REGISTRATION OF INDIAN DRUG PRODUCTS IN OVERSEAS MARKET

Export :

- Export is selling the drugs ,pharmaceuticals, medical devices etc. to other countries crossing the geographical frontiers of the country.
- A good example is India selling the drugs to U.S.A and England.
- Export earns a country lot of foreign exchange and helps in tilting the balance of payment.

Import :

- When a country purchases drugs from other country and brings them in to the country crossing the geographical borders of the country it is called import.

General procedure for export

The export procedure includes several steps :-

1. Receipt of indent
2. Receipt of license for export
3. Procurement of goods.
4. Packing and labeling
5. Appointment of forwarding agent
6. Dispatch of goods.
7. Foreign customs permit
8. Shipping order
9. Export duty and shipment bill
10. Dock dues or challan
11. Loading the goods
12. Mate's receipt

13. Bill of loading
14. Marine insurance
15. Forwarding agent advice
16. Preparation of export invoice
17. Payment
18. Advice to importer

Export Regulation of India

Registration

- It was compulsory for every exporter to obtain an exporters' code number from the Reserve Bank of India before engaging in export.
- Registration with Regional Licensing: Authorities (obtaining IEC Code Number) The Customs Authorities will not allow you to import or export goods into or from India unless you hold a valid IEC number.
- For obtaining IEC number you should apply to Regional Licensing Authority in duplicate . Before applying for IEC number it is necessary to open a bank account in the name of your company / firm with any commercial bank authorized to deal in foreign exchange. The duly signed application form should be supported by the following documents:
- Bank Receipt (in duplicates)/Demand Draft for payment of the fee of 1,000 USD.

Cont.

- Two copies of Passport size photographs of the applicant duly attested by the banker to the applicants.
- A copy of Permanent Account Number issued by Income Tax Authorities. If PAN has not been allotted, a copy of application of PAN submitted to Income Tax Authorities
- The number should normally be given within 3 days provided the application is complete in all respects and is accompanied by the prescribed documents.
- An IEC number allotted to an applicant shall be valid for all its branches/divisions as indicated on the IEC number

Cont..

Acquire Export License

- **Exports free unless regulated:** The current Export Licensing Policy of the Government of India is contained in the new Import Export Policy and Procedures, 1997-2002 as amended .

- It may be stated that all goods may be exported without any restriction except to the extent such exports are regulated by the ITC (HS) Classifications of Export and Import items

Application for an Export License:

- An application for grant of export license in respect of items mentioned in Schedule 2 of ITC (HS) Classifications of Export and Import items may be made in the form given in Appendix-18A or 18B or 18C.

Compulsory Quality Control & Preshipment Inspection

- An important aspect about the goods to be exported is compulsory quality control and pre-shipment inspection. Under the Export(Quality Control and Inspection) Act, 1963 pharmaceutical products are subject to compulsory pre-shipment inspection.

- At times, foreign buyers lay down their own standards / specifications which may or may not be in consonance with the Indian standards. They may also insist upon inspection by their own nominated agencies. These issues should be sorted out before confirmation of order.

Particulars of the consignment intended to be exported. A crossed cheque/draft for the amount of requisite inspection fees or an Indian Postal Order.

- Copy of the Commercial Invoice.
- Copy of letter of credit.
- Details of packing specifications.
- Copy of the export order/contract, indicating that products are strictly according to the prescribed specifications

The certificate is issued in the standardised form which is aligned pre-shipment export document. (Three copies for exporter, original copy for customs use, the second copy for the use of the foreign buyer and the third copy for the exporter's use, fourth copy for Data Bank, Export Inspection Council, New Delhi and the fifth copy is retained with the agency for their own office record).

Common Technical Document

- The **Common Technical Document** (**CTD**) is a set of specifications for an application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States.
- It is an **internationally agreed** format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries.
- It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, US) and the Ministry of Health, Labor and Welfare (Japan).
- The CTD is maintained by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use(ICH).

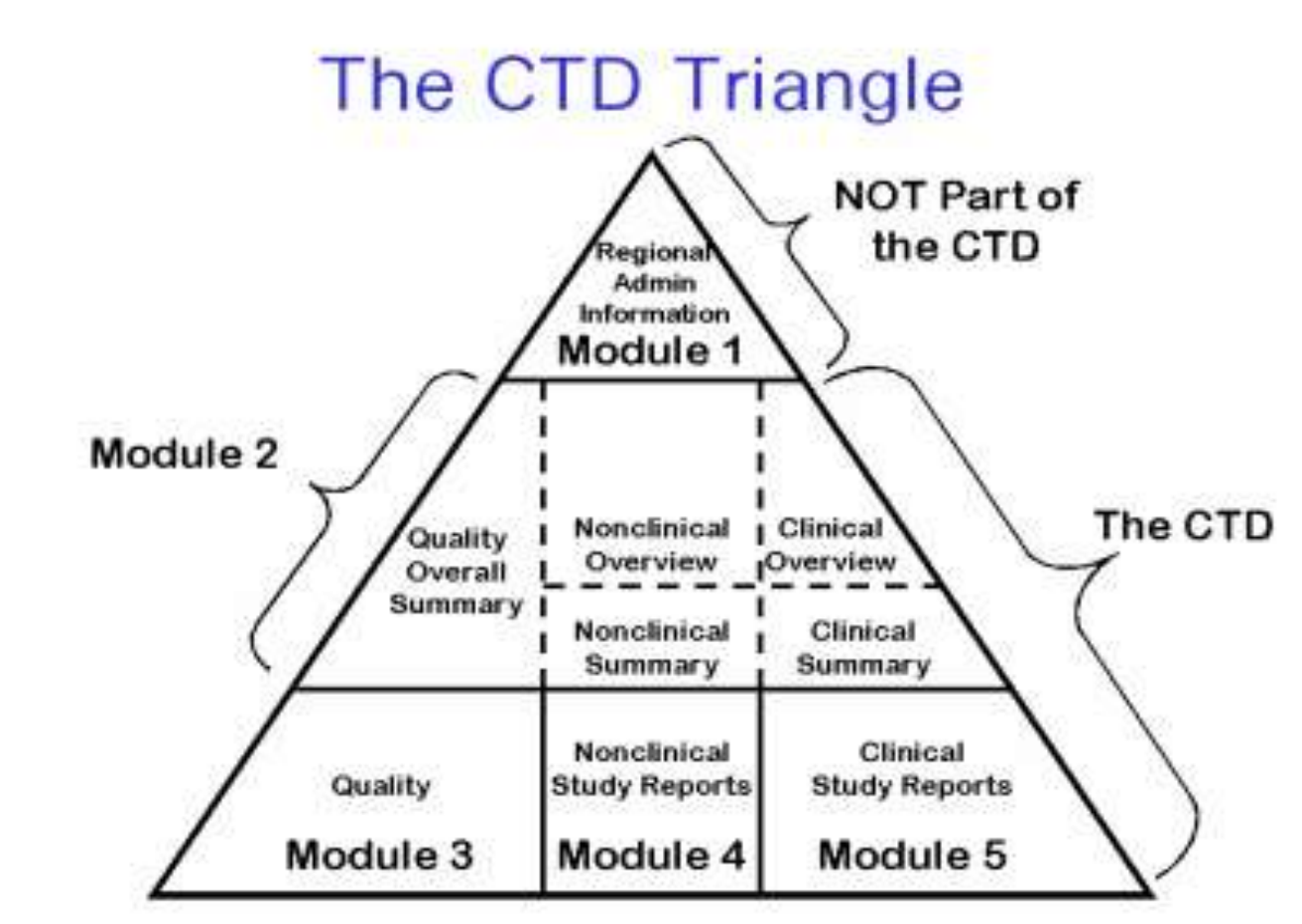
Subparts

- The Common Technical Document is divided into five modules:
  - Administrative and prescribing information
  - Overview and summary of modules 3 to 5
  - Quality (pharmaceutical documentation)
  - Preclinical (Pharmacology/Toxicology)
  - Clinical – efficacy and safety (Clinical Trials)
- After the United States, European Union and Japan, the CTD has been adopted by several other countries including Canada and Switzerland.
- The Paper CTD is destined to be replaced by its electronic counterpart, the eCTD

Structure of Common Technical Document

ICH CTD	ASEAN CTD	Description	Remarks
Module 1-Regional and Administrative Information	Part I	Contains documents that are specific to each region. This module is not part of CTD. Basically consists of administrative documents like Application form, legal documents (GMP, Licenses etc.), labeling etc.	Required for generics and New Drug
Module 2 - Overall Summary	Part II	This module summarizes the Module 3, 4 and 5. It includes Quality Overall summary, Non Clinical Overview and Summary and Clinical Overview and Summary. The summary provides reviewer the abstract of documents provided in the whole application	Required for generics and New Drug. For generics summary on Quality part only required
Module 3 - Quality		The documents related to Chemistry, manufacturing and Control of both Drug Substance and Drug Product is included in this module.	Required for generics and New Drug
Module 4 - Safety	Part III	Non Clinical Study Reports – Data on pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical product is provided.	Not required for generics
Module 5 – Efficacy	Part IV	Clinical Study Reports - A critical assessment of the clinical data and related reports is provided in this module.	Not required for generics except Bioequivalence study

The CTD Triangle



Electronic common technical document

- The **electronic common technical document** (**eCTD**) is an interface and international specification for the pharmaceutical industry to agency transfer of regulatory information.
- The specification is based on the Common Technical Document (CTD) format and was developed by the International Council for Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG)

Governing specifications

- An eCTD submission's structure is largely defined by the primary standard created by the ICH, the Electronic Common Technical Document Specification.
- However, additional specifications may be applied in national and continental contexts.
- In the United States, the Food and Drug Administration (FDA) layers additional specifications onto its requirements for eCTD submissions, including PDF, transmission, file format, and supportive file specifications.
- In the European Union, the European Medicines Agency's EU Module 1 specification as well as other QA documents lay out additional requirements for eCTD submissions.

Drug Master File

- The drug master file is provided in 21 CFR 314.20.
- Drug master file (DMF) is a set of documents submitted to food drug and administration (FDA) by a pharmaceutical manufacture.
- The drug master file may also provide information which may be confidential for the company.
- It may be required to regulatory authority for complete understanding of their product, facility, and the processes, systems, equipments and article used for various of process of manufacturing and quality assurance, or storage and distribution.
- The drug master file is used when two or more partners are engaged in developing and manufacturing of a drug product.
- The drug master filing allows a firm to protect its intellectual property from its partners while complying with regulatory requirements

- The drug master file is submitted by a pharmaceutical manufacturer to support various applications.
    i. Investigational new drug application (INDA)
    ii. New drug application (NDA)
    iii. Abbreviated new drug application (ANDA)
    iv. Export application
    v. Another DMF or amendments and supplements to any of these application

Contents of Drug Master File

1. Drug substance
2. Intermediates
3. Drug products
4. Excipients
5. Packaging materials
6. Flavors
7. Essence
8. Colorants
9. Substance used to make them
10. Stability data of drug products

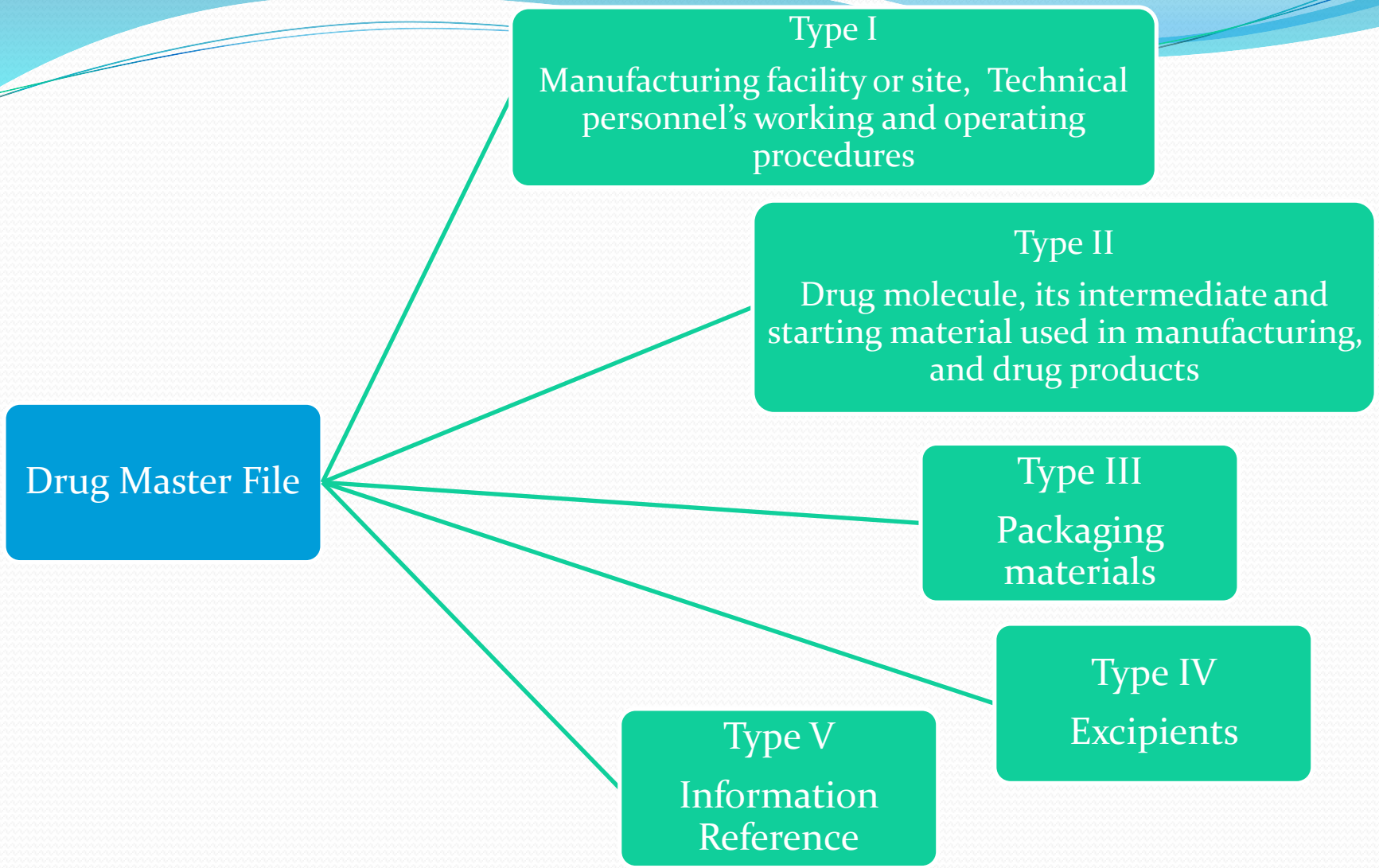


Fig: Classification of Drug Master File

Comparative Study of DMF in different Countries

Sr. no.	Requirement	US FDA	Europe	Japan	India	WHO
1	Regulatory Authority	Food And Drug Administration (FDA)	European Medicine Agency(EMA)	Ministry Of Health Labor And Welfare	Central Drug and Standard Control Organization (CDSCO)	WHO
2	Use Of DMF in Support of Application	IND, NDA,ANDA	MAA	PDMA	MAA	Prequalification Dossier Application
3	Mandatory	No	No	No	No	No
4	Provide Information	Drug Substance Intermediate, Drug Products , Flavors Etc.	Active Substance	Active Substance , Drug Substance	API, Drug Products, Flavors, Colorants, Etc.	API
5	Fees For Assessment	ANDA Case Only	No Fee	No Fee	No Fee	No Fee
6	Submission In CTD Format	Required	Required	Required	Required In Indian CTD Format	Required
7	Forms For DMF Filling	Not Applicable Except Type Ii DMF, Form FDA 3794	Not Applicable	Applicable Form No. 42	Not Applicable	Not Applicable
8	Language	English	English	English And Japanese	English	English
9	Electronic Submission	eCTD	eCTD	eCTD	eCTD	eCTD
10	DMF Number Assigned By Reviewers	Yes	No	Master File Registration Number	No	No
11	Approved/Disapproved by Regulatory Authority	Not Approved Only Accepted In Support Of Applications	Only Accepted	Only Accepted	Only Accepted	Only Accepted
12	Deficiency Letter	Applicable	Applicable	Applicable	Applicable	Applicable
13	Changes And Approved	Applicable	Applicable	Applicable	Applicable	Applicable
14	Appointment Of In-Country Care Taker	Applicable	Applicable	Applicable	Applicable	Applicable
15	Latter Of Authorization	Applicable	Applicable	Applicable	Applicable	Applicable
16	Closure Or Withdrawal	Applicable	Applicable	Applicable	Applicable	Applicable
17	Reactivation	Applicable	Applicable	Applicable	Applicable	Applicable

ASEAN Common Technical Dossier (ACTD)

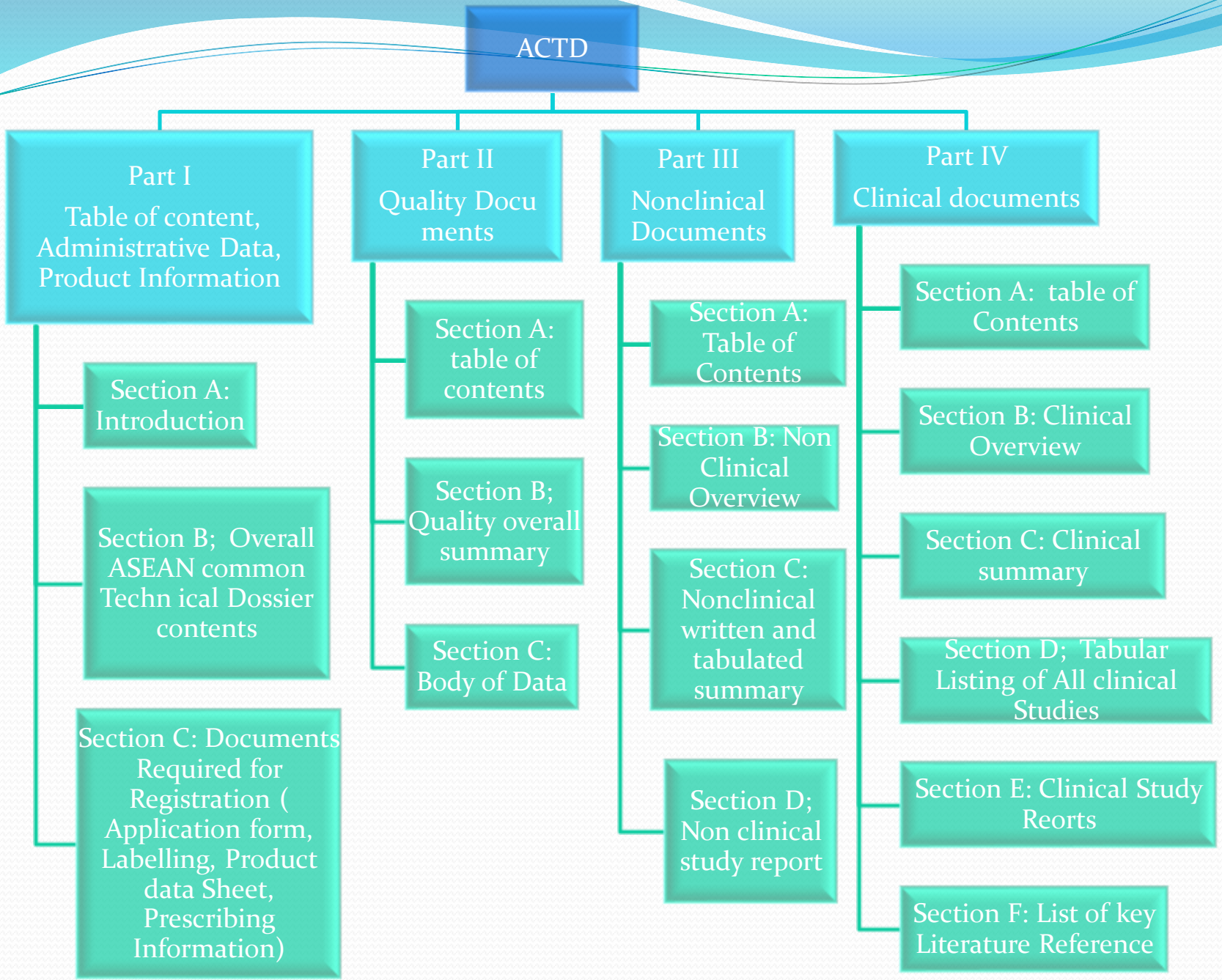
- This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use.

- This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration.

- Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.
- This guideline merely demonstrates an appropriate write-up format for acquired data.
- However, applicants can modify, if needed, to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results upon pharmaceutical registration.

Requirements/ Characteristics

- Trough the ACTD, display of information become unambiguous and transparent
- It helps the reviewer in quick review of 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 usedin each part.
- References should be cited in accordance with the 1979 Vancouver Declaration on Uniform requirements for Manuscripts Submitted to Biomedical Journals..


ACTD
Part I
Table of content, Administrative Data, Product Information
Section A: Introduction
Section B; Overall ASEAN common Techn ical Dossier contents
Section C: Documents Required for Registration (Application form, Labelling, Product data Sheet, Prescribing Information)
Part II
Quality Docu ments
Section A: table of contents
Section B; Quality overall summary
Section C: Body of Data
Part III
Nonclinical Documents
Section A: Table of Contents
Section B: Non Clinical Overview
Section C: Nonclinical written and tabulated summary
Section D; Non clinical study report
Part IV
Clinical documents
Section A: table of Contents
Section B: Clinical Overview
Section C: Clinical summary
Section D; Tabular Listing of All clinical Studies
Section E: Clinical Study Reorts
Section F: List of key Literature Reference

Scope of the Guideline

- This document is intended to provide guidance on the format of a registration application for drug products regarding ASEAN CTR (Association of Southeast Asian Nations Common Technical Requirements).
- This format is appropriate for NCE (New Chemical Entity), Biotech (Biotechnological Products), and G (Generics).
- To determine the applicability of this format for a particular type of product, applicant should consult with the appropriate National Regulatory Authorities.
- The “Body of Data” in this guideline merely indicates where the information should be located.
- Neither the type nor extent of specific supporting data has been addressed in this guideline and both may depend upon national guidance and or accepted leading international references (pharmacopoeias).