



Available online on 15 June 2019 at <https://ijdra.com/index.php/journal>

International Journal of Drug Regulatory Affairs

Open Access to Pharmaceutical and Medical Research
Associated with Delhi Pharmaceutical Sciences & Research University

© 2013-19, Publisher and Licensee IJRA.



Review Article



Regulatory requirements for preparation of Dossier for registration of Pharmaceutical products in ACTD & CTD format

Shrikant Godiyal*

Deputy Manager, Regulatory Affairs, Tirupati Medicare Ltd., Poanta Sahib, HP, India.

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. This agreed upon common format in the form of CTD format and ACTD format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will be more ease to submit the file having electronic database.

Keywords: Dossier, Registration, ACTD, CTD, ASEAN and Regulatory Authority.

Article Info: Received 15 May 2019; Review Completed 14 Jun. 2019; Accepted 15 Jun. 2019



Cite this article as:

Shrikant Godiyal. Regulatory requirements for preparation of Dossier for registration of Pharmaceutical products in ACTD & CTD format. International Journal of Drug Regulatory Affairs [Internet]. 15 Jun 2019 [cited 15 Jun 2019]; 7(2):51-61. Available from: <http://ijdra.com/index.php/journal/article/view/318>

DOI: [10.22270/ijdra.v7i2.318](https://doi.org/10.22270/ijdra.v7i2.318)

*Corresponding author Tel.: +91-9816777889;

E-mail address: shrikantgodiyal1988@gmail.com (S. Godiyal).

1. 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.

2. 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 (6, 7).

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 (1).

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

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.

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.

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.

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

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 the 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.

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

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.

Stability

Stability Summary and Conclusion

Stability studies are conducted for 3 consecutive batches on two conditions i.e. Long Term and Accelerated Condition. As per ICH and WHO long term is to be conducted for 24 months, 36 months and even 48 months based on the stability of the finished product. Based on the result of the last station the shelf life of the product is determined whereas Accelerated Condition is to be monitored for only 06 months. The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Some of the countries allow to submit the product for registration before completion of the Stability studies in that case we submit the declaration for post approval stability studies which declares that the stability will be on-going as per the stations mentioned on the Testing Protocol and when the stability will be finalized with the shelf life at that time the summary sheet with the compilation of the result will be submitted for evaluation.

DRUG PRODUCT (P)

Drug Product is denoted by the word 'P', In the drug Product section we will compile the complete documents of the Drug Product part w.r.t to the quality of the Finished Product i.e. Drug product which includes General Information of the Drug Product Manufacturer, Manufacturing Process, Critical Parameters of Drug Product, Specifications and Testing Procedure of Drug Product, Analytical Method Validations, Stability of Drug Product, Studies of the Container in which the Drug Product are packed.

Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example:

Description of the dosage form

This section have Composition, i.e., list of all components of the dosage form, and their amount on a per- unit basis (including overages, if any) the function of the components, and a reference to their quality

standards (e.g., compendial monographs or manufacturer's specifications).

Description of accompanying reconstitution diluent(s); and type of container and closure used for the dosage form and accompanying reconstitution diluent provided, if applicable.

Pharmaceutical Development

Information on Development Studies

The section of Pharmaceutical Development describes information and data on the development studies conducted to establish that the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality. Supportive data and result from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application.

Component of Drug Product

Active Ingredients

The compatibility of the drug substances with excipients listed in Item 2.1 should be discussed. Additionally, key physicochemical characteristics (e.g. Water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance, which may influence the performance of the drug product should be discussed.

Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

Finished Product

Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

Overages

Any overages in the formulation(s) described in Item P 1 should be justified.

Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

Manufacturing Process Development

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of construction, and performance such as reproducibility of the dose delivery from the device when present as part of the drug product.

Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Compatibility

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

Literature data are acceptable

Manufacture

Batch formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

- The actual quantities (g, kg, liters) etc. of ingredient should be stated.
- Overage: Supporting data and the reason for including the overage shall be enclosed.
- The total number of dosage unit per batch must be stated.

- A description of all stages involved in the manufacture of the dosage form is required.

Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

- All component used in the manufacturing and processing of drug w.r.t finished product shall be identified, stored, examined, tested and properly handled.
- Complete analysis of the product shall be undertaken as per the current specification and method of analysis.
- The full description of manufacturing process must have sufficient details to cover the essential point of testing at each stage of manufacture.
- Must ensure that all the raw materials used in the manufacturing of the product are tested by the Quality Control Department as per the established and approved specifications and test method.
- For sterile product the description includes preparation and sterilization of components. (i.e. Containers, closures, etc.).

Controls of Critical Steps and Intermediates

Critical Process Parameter shall be identified on the basis of experimental work carried out in the research and development department. The critical Process Parameter shall be closely monitored and recorded during manufacturing.

In-process controls and intermediate parameters shall be identified and their acceptance criteria are evolved based on experiments carried out during Research and Development program of the Drug Products.

To ensure batch to batch uniformity, examinations shall be conducted on in-process materials and intermediates during the manufacturing process. Specification and acceptance criteria shall be outlined and rigorously followed during the manufacturing operation.

All the critical process parameters and intermediates for Drug Products shall be identified and specifications thereof shall be developed to control the manufacturing process.

Process Validation and/or Evaluation

Process Validation is the documented evidence which assures that the products which are manufactured at our site are consistent to produce the results meeting the predetermined specifications. So therefore Process Validation shall be carried out for the Drug Products and all the critical process parameters shall be monitored as per the production batch details and control records to maintain the quality of the intermediates and the finished

products as per the limits mentioned in the specifications.

The quality of the intermediates and the Final drug substance shall meet their predetermined specifications.

Control of Excipients

Specification

The specification for the excipients shall be provided as per the official monograph mentioned in USP, EP or other relevant Pharmacopoeias. In case if the Excipients used are of In-House grade in that case proper justification shall be provided for the specifications of the Excipients.

Analytical Procedures

Validation of Analytical Procedure shall be done to ensure that the methods which we are using for testing the ingredients or the finished Drug Products are giving consistent results meeting its predetermined specifications. Complete Analytical Method Validation will be done for those products only which are not mentioned in any of the Pharmacopoeia, but for those other Drug Products which are mentioned or present in the Pharmacopoeias only compendial verification need to be performed as per the parameters mentioned to be performed as ASEAN and WHO Guideline which ensure the Testing procedure and Acceptance Criteria for the Drug Products.

Excipients of Human and Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, and viral safety data).

Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided

Control of finished Product

Section consists of Specification and justification of the specification, summary of the analytical procedure and validation, and characterization of impurities.

Specification

The specification for the finished product should be provided.

Analytical Procedures

The analytical procedures use for the testing the finished product should be provided.

Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures use for the testing the finished product should be provided.

Validation required for non-compendial method however, verification for the applicability of compendial method used is required for compendial method.

Batch analyses

Description (including size, origin and use) and test result of all relevant batches e.g. pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided. A tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided.

Characterization of Impurities

The potential impurities shall be classified in the following categories-

- Organic Impurities
- Inorganic Impurities
- Residual Solvent

So proper testing shall be carried out to ensure that the impurities are within specification as per the guideline of ICH Q3B(R2), Q3C(R7).

Justification of Specification

Justification for the In-House Specifications shall be provided.

Reference Standards or Materials

Requirement: Quality information and tabulated presentation of Reference standard or materials used for testing of drug product should be included.

Container closure system

A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specification.

The specifications should include description and identification (and critical dimensions with drawings where appropriate). Noncompendial methods (with validations) should be included where appropriate. For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

Product Stability

Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life that toxic decomposition products are not produced in significant amount during this period, and that potency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion

All criteria under ICH Guidelines are acceptable with the exception of real time storage conditions which should be 30°C, 75% RH.

Provision of moisture protection of the packaging should be taken into consideration.

Post-approval stability protocol and stability commitment

The post-approval stability protocol and stability commitment should be provided.

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, and narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Product Interchangeability

The Multisource Pharmaceutical Products shall be conform with the same appropriate standards such as Quality, Safety, Efficacy in comparison of the Innovator Product, proper justification shall be provided that the multisource product is therapeutically equivalent and interchangeable with the Innovator Product.

The type of studies conducted, shall be justified according to BCS Classification, Dissolution Profile in three different pH such as pH 1.2, pH 4.5, pH 6.8 and meet the criteria of dissolution profile similarity $f_2 \geq 50$.

PART III

It contains the **Non Clinical Documents** having four sections namely: SECTION A contains the Table of content for the entire Part III, SECTION B contains the Non clinical Overview means the summary of the Non clinical studies SECTION C contains the written and Tabulated summaries of the Pharmacological, Pharmacokinetics and Toxicological data, SECTION D contains the Nonclinical Study Report of Pharmacology, Pharmacokinetics and Toxicology data.

PART IV

It contains the Clinical Studies having Six Sections namely: SECTION A: Table of Content for the entire Part IV, SECTION B: comprises of Clinical Overview of the complete Clinical Studies documented in Part IV, SECTION C: Summary of Biopharmaceutics and Associated Analytical Methods, Clinical Pharmacology Studies, Clinical Efficacy, Clinical Safety and Synopses of Individual Studies, SECTION D contains tabular listing of all clinical studies, SECTION E: contains the Clinical Study Reports; SECTION F: contains the list of Key References from where all the clinical Studies are Published and Documented.

3. CTD format

CTD Format was introduced by three regulatory Bodies i.e United Nation, Japan and Europe to assemble all the Quality, Safety and Efficacy of the drug under a single for format known as Common Technical Dossier. For Industries it works as a good Format because it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities (8).

Module I is for administrative information and should contains documents that are specific to region in which the dossier is filled. Module II contains the CTD summaries and should begin with a general introduction to the drug, including its pharmacological class, mode of action and proposed clinical use. Module 2 should also provide the overall summary of the 'quality' information provided, the non-clinical overview and the clinical overview, as well as the non-clinical written summaries and the tabulated summaries, and the clinical summary. As a foundation for the aforementioned material, Module III contains information on QUALITY topics, Module IV contains the nonclinical study reports and Module V contains the clinical study reports (8).

CTD Format comprise of Five Modules namely:

Module 1: Administrative Information and Prescribing Information

Module 2: Common Technical Document Summaries

Module 3: Quality

Module 4: Nonclinical Study Reports

Module 5: Clinical Study Reports

Brief Summary

ACTD format of Dossier Compilation for registration of Pharmaceutical Product in ASEAN countries is derived from CTD Format therefore the availability of documents required for compilation of Dossier in CTD Format is almost same as mentioned earlier in ACTD format., so therefore in the CTD part of Dossier compilation we had focused only on the documents which are different and are part of CTD format only. CTD format are applicable for registration of Pharmaceutical Product in Regulated Countries such as United Nation, Europe and Japan and these three countries are the founder of ICH as well as CTD format.

Module 1 Administrative Information and Prescribing Information

Administrative Part of CTD Module 1 contains documents that are specific to each region as per the requirement of each region/ country. So we are not discussing any further detailed studies for the requirement of documents required for compilation of Module 1.

Regional Administrative Information Module 1 is for administrative information and prescribing information and should contain documents that are specific to each region.

Module 2 Common Technical Document Summaries

Introduction

The introduction shall contain the general information of the drug Product including its Pharmaceutical and Clinical Use, its mode of action, its Pharmacological class, Therapeutic Category of the product shall be mentioned in short the overall view of the drug product. General introduction shall not exceed more than one page.

Quality Overall Summary (QOS)

This section contains the summary of the overall quality part of the dossier which contains summary of the Active Moiety present in the Drug Product as well as the studies of Drug Product required for preparation and compilation of dossier. The structure of the QOS broadly follows the structure of the data included in Module 3. The QOS (Quality Overall summary) shall discuss the critical parameters of the product. The QOS should not exceed more than 40 pages of the text, excluding figure.

Nonclinical Overview

This sections summaries the Overview of Non-clinical Written and Tabulated Summaries i.e. 2.4 & 2.6 content of the QOS. Basically the content and the structure of the Non Clinical Part mentioned in this module are specified from ICH M4S (9). Guidelines. The reason behind preparation of Non-Clinical Written and Tabulated Summaries in Module 2.6 is to give the information about pharmacology, pharmacokinetics, and toxicology. 34 No. of templates are provided for the preparation of the Tabulated Summaries in the ICH M4S guidelines. Non Clinical overview is the important step for assessment of criticality of the pharmacological, pharmacokinetic, and toxicological aspects of Medicinal product in animals. Reference of the Scientific Literature of the similar or related Medicinal product should also be taken into consideration while addressing the Non Clinical aspect of the Medical Product.

Clinical Overview and Module 2.7 Clinical Summary

These modules are usually the documents a medical writer is most likely to be asked to write. The structure and content of Modules 2.5 and 2.7 are specified in the ICH M4E guidelines, with answers to common issues raised provided as a separate document. The Clinical Overview is a short document that provides a Critical Assessment of the clinical data, whereas the Clinical Summary is a longer document that focuses on data summarisation and integration. The Clinical Summary and Clinical Overview provide the supporting information for the Summary of Product Characteristics (SmPC) or the product label (included in Module 1 of the CTD), so it is important these documents are consistent.

The primary purpose of the clinical summary is to provide a comprehensive factual summary of the clinical data. This includes information provided in the clinical study reports located in Module 5, information from any meta-analyses or other cross-study analyses that have been conducted, and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations and should not provide any interpretation of the data—this is covered within the Clinical Overview. The Clinical Summary is divided into sections covering biopharmaceutics and associated analytical methods, clinical pharmacology, efficacy, and safety. The synopsis from each study report is also included in this module (or appropriately hyperlinked in an eCTD). The clinical summary is between 50 and 400 pages long,

although it may be longer if more than one indication is included. The Clinical Overview is a key document in the CTD dossier. The Clinical Overview is divided into six sections: product development rationale, biopharmaceutics, and clinical pharmacology, efficacy, safety, and risk/benefit conclusions. In contrast to the factual presentation in the Clinical Summary, the Clinical Overview provides a critical analysis of the drug development programme and its results, including discussion and interpretation of clinical findings, and the relevance of other information (e.g. pertinent animal data or product quality issues that may have clinical implications). It is important to remember that the Clinical Overview presents the conclusions and implications of the data and it should not repeat the information presented in the Clinical Summary or elsewhere in the CTD. The Clinical Overview should present the strengths and limitations of the development programme and study results, analyse the benefits and risks of the IMP in its intended use, and describe how the study results support critical parts of the prescribing information. The quality of the clinical programme and performance of the studies, including a statement regarding Good Clinical Practice (GCP) compliance should also be included. The clinical overview should also discuss the place of the IMP in the clinical armamentarium if approval is given for a license. Appropriate reference should be made to the literature to put the results into context. Finally, the Clinical Overview should provide an evaluation of the benefits and risks of the IMP (Investigational Medicinal Product based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimize benefits and manage risks. The Clinical Overview should be a relatively short document of approximately 30 pages (10).

Module 3 Quality

Quality part contains the detailed information about the Drug Product w.r.t Chemistry, Manufacturing and control and the detailed studies of the same is to be introduced in the Dossier which is required for registration of Drug Product in the Regulatory countries.

Quality Part consists of two sections namely:

- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- 3.2. S Drug Substance
- 3.2. P Drug Product
- 3.3 Literature References

For preparation of Dossier in CTD format and registration of Pharmaceutical Product in Regulated Market basically the Drug Substance of USP grade along with the requirement of USDMF (United State Drug Master File), EP grade along with the requirement of EUDMF (European Nation Drug Master File) or CEP certificate is required. CEP certificate denotes Certificate of suitability means the drug substance is approved and registered under European Nation and the CEP grade of

Drug Substance can be used for the registration of Pharmaceutical Product in EU Nation. Similarly for registration of Product in Japan the Drug Substance of JP grade (Japanese Pharmacopoeia) is preferred.

Basically the Manufacturing process of Drug Product shall be developed in the Research and Development Department according to the following ICH Guideline which will be key reference for development or manufacturing of Drug Products for registration of Drug Product in Regulated Market which are mentioned below:

ICH Q8: Pharmaceutical development

ICHQ9: Quality Risk Management.

ICH Q10: Pharmaceutical Quality System.

ICH Q11: Drug Substance Development and Manufacturing.

Module 4: Non-clinical study reports

This represents the Non- Clinical report that is to be included in the Dossier. The content of and the subject to be covered under this module is already discussed. The main heading that shall be included in the dossier are:

- 4.1 Table of contents of Module 4
- 4.2 Study reports
 - 4.2.1 Pharmacology
 - 4.2.2 Pharmacokinetics
 - 4.2.3 Toxicology
- 4.3 Literature references used in Module 4.

Module 5: Clinical study reports

Table 1 Difference between CTD & ACTD format

CTD Format	ACTD Format	Description
It Consist of V Modules	It Consist of IV Sections	
Module I Administrative Part	Section I- Administrative Part	It consists of documents which are region specific. This module is not Part of CTD and ACTD format. This Module basically consist of Administrative Documents like Application form, legal documents (GMP, Licenses etc.), labelling etc.
Module II Quality Overall Summary	Section II-Quality Overall Summary incorporated in Section II, Section III & Section IV	This module consists of Module 3, 4 and 5. It consists of Quality Overall summary, Non Clinical Overview and Summary of Clinical Overview.
Module III Quality Documents	Section II	This part consists of documents of Chemistry Manufacturing and Control (CMC) for both Drug Substance and Drug Product.
Module IV Non Clinical Documents	Section III	This module consists of documents related to Non Clinical Study Report – Report on pharmacologic, pharmacokinetic, and toxicological.
Module V Clinical Documents	Section IV	A complete study of product related to safety and efficacy of the product related to clinical studies is provided in this module.

Harmonization in Dossier application format

The urgent requirement to rationalize and harmonize regulation was impelled by instance of rising cost of Health care, Research and Development and need to meet the public requirement to approach for the safe and efficacious treatments to patient in need. ICH committee has given priority to harmonize the format of reporting data for quality, safety and Efficacy in the application dossier. For the dossier application part CTD provides harmonized format for product application. Earlier all

This represents the Clinical report that is to be included in the Dossier. The content of and the subject to be covered under this module is the complete clinical studies of the drug product which assures to the importing or Drug Product Registering Country that the product is safe to use and all the studies w.r.t the safety and efficacy of the product had been completed. Under this module that is Clinical part the report on Biopharmaceutics studies and Pharmacokinetic and pharmacodynamic studies are to be conducted which assures that the Drug Product are effective and safe to use. Individual Case Report form of Individual Patients is also submitted in the report.

4. Difference between CTD & ACTD format

This section provides the basic differences in structure between the CTD (Common Technical Dossier) and ACTD (ASEAN Common Technical Dossier).

1. CTD format is a harmonized format for registration of Pharmaceutical product in Regulatory Countries i.e. EU, US & Japan whereas ACTD format is required for registration of Drug product in ASEAN Nation (Association for South East Asians Nation).
2. CTD Format contain 5 Module representing Module 1 for administrative Part, Module 2 for Quality Overall Summary, Module 3 for Quality, Module 4 for Non Clinical Studies, Module 5 for Clinical Part whereas ACTD format contains only 4 Parts namely Part 1 for administration, Part 2 for Quality and quality Overall Summary, Part 3 for Non Clinical Studies, and Part 4 for Clinical Part.

the submissions sent to regulatory authorities in CTD, Paper format but it was a tedious job requiring lot of Time to review ,documentation and paper work.

Due to the advancement in Information technology, regulatory authorities from regulated countries throughout the globe started to accept data in electronic format either in eCTD (Electronic common technical document)/ NeeS (Non eCTD electronic submission).

The eCTD was developed subsequently by the ICH M2 Expert working group and allows for the electronic submission of the CTD from the applicant to regulator and provides harmonized technical solution for CTD electronically. Many regulatory authorities completely eliminated the Paper submission and made eCTD mandatory.

This is the centralized approach, saves time, cost, facilitate review process and greater transparency can be achieved via central processing of submissions. Harmonization can also be seen in IPR stream by treaties and conventions. These international treaties and conventions contribute to the process of harmonization of patent laws (11).

Regulatory filing process:

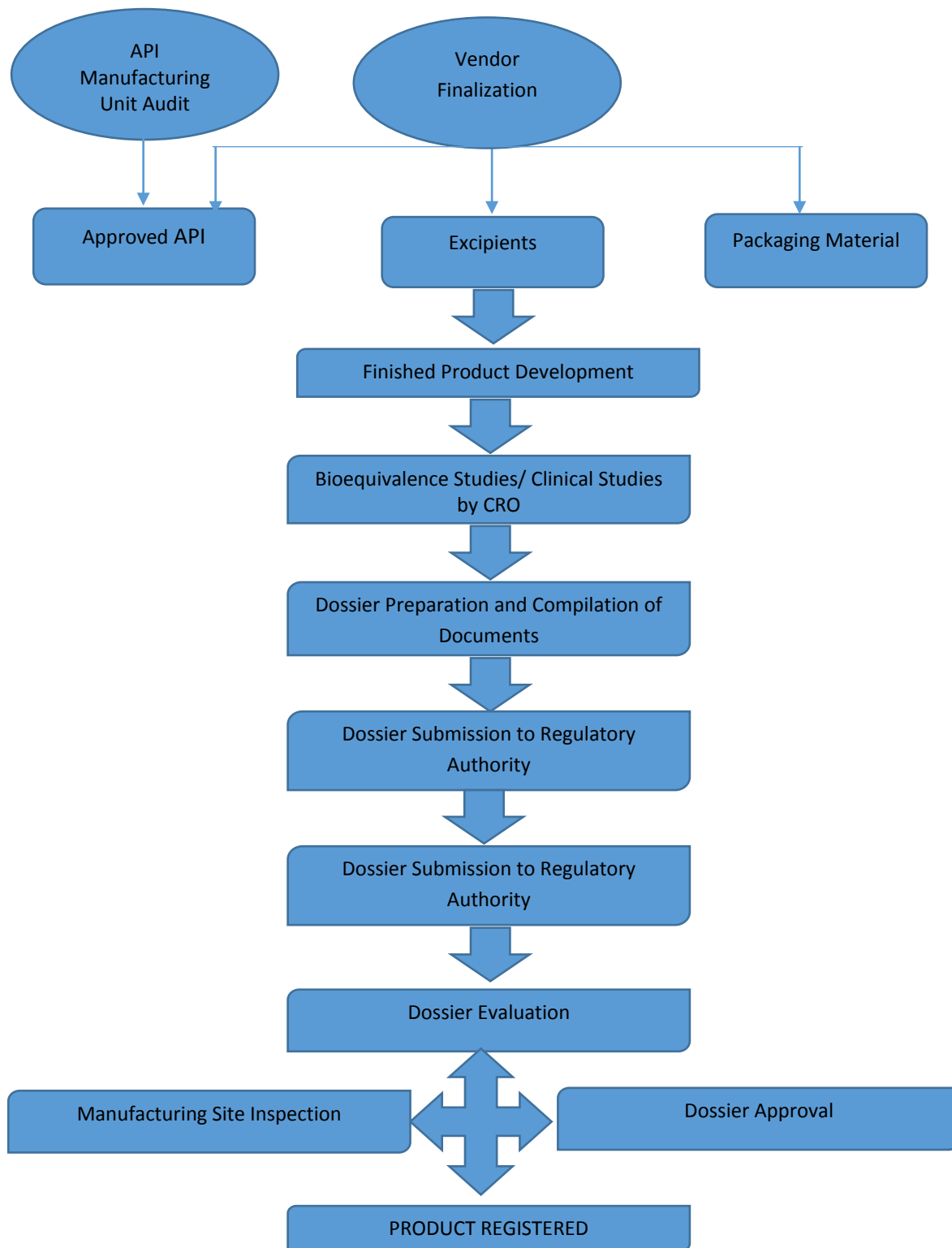


Figure 1. Regulatory filing and registration of product in regulatory authority

5. Conclusion

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.

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs who gave me the opportunity to publish the article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

References

1. ASEAN Common Technical Dossier (ACTD) Jakarta, ASEAN Secretariat; 2016 Dec.
2. U.S. Department of Health and Human Services Food and Drug Administration, ICH; 2017 Oct.
3. The ASEAN Declaration (Bangkok Declaration) Bangkok, 8 August 1967; 2015.
4. "Background Note: Brunei Darussalam/Profile:/ Foreign Relations" US State Department; 2007.
5. "Vietnam in ASEAN: Toward Cooperation for Mutual Benefits". ASEAN Secretariat; 2011.
6. Carolyn L. Gates; Mya Than. ASEAN Enlargement: impacts and implications. Institute of Southeast Asian Studies. ISBN 981-230-081-3; 2001.
7. "Statement by the Secretary-General of ASEAN Welcoming the Kingdom of Cambodia as the Tenth Member State of ASEAN, ASEAN Secretariat; 1999.
8. ICH. The Common Technical Document [Internet]. ICH; 2019 [cited 2019 Mar 26]. Available from: <https://www.ich.org/products/ctd.html>
9. ICH M4S Guideline: Nonclinical Overview and Nonclinical Summaries of Module 2 and Module 4: Safety (R2) [Internet]. ICH; 2002 Dec [cited 2019 Mar 26]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R2_Safety/M4S_R2_.pdf
10. Jordan D. An overview of the Common Technical Document (CTD) regulatory dossier, The European Medical Writers Association, VOL.23 NO.2; 2014.
11. Badjatya J, and Bodla R. "Harmonization & advancement in pharmaceutical industry". International Journal of Drug Regulatory Affairs, Vol. 1, no. 2, Feb. 2018, pp. 7-10, doi:<https://doi.org/10.22270/ijdra.v1i2.4>.