UNIT-III

Registration of Indian drug product in overseas market

Points to be covered in this topic

- Procedure for export of pharmaceutical products
- Common Technical Document (CTD)
- Drug master files (DMF)
- Electronic Common Technical document (eCTD)
- ASEAN Common Technical document (ACTD) research

Procedure for export of pharmaceutical products

India has a separate policy for import and export known as the "EXIM" policy. This policy encourages both quantitative and qualitative advances in Research & Development activity.

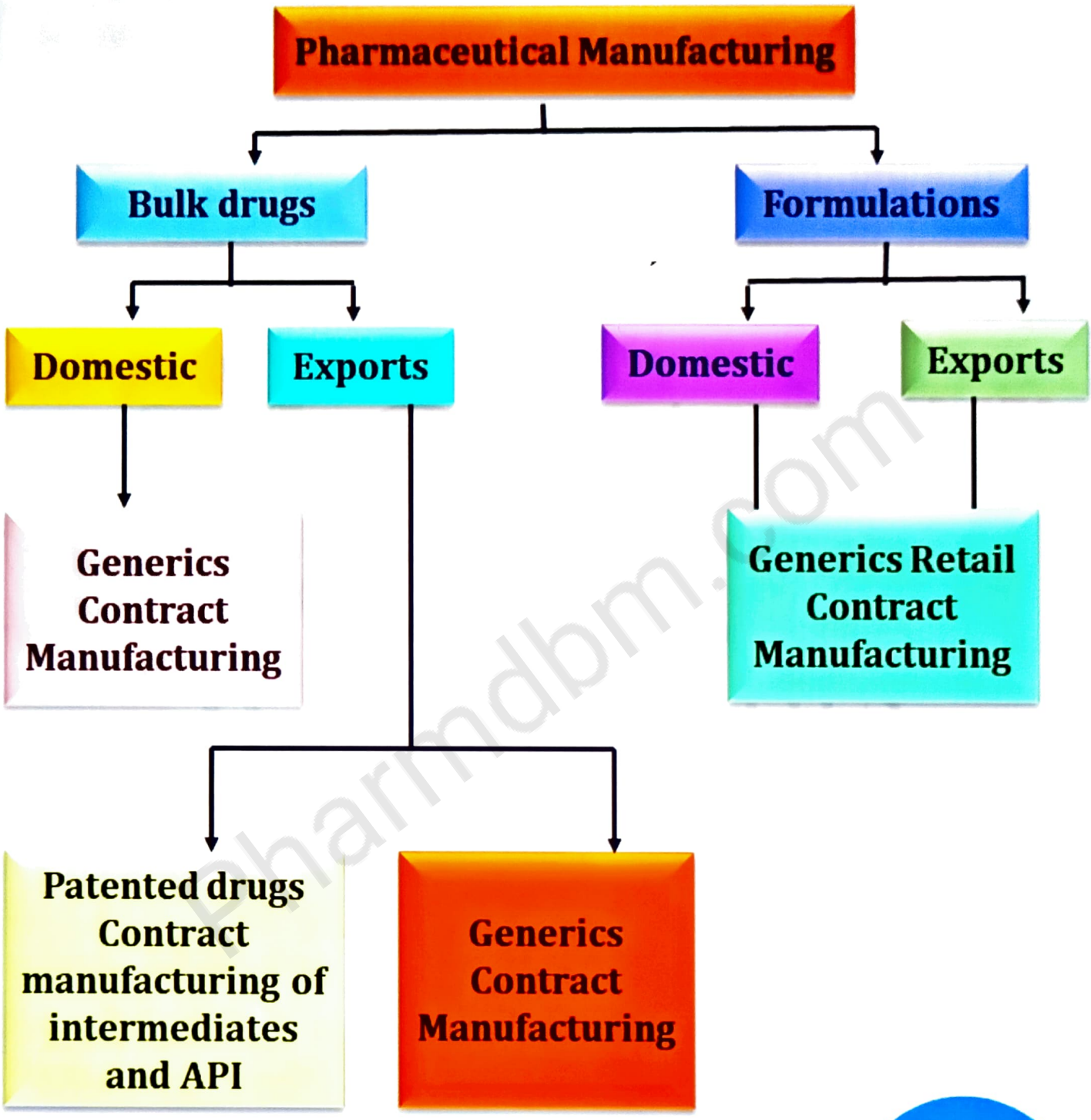
The Central Drugs Standard Control Organisation (CDSCO) regulates drug import and export in the country through 11 port offices situated around the country. CDSCO regulates the manufacture, sale, import, export, and clinical research of drugs in India by the following rules and acts.

- ✓ Drugs and Cosmetics act, 1940 and Rules, 1945
- ✓ Pharmacy act, 1948
- ✓ Drugs and Magic Remedies act, 1954
- ✓ Medicinal and Toilet Preparation act, 1956
- ✓ Narcotic and Psychotropic Substances act, 1985
- ✓ The Drugs (Prices Control) order, 1995

The industry offers several opportunities for investments and trade owing to the following advantageous features:

- Self-reliance displayed by the production of 70% of bulk drugs and almost the entire requirement of formulations within the country
- Low cost of production and R & D of quality bulk drugs and formulations
- Strong scientific, innovative and technical manpower
- Increasing balance of trade in pharma sector
- Efficient and cost-effective source for producing generic drugs, especially the drugs going off patent in the next five years
- Excellent center for clinical trials in view of the diversity in population
- Fast growing biotech industry which has great potential in the international market.

The structure of Indian Pharmaceutical industry is detailed in the figure below :



Export of pharmaceutical from India

Export process of pharmaceutical products, government rules to export pharmaceutical product, export documentation to export pharmaceutical products :

A. **Introduction :** A manufacturer holding valid license copy in **form-25** and **form-28** can obtain No objection Certificate from zonal/sub zonal offices of Central Drugs Standard Control Organization (CDSCO) for export only for approved/unapproved new drug/banned drug in India.

B. **Purpose :** Requirement for the common submission format for issuance of No objection certificate for export of unapproved/approved new drugs/Banned drugs from India.

C. **Scope :** This document is applicable for the manufacturer to obtain No Objection Certificate Zonal/sub zonal offices of Central Drugs Standard Control Organisation (CDSCO) for export purpose.

D. **Procedure :** Requirement for Common submission format for issuance of No Objection Certificate for export of unapproved/approved new drugs/Banned drugs from India.

Requirement for Common Submission Format for Issue of NOC for Export

- **Covering letter :** The covering letter mentioning list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size along with quantity and country to be exported duly signed and stamped by the authorized signatory, indicating the name and designation of the authorized signatory along with the name and address of the film.
- **Purchase order :** Order from the foreign buyer either in the name of the manufacturer or trader with the list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size duly signed by the competent authority with specific destination point of the importing country.

- **Manufacturing license :** license issued by the State Licensing Authority should be enclosed along with each application for the required location to manufacture the drug for export purpose.
- **Performa invoice :** A copy of performa invoice from the importing country should accompany with application for import of unapproved Active Pharmaceutical Ingredients, used in the drug formulation.
- **Registration certificate :** A copy of registration certificate from the specific importing country along with composition and strength of the drug should accompany with the application.

Rules Related to Export of Drugs from India

A) Rule 94: Packing and labelling of drugs other than Homeopathic Medicines:

Labels on packages or containers of drugs for export shall be adapted to meet the specific requirements of the law of the Country, to which the drug is to be exported,

- Name of the drug
- The name, address of the manufacturer and the number of the license under which the drug has been manufactured
- Batch or lot number
- Date of expiry

The medicine is labelled with the following particulars:

- The name and address of the supplier
- The name of the patient and the quantity of the medicine
- The number representing serial number of the entry in the prescription register
- The dose, if the medicine is for internal use
- The words -FOR EXTERNEL USE ONLY shall be printed on the label if the medicine is for external application.

B) Rule 95 : Prohibition of sale or distribution unless labelled. Subject to the other provisions of these Rules, no person shall sell or distribute any drug unless it is labelled in accordance with these Rules.

C) Rule 96 : The following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any drug and on every other covering in which the container is packed, namely :

(i) The name of the drug

For this purpose, the proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name and shall be :

(a) For drugs included in the schedule F or schedule F1

(b) For drugs included in the Indian Pharmacopoeia or the official pharmacopeia and official compendia of drug standards prescribed in Rule 124

(c) For drug included in the National Formulary of India, the name or synonym specified therein followed by the letters N.F.I

(d) For other drugs, the international Non-proprietary names, if any, published by The World Health Organization or where an international non-proprietary name is not published, the name descriptive of the true nature or origin of the substance.

Guidelines for the Export of Drug issued by Ministry of Health and Family Welfare :

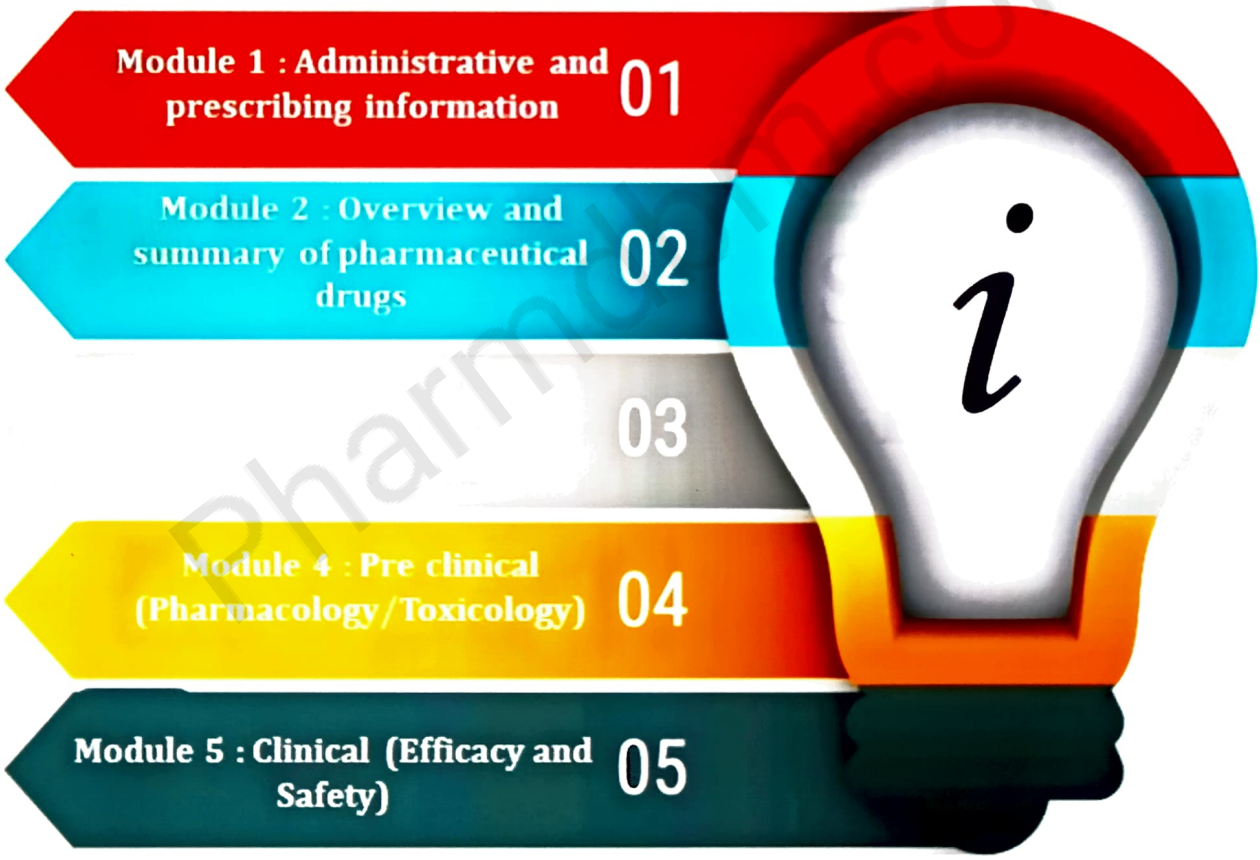
- The application shall provide copy of valid export order and NOC will be issued on a case by case basis against each such order.
- The applicant shall identify the premises where the drug will be manufactured for export.
- The applicant should mention whether the batch to be exported has undergone Quality control testing or shall be tested at the destined site.

- The applicant shall ensure that the drugs manufactured on the basis of NOC given as per the first condition and it is exported and that no part of it is diverted for domestic sale in India.
- The applicant shall make available for inspection of the appropriate authorities, on completion of the export orders, information regarding each consignment dispatched, remaining stock of drug and related raw materials and intermediates in hand.
- The applicant shall ensure physical destruction of all un exported quantity of drugs. This should be included as a condition of manufacturing license issued to the applicant by the State licensing authority.
- The applicant shall ensure that the drug for which NOC has been given shall cease to be manufactured or exported if the drug is prohibited in future in the country or in the importing country.

Common Technical documentation

Common Technical Document (CTD) is a set of specifications for application dossier for the registration of pharmaceutical products in Europe, Japan and the United States. Common Technical Documents or CTDs are critical sets of information of a new drug that comprise the application dossier. The application dossier is then submitted for the purpose of obtaining approval by regional regulatory authorities before the drug can undergo clinical trials and subsequently be introduced in the market.

Each CTD is segmented into five modules:



Module 1 : Administrative and prescribing information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Organisation of the common technical document for the registration of pharmaceuticals for human use:

- Table of content of the submission including Module 1
- Documents specific to each region

Module 2 : Overview and summary of pharmaceutical drugs

These begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and propped clinical use. In general, the introduction should not exceed one page.

Organisation of the common technical document for the registration of pharmaceuticals for human use:

- CTD table of contents
- CTD introduction
- Quality overall summary
- Non-clinical overview
- Clinical overview
- Non-clinical written and tabulated summaries
    - Pharmacology
    - Pharmacokinetics
    - Toxicology
- Clinical summary
    - Biopharmaceutic studies and associated analytical methods
    - Clinical pharmacology studies
    - Clinical efficacy
    - Literature references
    - Synopses of individual studies

Module 3 : Quality (pharmaceutical documentation)

Information on quality should be presented in the structured format described in guidelines M4Q

Organisation of the common technical document for the registration of pharmaceuticals for human use:

- Table of content of Module 3
- Body of data
- Literature references

Module 4 : Pre clinical (Pharmacology/Toxicology)

The non-clinical study reports should be presented in the order described in the guidelines M4S

Organisation of the common technical document for the registration of pharmaceuticals for human use:

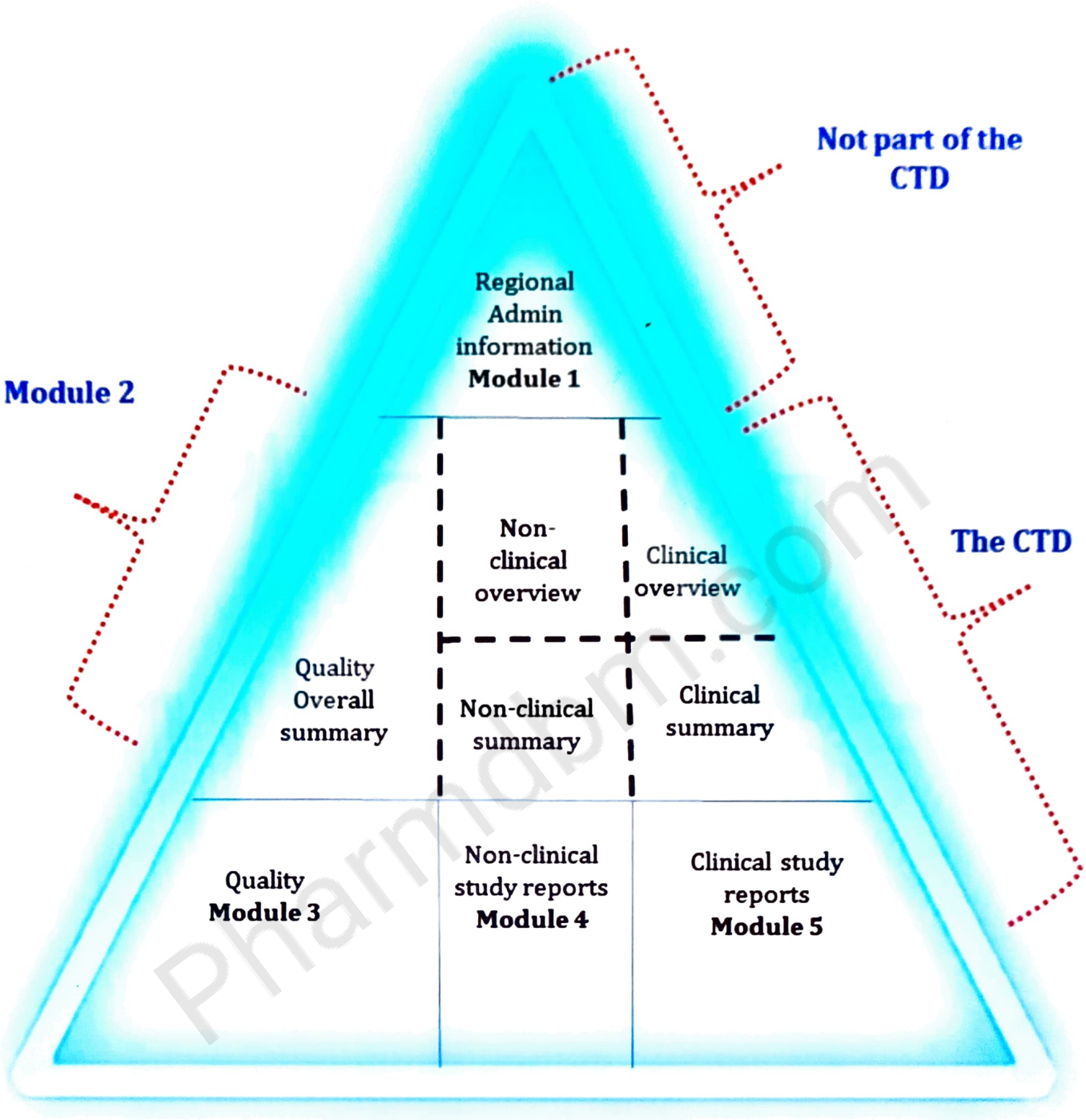
- Table of contents of Module 4
- Study reports
- Literature references

Module 5 : Clinical (Efficacy and Safety)

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

Organisation of the common technical document for the registration of pharmaceuticals for human use:

- Table of contents of Module 5
- Tabular listing of all clinical studies
- Clinical study reports
- Literature references



- **Diagrammatic Representation of the Organisation of the ICH CTD**

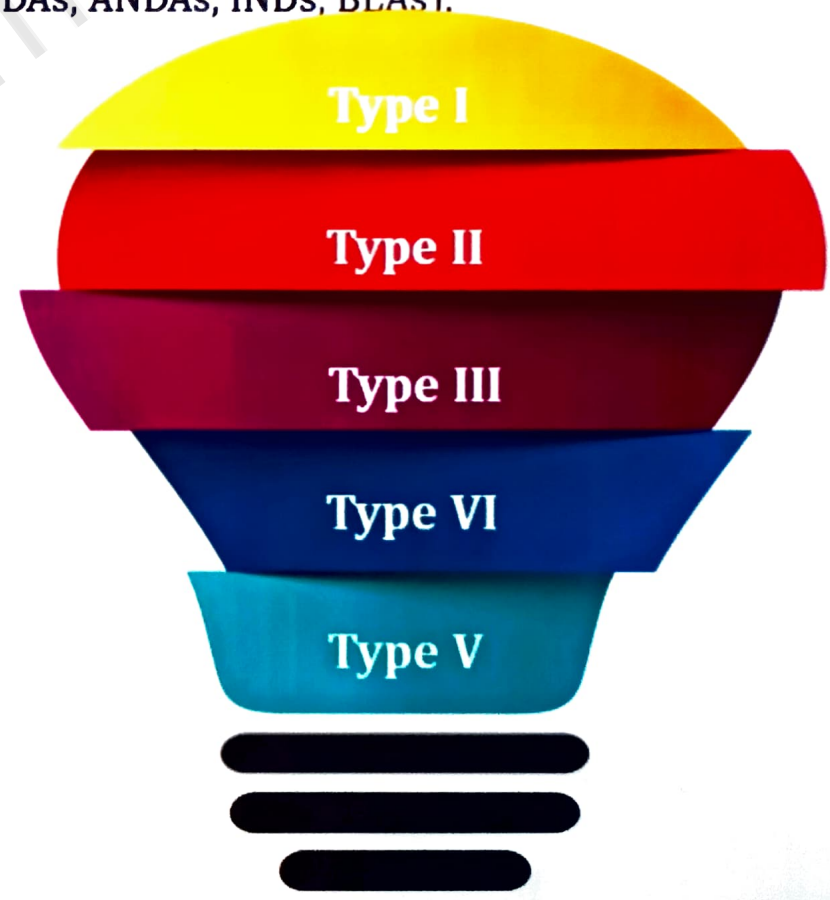
Drug Master File (DMF)

Definition :

DMFs are submission to FDA used to provide confidential, detailed information about facilities, processes or article used in the manufacturing, processing, packaging and storing of human drug products. They :

- Allow parties to reference material without disclosing DMF contents to those parties.
- Are not required by statute or regulation
- Are neither approved nor disapproved. Instead, FDA reviews the technical contents of DMFs in connection with the review of applications that reference them (e.g., NDAs, ANDAs, INDs, BLAs).

Types of DMF:



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

Type II : Drug Substance, Drug Substance intermediate, and Material used in their preparation, or drug Product.

- A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation.
- Summarize all significant steps in the manufacturing and controls of the drug intermediate or substance.
- Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in an IND, NDA, ANDA, or Export Application. If this information cannot be submitted in an IND, NDA, ANDA, or Export application, it should be submitted in a DMF.

Type III : Packaging Material.

- ✓ Each packaging material should be identified by the intended use, components, composition, and controls for its release.
- ✓ The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given.

Type IV : Excipient, Colorant, Flavour, Essence, or Material Used in their preparation.

- ✓ Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods.
- ✓ Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document.

Types V : FDA Accepted Reference Information

- ✓ FDA discourages the use of Type V DMF's for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMF's.
- ✓ If any holder wishes to submit information and supporting data in a DMF that is not covered by Types II to IV, a holder must first submit a letter of intent to the Drug Master File Staff. FDA will then contact the holder to discuss the proposed submission.

Contents of DMF submission :

- There are certain requirements for each DMF submission such as; transmittal letters, administrative information about the submission and the specific information to be included in the DMF all of which must be written in English.
- Aside from the users fee form, no other forms should be filled out or submitted along with a DMF submission.
- Each page of each copy of the DMF should be dated and consecutively numbered and any updates should include updated table of contents.

The transmittal letter for an original DMF should cover the following :

- ✓ Identification of submission: Original, the type of DMF as classified in Section III, and its subject.
- ✓ Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers.
- ✓ Signature of the holder, authorized representative or agent.
- ✓ Name and tittle of the signer.

The Administrative information required is as follows :

The names and the address of the following must be provided:

- DMF holder
- Manufacturing / processing facility
- Contact of FDA correspondence
- Agents, if any
- The specific responsibility of each person
- A statement of commitment
- A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

Electronic Common Technical Document (eCTD)

- eCTD (electronic Common Technical Document) is a standard format of submitting Regulatory information (such as applications, supplements, and reports) to the concerned Health Authorities (HAs).
- It provides a harmonized solution to implement the Common Technical Document (CTD) electronically.
- An eCTD consists of individual documents in PDF format which are arranged in a hierarchical form as per the CTD structure.
- It also has an XML backbone which cross-links required documents and provides information regarding the submission.
- The purpose of introducing eCTD was to reduce the burden on the reviewers of the HAs.
- It also simplifies the process of submission as all the Regulatory authorities use it as a standard format.

❑ There are total five modules in eCTD

Module 1 Region-specific information

Module 2 Summary documents

Module 3 Information related to quality

Module 4 Non-clinical study reports

Module 5 Clinical study reports (CSRs)

Module 1 : Region-specific information :

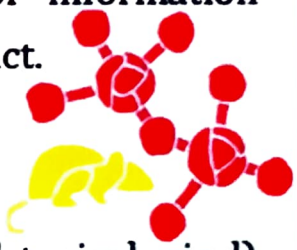
This module contains information specific to the region to which the dossier is being submitted. The relevant regulatory authorities specify the content and format of this module. Module 1 of the eCTD (regional information) contains 3 additional XML files (for each region). These contain meta-information (e.g. applicant, product, submission date), and links to the files with the actual submission information.

Module 2: Summary documents :

This module contains summaries and overviews of the 3 CTD technical sections: Quality Safety, and Efficacy. The organization of these summaries is described in separate guidance documents for each discipline (quality, safety, and efficacy).

Module 3 : Information related to quality :

This module contains information pertinent to the quality of the pharmaceutical substance and product. This consists of information concerning the CMC of the drug/biologic substance and product.



Module 4: Non-clinical study reports :

This module contains information on pharmacokinetic, and toxicological) evaluation of the drug/biologic substance and product. the non-clinical (pharmacological, The information is typically provided in the form of study reports and publications.

Module 5: Clinical study reports (CSRs) : This module contains information on the clinical evaluation of the drug/biologic product. This module typically includes clinical study reports describing each conducted clinical study. Supportive publications are also provided here.

Specification : Describes the way the files should be constructed for the inclusion in the eCTD. The commonly used format in the electronic submission are as follows

PDF : Portable Document Format (PDF) is a published format compliant to the international organisation for standardization (ISO) standard ISO 32000-1:2008

XML : The working group at the world web consortium (W3C) developed the extensible markup language (XML). It is a non-proprietary language developed to improve on previous markup languages

Study Dataset Files : Specific regions includes; study datasets and may have different rules regarding the following topics- Allowable file formats, Datasets files formats, Datasets files name and allowable characters

Benefits of eCTD :

- Improved handling and archiving of submissions
- Better management of information
- Support of life cycle management
- Immediate access to complete and up to date information
- Increased tracking ability
- Facilitated evaluation and better visibility of the process
- Reduced external interference and proper communication
- Good utilization of resources

Comparison between paper CTD and eCTD

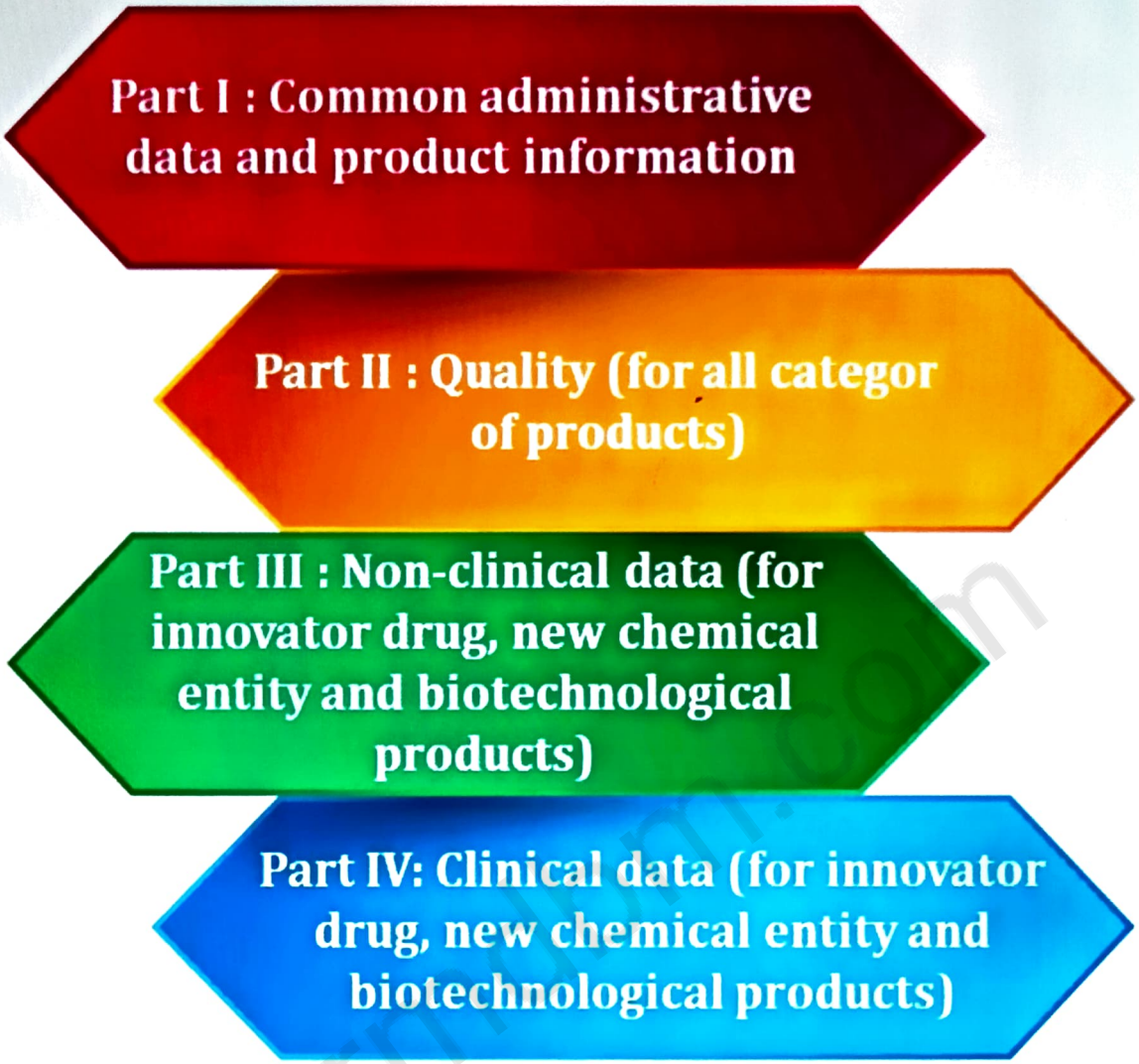
Paper CTD	eCTD
Well organized in format with Tabs, Volumes and sheets then printed to paper	Compiled electronically with e-documents in folder
Paper volumes must be A4	E-documents can be A4 or US letter size
CTD navigation by TOCs and volume	eCTD navigation by XML backbone
Cross-references includes target CTD section	Cross-references are hyperlinked to targets.
Submitted in binders in boxes	Submitted in CD or DVD and email

ASEAN common technical dossier (ACTD)

- ✓ 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) application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals and biologics 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. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.
- ✓ The ACTD's advantage is that one dossier can be prepared for all ASEAN countries, reducing efforts and facilitating the regulatory review process.

❑ Ten countries of ASEAN :

The ACTD is organized into four parts as follows:



Part I : Common administration data and product information – Part I contains initially the overall Table of Contents of the whole ACTD to provide basically the information that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in detail is put together such as application forms, label, and package insert etc.

Section A – Introduction

Section B – ACTD Table of contents

Section C – Administration documents (Application form, letter of authorization, certification documents, labelling, product data sheet, prescription information, etc)

Part II : Quality (for all category of products) – It should provide the Quality Overall Summary followed by the Body of Data.

Section A – Table of contents

Section B – Quality overall summary

Section C – Body of data

S – Drug substances

Part III : Non-clinical data (for innovator drug, new chemical entity and biotechnological products) – Part III should provide the Nonclinical Overview, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The documentation 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, Biological 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 III contain four sections

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

Section D – Nonclinical Study Reports

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Part IV: Clinical data (for innovator drug, new chemical entity and biotechnological products) – Part IV should provide the Clinical Overview and the Clinical Summary. The documentation of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products.

The overall organisation of the Common Technical Dossier is presented on the following in Parts:

Section A – Table of Contents

Section B – Clinical Overview

Section C – Clinical Summary

1. Summary of Bio-pharmaceutics 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 Reference