documents.

ACTD format

ASEAN was antecede by the organization formed in 31 July 1961 called the Association of Southeast Asia (ASA), a consisting of the Philippines, Federation of Malaya, and Thailand. ASEAN itself was created on 8 August 1967, when the foreign ministers of five countries: Indonesia, Malaysia, the Philippines, Singapore, and Thailand, signed the ASEAN Declaration (3).

In 1984, Brunei became ASEAN's sixth member (4) and on 28 July 1995, Vietnam joined as the seventh member (5). Laos and Myanmar (Burma) joined two years later on 23 July 1997 (6). Cambodia was to have joined at the same time as Laos and Burma, but its entry was delayed due to the country's internal political struggle. It later joined on 30 April 1999, following the stabilization of its government.

ASEAN Countries (Association of Southeast Asian Nations) namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia follows ACTD (Asian Common Technical Dossier) format.

ACTD Format comprise of Four Parts namely

Part I: Table of Content, Administrative Information and Prescribing Information
Part II: Quality Document
Part III: Nonclinical Document
Part IV: Clinical Document

Brief Summary

For compilation of Dossier in ACTD format it‟s important to compile the documents as per the requirement of the harmonized countries which follows the ASEAN Guideline and Format for registration of Pharmaceutical Product in their respective countries/ region.

PART I

This contains the Table of content of the entire ACTD format to provide the initial information of the documents compiled in the dossier secondly its contains the Administrative Information which require specific documents in details along with the Application for registration of Product like Certificate of Pharmaceutical Product, Free Sale Certificate, Letter of Authorization, Company certifications and Prescribing Information.

Part I is not compulsory to contain the same documents for registering the Product in the entire ASEAN Market its region specific. A general introduction of the pharmaceutical product, including its pharmacologic class and mode of action shall be included.

PART II

It contains the brief documentation of the Quality Part, this is further divided into three sections, SECTION A contains Table of Content, SECTION B contains Quality Overall Summary, and SECTION C

contains Body of Data i.e. Quality Part. Section A contains the Table of Content of the entire documents present in Part II, Section B contains the Summary of the Quality Part and Section C contains the Quality Part. SECTION C: Body of Data (Quality Part)

1. Drug Substance
2. Drug Product

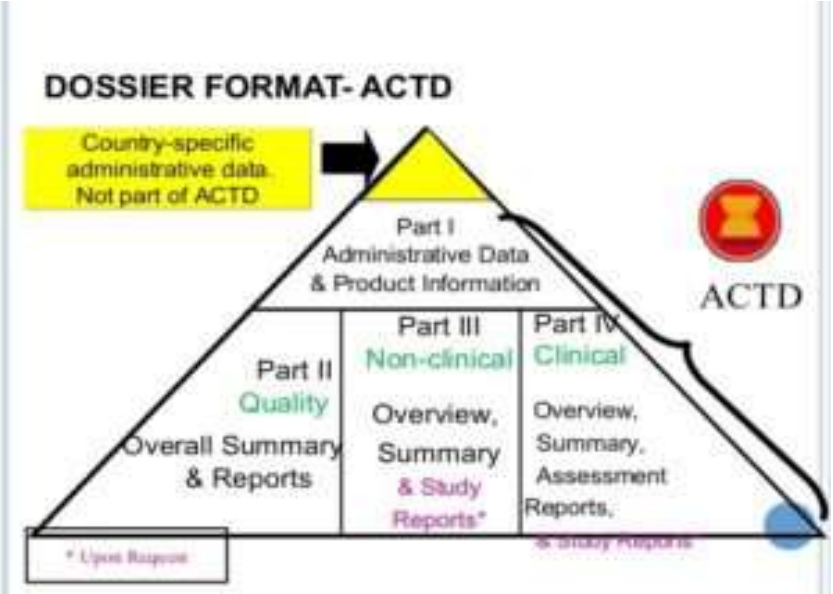

Fig 1: Dossier format- ACTD

Drug Substance (S)

Drug Substance is denoted by the word 'S', In the drug substance section we will compile the complete documents of the Drug Substance part w.r.t to the quality of the API which includes General Information of the API Manufacturer, Characterization of the API, Specifications, Analytical Method Validation, Stability and Studies of the Container in which the Drug Substance are packed. While selecting the grade of the API for registration of product in the ASEAN countries British Pharmacopoeia, United State Pharmacopoeias, European Pharmacopoeia, International Pharmacopoeia grade of materials are acceptable, so simply we require the BP, USP, EP grade DMF (Drug Master File) for registration of Product in ASEAN Market with the below mentioned information.[3]

General Information

Under General Information section the primary study of the API is done such as: **Nomenclature-** of the API which includes IUPAC Name, International non–proprietary name, Compendial name if any, Registry number of chemical abstract service (CAS) and Chemical Name.

Structural Details

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

General Properties

All the Physiological properties of the drug substance shall be included along with the biological properties of the drug such as Physical Form, Melting Point, Solubility, Chirality, Polymorphism, pH and Storage Condition. Manufacture Manufacturer(s) Name and full addresses including the city and country of the manufacturer of active ingredient along with the details of Corporate Head Office, Manufacturing Facilities and Authorized Person.[4]

Description of Manufacturing Process and Process Controls

The complete flow diagram in the systemic form shows the synthetic Process which shall include its molecular formula, yield, chemical structure of the starting material, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents. Alternative process

should be explained and described with the same level of details as the primary process. Reprocessing steps should be identified and justified.

Control of Materials

Complete list of materials used in the manufacturing of the Drug Substance should be prepared listing the use of each material in the process. Information of the quality and control of these materials should be provided.

Controls of Critical Steps and Intermediates All the steps which are critical along with the Test and their acceptance criteria with the justification including the proper references and experimental data which ensure that the manufacturing process and the quality parameters of the drug substance are properly handled and controlled are provided in this section.

Process Validation and/or Evaluation Process Validation shall be carried out to study the results, analysis and conclusion of the executed batches. In process validation the complete studies of the batches shall be carried out w.r.t the Batch Size, Manufacturing Process, critical parameters. The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits.[5]

Manufacturing Process Development

Manufacturing Process Development shall be carried out for drug substance batches which are developed in the research and development, such as the batch number, manufacturing scale and use (e.g. stability) in relation to the process development. The manufacturing process shall be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). A discussion of the data including a justification for selection of the test and assessment of results, should be included. Testing used to assess the impact of manufacturing process of the drug substance(s) and the corresponding drug product(s) may also include non-clinical and clinical studies in other modules of the submission should be included.

Characterizations

Elucidation of Structure and Characteristic[6]

The following studies shall be undertaken on Drug Substance to investigate the evidence of structure and chemical and physico-chemical properties-

Description, Solubility, Chemical Name, Chemical Structure, Molecular Weight, Molecular Formula, Spectral Analysis like NMR, IR, Mass spectra, Elemental Analysis, Specific Optical Rotation, Polymorphism, Synthesis and Conclusion. All the above mentioned physico-chemical characteristics of Drug Substance shall be provided in the DMF with justification to support the structure of Drug Substance.

Impurities

Information on impurities should be provided as per ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

Control of Drug Substance

Specifications and Justifications for Drug Substance, Testing Procedures, and Analytical Validations along with Certificate of Analysis shall be provided.

Specification

Detailed specification, tests and acceptance criteria for the drug substance should be provided. Compendia specifications are adequate. Indicate clearly whether the drug substance is purchased based on specification with a certificate of analysis, or tested by applicant.

Analytical Procedures

The analytical procedure used for testing the drug substance shall be justified using the compendia method or, if the method used is out of compendia the adequate information on the same shall be provided from the supplier.

Validation of Analytical Procedures

The analytical procedures used for ble 1 Overview of required additional documents for initial application according to CMDh overviews [27, 31]. For exact information please see Annex IV. Additional documentation required for initial application Countries Signature for different types of LoAs BG, CZ, HR, HU, LT, PL, RO, SK Contract (original, certified, or only copies) between the MAH and different manufacturing sites BG, HR, LT Pharmacovigilance responsible in National Territory BG, CY,EL, HR Statement for the MA transfer to the local subsidiary EL, FI, SK Person/site responsible for placing the product on the market FR Proof of

establishment HR Extract from the register of entrepreneurs PL, SK Proof that the applicant is the same as the MAH PL Cover letter in local language HR, SK Cover letter, originally signed HU Application form, originally signed BG, HU, LT, PL, RO Application form signed by the MAH in the RMS IT Completion of National Data Base ES Statement from MAH naming its local representative in Croatia HR Declaration of patent and data exclusivity HU Originally signed confirmation of identical dossier BG, HU, LV, LT, RO Documents/Statements to be provided in original or as legalized copies IT (when acting as RMS); LT Trade mark EL Certified copy of the marketing authorization granted by RMS LT Samples (finished product and API) to be submitted before day 0 HU Declaration of conformity of national translations of the SmPC, Pl and labellingthe testing of excipient should be provided, for all the ingredients which are used in the manufacturing of the drug substance. Kindly ensure that the analytical Procedures shall be same as mentions or provided in the Official Monographs or as per ASEAN and WHO Guideline which ensure the Testing procedure and Acceptance Criteria for the Drug Products.[7]

Batch Analyses

Batch Analysis need to be performed for the Three Batches as per the pre-approved Specifications and the Testing Procedures. The COA of the Batch Analysis shall be performed which ensures that the results of the Drug Substances are within Specifications.

Justification of Specification

Justification for the drug substance specification should be provided for the In-House specifications.

Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided.

Container Closure System

A complete description of the packaging material shall be provided in which the drug substances are packed, including the identity of materials of Shrikant International Journal of Drug Regulatory Affairs. 2019; 7(2):51-61 e-ISSN: 2321-6794 [54] construction of each primary packaging component, and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). If methods compendial methods are not available for testing of container closure system for that complete validations shall be provided. For functional secondary packaging components, additional information should be provided. The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.[8]

Common Technical Document (CTD) [5][9]

CTD is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labor and Welfare (Japan). The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The agreement to assemble all the quality, safety and efficacy information in a common format has revolutionized the regulatory review processes.

General Consideration

- CTD is -

* Only a harmonized format for submission of information to relevant regulatory authorities.
* Template for presenting data in the dossier.
* A guideline that merely indicates an appropriate format for the data that have been acquired.

- CTD is not -

* A statement of data for application of data.
* A guideline that intends to indicate what studies are required.
* Define the content.

- CTD should be -

*Have clear and unequivocal information.
*Have style & font size that is large enough to be easily readable.
*Follow the ICH guidelines for:

Document pagination and segregation.
Submission requirements/ methodology for CTD.
* Contained all abbreviation that are used & be listed at the end of the dossier.
* Give proper information of source of bulk drug(s) for manufacturing finished formulation.

Regulation & regulatory bodies of CTD[10]
1) The regulation under Drugs and Cosmetics Act & Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.
2) Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue guidelines for drug development, licensing, registration, manufacturing, marketing and labeling of pharmaceutical products.
3) Almost all the independent countries of the world have their own regulatory authorities.

Evolution of CTD

Effort over the past 15- 20 years by ICH of technical requirements for "registration of pharmaceutical for human use" have resulted in a uni-field dossier for drug applications. CTD was officially signed off in November 2000, at 10th anniversary of ICH; San Diego, California.

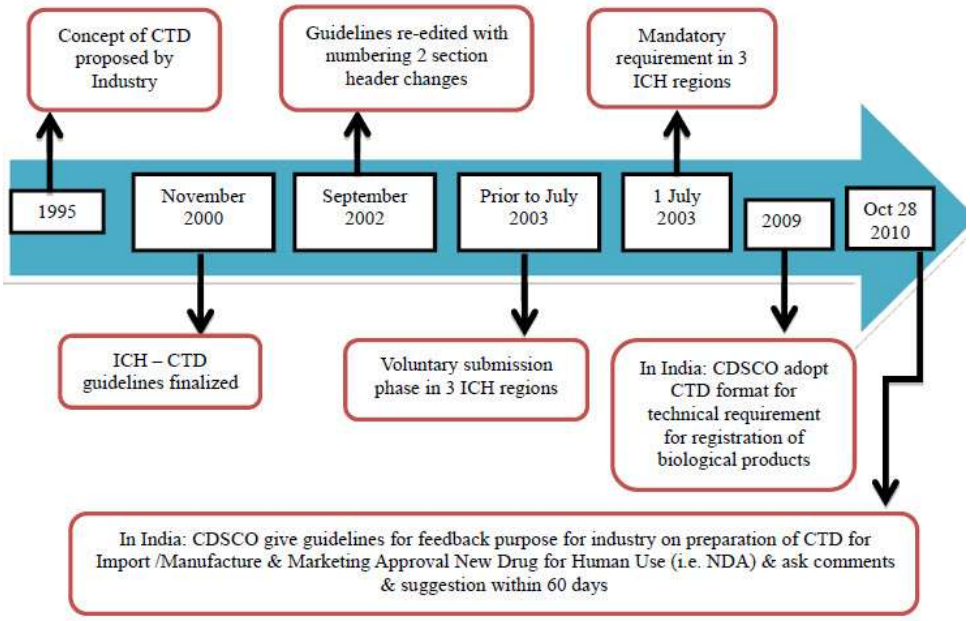

Fig 2: Evolution of CTD

Progress In International Harmonization

There have been enormous changes in the technical and scientific requirements for the dossier, as the work of the ICH has continued to devise and approve new guidelines in the categories of Quality, Safety, Efficacy, and Multidisciplinary. The CTD harmonized structure and modular format for new medicinal product registration files that were adopted in San Diego, is now the obligatory format in the European Union (EU), Japan, Canada, Switzerland, and Australia. It is the recommended format in the United States.

The Ctd—A Common Format, Not A Harmonized Content For Submissions

Enormous efforts have been expended by the staffs of the regulatory agencies and the pharmaceutical industry in the work of the ICH, and this has achieved a remarkable degree of harmonization in many scientific and technical areas of the dossier. Despite this there are still national differences in the content of submissions not only in Module 1, the administrative and prescribing information, but also in other areas of the dossier. These arise from differences in regulatory practice and procedures, different practices of medicine and pharmacy, and differences in access to diagnostic and therapeutic procedures. We are, however, still far from a genuinely global single registration dossier.

Aim and objectives

- To describe a compilation and array of documents.
- To provide the safety, efficacy, and quality information of a medical product.
- The goals of the dossiers are to provide enough information to permit Regulatory Agencies' reviewers to establish the following:
  Is the drug safe and effective in its proposed use(s) when used as directed and do the benefits of the drug outweigh the risks.

The process of is governed and permitted by Drug Regulatory Authority of a particular country and process is called as NDA in USA, MAA in EU and other countries as simply Registration Dossier. There are basically two formats for dossier preparation i.e. ICH-CTD and ACTD. ICH-CTD followed by ICH countries as well as low economical or developing countries where as ACTD is followed by ASEAN countries. ACTD act as bridge between regulatory requirements of developed and developing countries.

CONCLUSION

From the study it could be understood that getting a market authorization for registration of a drug in any territory requires a particular format, and that each country follows a specific guideline in addition to its own regulations which are laid down by the respective drug regulatory authority. There are basically two formats available in most of the countries of world one is , ICH-CTD and the other is ACTD. ICH-CTD is followed by ICH countries where as ACTD is usually adopted by ASEAN countries. For registration of Pharmaceutical Product in any of the Exporting country it‟s important to compile the documents in the format which is accepted internationally for Regulated and Non-Regulated Market. Due to major difference in the regulatory requirement for registration of dossier for Pharmaceutical Product CTD and ACTD format was introduced. This helps to compile the documents in the defined format as mentioned above as per the requirement of the registering country. The process for smooth registration of drug product becomes easier by complying all the requirements to get approval of global market at the same time and to launch the product at once in different market. So before introducing the product in any of the country one should understand the requirement. Deciding on a suitable regulatory strategy plays an important role in gaining time on the marketing authorization of a medicinal product in the European Union.

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