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Research Article

**REGULATORY DOSSIER- ASEAN COMMON TECHNICAL  
DOCUMENT (ACTD) FOR ASEM COUNTRIES****J. Neelima<sup>1</sup>, K. Anie Vijetha<sup>2</sup>, A. Srivani<sup>2</sup>, P. Sravanthi<sup>2</sup>**<sup>1</sup>Mallareddy Institute of Pharmaceutical Sciences, Hyderabad<sup>2</sup>Centre for Pharmaceutical Sciences, JNTUH, Hyderabad**Abstract:**

*The Regulatory Affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of Regulatory Affairs Professionals will condition the perceptions of the government officials to the company. Dossier is a collection or file of documents on the same subject, especially a file containing detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "pharmaceutical product for human use". This guideline merely demonstrates an appropriate write-up format for acquired data. Throughout the ACTD, 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. This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future, will ease the preparation of electronic documental submissions. ICH-ECTD is an internationally driven standard designed to reduce cost in the administration, assessment and archiving of applications for marketing authorization of medicinal products for human use, to reduce the use of paper and streamline the assessment process making the system more efficient.*

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**INTRODUCTION:**

The Regulatory Affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of Regulatory Affairs Professionals will condition the perceptions of the government officials to the company. Dossier is a collection or file of documents on the same subject, especially a file containing detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient is called as “pharmaceutical product for human use”. Process of reviewing and assessing the dossier of a pharmaceutical product containing its detailed data (administrative, chemistry, pre-clinical and clinical) and the permission granted by the regulatory agencies of a country with a view to support its marketing/ or approval in a country is called as “Marketing Approval” or the “Registration” “Marketing Authorization” or the “Product Licensing” [1].

The goals of dossiers are to provide enough information to permit Regulatory Agencies. ICH is a joint initiative involving both regulators and research based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines. The goal of ICH is to promote international harmonization by bringing together representatives from the three ICH regions (EU, Japan and USA) to discuss and establish common guidelines [2,3].

The authorities in the United States, European Union and Japan ask for the Common Technical Document (CTD) format set out by the 2003 International Conference on Harmonization (ICH). CTD provide a common format for the submission of information to the Regulatory Agencies for the registration of the pharmaceutical product [4].

The Asia-Europe Meeting (ASEM) [4] was initiated in 1996 when the ASEM leaders met in Bangkok, Thailand. ASEM is an informal trans- regional platform for dialogue and cooperation between the two regions and has risen out of a mutual recognition that the relationship between Asia and Europe needed to be strengthened in light of the challenges and opportunities of the 21<sup>st</sup> century. The Asia-Europe Meeting (ASEM) is an informal process of dialogue and cooperation bringing together the 27 European Union member states, 2 European Countries and the European Union with 20 Asian Countries and the

ASEAN Secretariat. The initial ASEM partnership in 1996 consisted of 15 EU member states and 7 ASEAN member states plus China, Japan, Korea and the European Commission. ASEM saw the first enlargement during the 5<sup>th</sup> ASEM summit in 2004 in Hanoi (Vietnam), where the 10 EU member states (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia) and three new ASEAN countries (Cambodia, Laos and Myanmar) became officially part of the ASEM process [2,4].

The second round of enlargement in 2008 during the 7<sup>th</sup> summit in Beijing (China) brought in Bulgaria, India, Mongolia, Pakistan, Romania and the ASEAN secretariat, increasingly total ASEM membership to 45 partners. In October 2010, the 8<sup>th</sup> ASEM summit of Heads of Government and State in Brussels (Belgium) welcomed three member states to the ASEM process: Australia, New Zealand and Russia. This third round of enlargement increased total ASEM membership to 48 partners. During the 9<sup>th</sup> ASEM summit of Heads of Government and State in Vientiane (Laos) in November 2012, ASEM was joined officially by Bangladesh, Norway and Switzerland. This latest round of enlargement brings the total ASEM membership to 51 partners. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future. This will ease the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements [4].

This guideline merely demonstrates an appropriate write-up format for acquired data. Throughout the ACTD, 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 either A4 or 8.5 x 11 paper. The left hand margin should be sufficiently large that information is not obscured by the method of 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. References should be cited in accordance with the

1979 Vancouver declaration on uniform requirements for manuscripts submitted to biomedical journals<sup>5</sup>. The Common Technical Document is organized into four parts as follows [6-8]:

**PART I: Table of contents, administrative data and product information:**

Part I contains initially the overall Table of Contents of the whole ACTD to provide basically the information's that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in details is put together such as application forms, label, package insert, etc. the last section of this part is Product Information where necessary information includes prescribed information, mode of action, side effects etc. A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included.

**PART II: Quality document:**

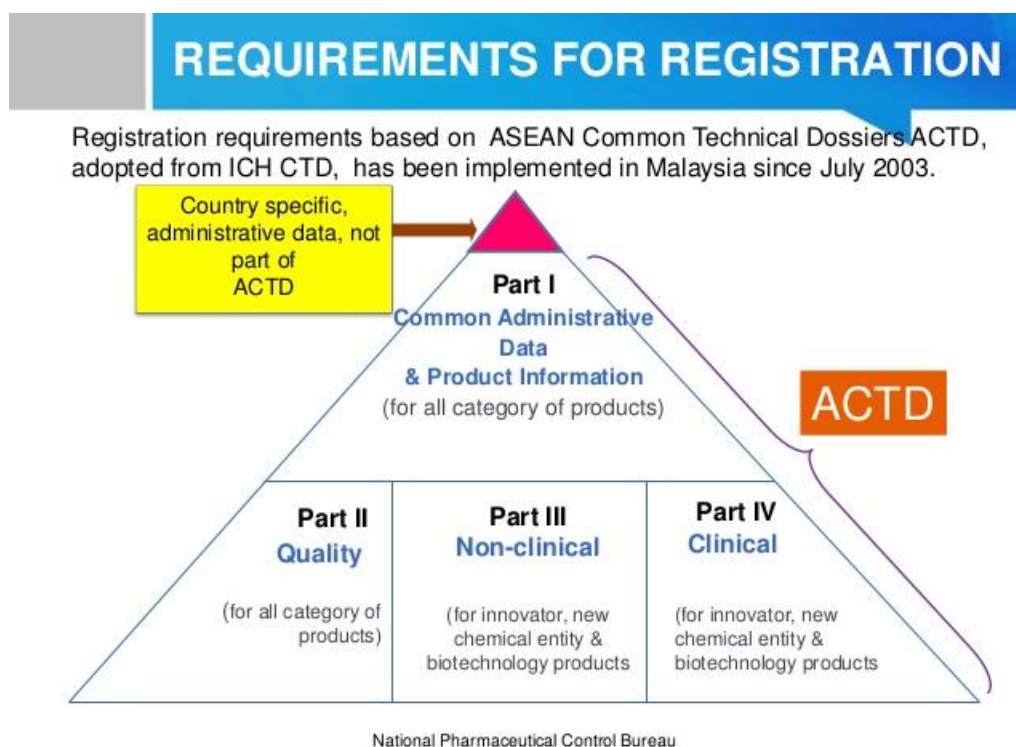
Part II should provide the overall summary followed by the study reports. The quality control document should be described in details as much as possible.

**PART III: Nonclinical document:**

Part III should provide the Nonclinical overview, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The document of this part is not required for generic products, minor variation products and some major variation products. For ASEAN member countries, the study reports of this part may not be required for NCE, Biotechnological products and other major variation products if the original products are already registered and approved for market authorization in reference countries. Therefore, the authority who requires specific study reports should ask for the necessary documents.

**PART IV: Clinical document:**

Part IV should provide the clinical overview and the clinical summary. The document of this part is not required for generic products, minor variation products and some major variation products. For ASEAN member countries, the study report of this part may not be required for NCE, Biotechnological products and other major variation products if the original products are already registered and approved for market authorization in reference countries. Therefore, the authority who requires specific study reports should ask for necessary documents.



The overall organization of Common Technical Dossier is presented on the following in parts:

**PART I: Table of content, administrative information and prescribing information**

Section A: Introduction

Section B: overall ASEAN Common technical dossier Table of Contents

Section C: Documents required for registration (for example application forms, labeling, Product Data Sheet, prescribing information)

**Detailed Overview of part-I**

Administrative information

Manufacturing information

Application forms

Labeling parameters required for Unit carton

- Product name
- Dosage form
- Name of active ingredient (s)
- Strength of active ingredient(s)
- Batch number
- Manufacturing date
- Expiration date
- Route of administration
- Storage condition
- Country's registration number
- Name and address of marketing authorization holder
- Name and address of manufacturer
- Special labeling (If applicable) e.g. sterile, external use, cytotoxic, alcohol
- content, animal origin (Bovine, Porcine)
- Recommended daily allowance (For Vitamins and Minerals)
- Warning (if Applicable)
- Pack sizes (Unit/Volume)

Labeling parameters required for inner label

- Product name
- Dosage form\*
- Name of active ingredient (s)
- Strength of active ingredient(s)
- Batch number
- Manufacturing date\*
- Expiration date
- Route of administration
- Storage condition\*
- Country's registration number\*
- Name and address of marketing authorization holder\*
- Name and address of manufacturer\*
- Special labeling (if Applicable) e.g. sterile, external use, cytotoxic, alcohol

- content, animal origin (Bovine, Porcine)\*
- Recommended daily allowance (For vitamins and minerals)\*
- Warning (if Applicable)\*
- Pack sizes (Unit/Volume)

Labeling parameters required for blisters/strips<sup>9</sup>

- Product name
- Name of active ingredient(s)#
- Strength of active ingredient(s)#
- Batch number
- Expiration date
- Name/logo of manufacturer/product owner/marketing authorization holder
- (country specific)
- Country's registration number (country specific)

Package insert

- Product name
- Name and strength of active ingredient(s)
- Product description
- Pharmacodynamics/Pharmacokinetics
- Indication
- Recommended dose
- Mode of administration
- Contraindication
- Warnings and Precautions
- Interaction with other medicaments
- Pregnancy and lactation
- Undesirable effects
- Overdose and treatment
- Storage condition
- Dosage forms and packaging available
- Name and address of manufacturer/marketing authorization holder
- Date of revision of package insert

Summary of product characteristics (Product data sheet)

- Name of the Medicinal Product
- product Name
- Strength
- Pharmaceutical Dosage Form
- Quality and Quantitative Composition
- Qualitative Declaration
- The active substance should be declared by its recommended INN
- Quantitative Declaration
- The quantity of the active substance must be expressed per dosage unit)
- Pharmaceutical Form
- Visual description of the appearance of the product (colour, markings, etc) e.g.:
- "Tablet White, circular flat beveled edge tablets marked '100' on one side

- Clinical Particulars
- Therapeutic indications
- Posology and method of administration
- Contraindications
- Special warning and precautions for use
- Interaction with other medicinal products and other forms of interactions
- Pregnancy and lactation
- Effects on ability to drive and use machine
- Undesirable effects
- Overdose

#### Pharmacological Properties [10]

- Pharmacodynamic Properties
- Pharmacokinetic Properties
- Preclinical safety Data
- Pharmaceutical Particulars
- List of excipients
- Incompatibilities
- Shelf life
- Shelf life of the medicinal product as packages for sale. Shelf life after dilution or reconstitution according to directions. Shelf-life after first opening the container.
- Special precautions for storage
- Nature and contents of container
- Marketing Authorization Holder
- Marketing Authorization Numbers
- Date of first authorization/renewal of the authorization
- Date of revision of the text

#### Patient information leaflet (PIL)

- Name of Product
- Description of Product
- What is in the medicine?
- Strength of the medicine
- What is this medicine used for?
- How much and how often should you use this medicine?
- When should you not take this medicine?
- Undesirable effects
- What other medicine or food should be avoided whilst taking this medicine?
- What should you do if you miss a dose?
- How should you keep this medicine?
- Signs & Symptoms of over dosage
- What to do when you have taken more than the recommended dosage?
- Name/logo of manufacturer/importer/Marketing Authorization Holder
- Care that should be taken when taking this medicine?
- When should you consult your doctor?

## **PART II: Quality document**

Section A: Table of contents

Section B: Quality overall summary

Section C: Body of data

### **Detailed overview of part-II**

Table of contents

A table of contents for the filed application should be provided.

Drug substance

General information

- International non-proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)
- Structural formula

Pharmaceutical development [11,12]

- Component of drug product
- Active ingredients
- NCE and Biotech:  
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, and particle size distribution, polymorphic or solid state form) of the drug substance, which may influence the performance of the drug product should be discussed.
- Formulation development
- Overages
- 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 [10,11].
- 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 anti microbial 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.
- 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.
- Novel excipients  
For excipient(s) used for the first time in a drug product or by a new route of administration, details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided.
- Control of finished product
- The specification for the finished product should be provided.
- 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 used for the testing the finished product should be provided.
- 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). Non-compendial methods (with validations) should be included where appropriate.
- 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 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.

### **PART III: Nonclinical document [13-15]**

Section A: Table of contents

Section B: Nonclinical overview

Section C: Nonclinical written and tabulated summaries

- 1) Table of contents
- 2) Pharmacology
- 3) Pharmacokinetics
- 4) Toxicology

Section D: Nonclinical study reports

- 1) Table of contents
- 2) Pharmacology
- 3) Pharmacokinetics
- 4) Toxicology

### **Detailed overview of Part-III**

Table of contents

Guide on Nonclinical overview and summaries:

- This guide provides recommendations for the harmonization of the Nonclinical Overview, Nonclinical Written and Tabulated Summaries. The primary purpose of nonclinical written and tabulated summaries should be to provide a comprehensive, factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e. as applicable to labeling) should be addressed in the nonclinical overview.

Nonclinical overview

The nonclinical overview should provide an integrated, overall analysis of the information in the Common Technical Document.

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature citations
- 

Order of presentation of information within sections:

When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type are summarized within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

Mouse, Rat, Hamster, Other rodent, Rabbit, Dog, Nonhuman primate, other non-rodent mammal, Non mammals etc.

Routes of administration should be ordered as follows:

The intended route for human use

- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

#### **PART IV: Clinical document [13-15]**

Section A: Table of contents

Section B: Clinical overview

Section C: Clinical summary

- 1) Summary of biopharmaceutics and associated analytical methods
- 2) Summary of clinical pharmacology studies
- 3) Summary of clinical efficacy
- 4) Summary of clinical safety
- 5) Synopses of individual studies

Section D: Tabular listing of all clinical studies

Section E: Clinical study reports

Section F: List of key literature references

#### **Detailed overview of part-IV**

Table of contents

- A table of contents for the filed application should be provided.

Clinical overview

- The Clinical Overview [13] is intended to provide a critical analysis of the clinical data in the ASEAN Common Technical Dossier (ACTD).
- Product development rationale
- Overview of biopharmaceutics

- The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to -be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to -be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).
- Overview of Clinical Pharmacology
- Overview of efficacy
- Overview of safety
- Benefits and risks
- Clinical summary

#### **International conference on harmonization of technical requirements for registration of pharmaceutical for human use is as per ICH M2 EWG**

The ICH M4 Expert Working Group (EWG) [14-16] has defined the Common Technical Document (CTD). The ICH M2 EWG has defined, in the current document, the specification for the Electronic Common Technical Document (ECTD). The ECTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission<sup>17,18</sup>. The ECTD specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority. Industry to industry and agency to agency transfer is not addressed.

The specification for the ECTD is based upon content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organization of modules, sections and documents. The structure and level of detail specified in the CTD have been used as the basis for defining the ECTD structure and content but, where appropriate, additional details have been developed within the ECTD specification [19].

#### **ECTD in the centralized procedure [20]**

In centralized procedure the EMA now only accepts submissions received in ECTD format. We understand that there may be occasions when applicants are unable to comply with this electronic requirement and in those circumstances we will accept paper submissions. Since January 2013 and "**Mandatory from March 2014**" all ECTD submissions must be sent using the dedicated

submission channels: eSubmission Gateway or the related eSubmission Web Client

### CONCLUSION:

This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future, will ease the preparation of electronic documental submissions. ICH-ECTD is an internationally driven standard designed to reduce cost in the administration, assessment and archiving of applications for marketing authorization of medicinal products for human use, to reduce the use of paper and streamline the assessment process making the system more efficient.

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