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Regulatory Pathway for Registration and Approval of Indian Drug Products in Overseas Market.

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Abstract:

Pharmaceutical products in India are being regulated under Drugs and cosmetics act, 1940 and rules 1945. India, mainly a generic hub and leading supplier of generic drugs worldwide, contributes to 70% of the market. Indian pharmaceutical exports include Intermediates, Drug formulations, API, Bulk drugs, Herbals, Biologics and Surgical. Registration of Pharmaceutical product or a drug is a process or a system where it subjects to evaluation of certain documents and need to conform to standards for approval thereby getting authority to sell in the particular market. This article covers the processes involved and requirements like import export code, technical documentation, filing and reviewing process of drug master file, certificate of pharmaceutical product, common technical document (CTD), eCTD and ACTD, for the registration and approval of Indian drug products in overseas market.

Key Words: Import Export Code, DMF, LOA, CTD, eCTD, Electronic Submission Gateway.

ABBREVIATIONS:

1. R & D- Research and Development.
2. API- Active Pharmaceutical Ingredient.
3. ICH- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.
4. WHO- World Health Organization.
5. IEC- Import Export Code.
6. DGFT- Directorate General of Foreign Trade.
7. GMP- Good Manufacturing Practices.
8. CTD- Common Technical Document.
9. eCTD - Electronic Common Technical Document.
10. ACTD- ASEAN Common Technical Dossier.
11. COA- Certificate of Analysis.
12. DCGI- Drug Controller General of India.
13. ADC- Assistant Drug Controller.
14. COPP- Certificate of Pharmaceutical Product.
15. DMF- Drug Master File.
16. MFR- Master Formula Record.
17. BMR- Batch Manufacturing Record.
18. BA/BE- Bioavailability/ Bioequivalence.
19. NDA- New Drug Application.
20. ANDA- Abbreviated New Drug Application.
21. LOA- Letter of authorization.
22. OTC- Over the counter drugs.
23. ESG- Electronic Submission Gateway.

INTRODUCTION:

India comes under Asian market. India, mainly a generic hub is the leading supplier of generic drugs worldwide (20 to 22 per cent of global volume). Indian pharma sector is the third largest by means of volume and thirteen largest by means of value. India is the leading country in global manufacturing and research hub for generic medicines which contribute 70% of the market [1].

Advantages for Indian Pharmaceutical Industry,

1. E government policies like Government of India's pharma vision 2020, which is having prior objective to make India a global leader in complete drug manufacturing.
2. Increasing investment by private sector for R & D.
3. Low cost of production and increasing expenses on R & D [2].

Indian pharmaceutical exports like Intermediates, Drug formulations, API, Bulk drugs, Herbals, Biologics and Surgical. Registration of Pharmaceutical product or a drug is a process or a system where it subjects to evaluation of certain documents and need to conform with standards for approval thereby getting authority to sale in that particular market or area [3].

Not only Indian drugs, each and every pharmaceutical products needs to be registered and approved by the regulatory authority. Before the products needs to be registered, the manufacturing company needs to be registered and licensed for the same.

Overseas markets means the foreign countries, these countries we call in regulatory affairs as markets. They are classified as,

i. Regulated markets (For example: USA, Canada, Europe, Australia, Japan)
ii. Semi regulated markets (For example: Asian, ASEAN, Gulf countries, African countries etc.)

The registration requirements will differ from country to country. Regulated markets have stringent regulations which is harmonized by ICH. But the semi regulated countries does not have stringent regulation but asks for general requirements related to drug product and drug substance. But the regulated markets have their own checklist for drug substance, drug product etc. [3].

While filing an application for regulated market, one has to read and comply with the guidelines as per the country requirements related to documents required, language, packaging and labelling instructions etc.

So that the company should carefully prepare the documents and files while registering in each country. For all these preparation, regulatory affairs team plays an important and significant role and acts as link or connection between pharma industry and the regulatory bodies. Registration of the drug does not require more documents and time, it is immediate process it takes maximum 6 months, minimum 1 month. Whereas approval takes more than 6 months and even a year also depending upon the country, dossier review process and queries.

So we can say registration is easy and approval process is difficult because registering a drug product is nothing but recoding the name of the product in official list just to identify that drug product. Whereas approval is nothing but saying that the drug product is safe and effective for intended disease and acceptable for human use in terms of quality, safety and effectiveness.

As mentioned above, regulated and semi regulated markets are there. Here in some countries like south East Asian countries, applicant can sale the drug product once the product is registered. But in western countries, applicant needs to get approval (Marketing authorization) prior to sale the drug product. For this they might come for GMP inspection/ audit etc.

Regulated countries have clear cut guidelines and one should comply with that. To approve the drug in overseas market people think only the 5 modules of CTD are important but some legal formalities are there which the proprietor will consider as important for export purpose. In general people knows only about the CTD module but beyond that things which we don't know which is mandatory to know by the proprietor.

India is one of the highest number of USFDA approved plants. Indian drugs are exporting to more than 200 countries [4]. For the Registration, approval and Export of drugs from India to overseas market one has to understand and comply with the Drugs and Cosmetics Act 1940 and Rules 1945.

Total export of medicinal and Pharmaceutical products in India [5]: The below table demonstrates the total export of products in rupees year wise.

TABLE 1- Total export of medicinal and pharmaceutical products in India.

Year	Export (Rupees in crore)
2013-14	90,356.00
2014-15	94,350.00
2015-16	1,10,522.77
2016-17	1,12,915.48

PROCEDURE FOR EXPORT OF PHARMACEUTICAL PRODUCTS

Indian products needs to be registered and approved prior to export. Export means selling of the drugs and pharmaceuticals to other countries without trade barrier and crossing the geographical frontier.

Rules and acts responsible for import and export of pharmaceutical products [6]:

1. Drugs and Cosmetics act, 1940 and Rules, 1945.
2. The Drugs (Prices Control) order, 1995.
3. Medicinal and Toilet Preparation act, 1956.
4. Pharmacy act, 1948
5. Narcotic and Psychotropic Substances act, 1985.
6. Drugs and Magic Remedies act, 1954.

Documents required for export of drugs from India:

1. Covering letter.
2. Import export code Number (IEC) given by DGFT.
3. Purchase order.
4. Manufacturing license.
5. Performa invoice.
6. Indent.
7. Custom clearance certificate.
8. Registration certificate.
9. Certificate of Analysis (COA).
10. GST
11. Consignment sample.
12. Pre-shipment sample.
13. Department of Economic Affairs [7].

Flow chart for export of pharmaceutical products from India: The figure below explains about the steps involved in export of pharmaceutical products from India.

FIGURE 1. Flow chart for export of pharmaceutical products from India

Steps involved in export of Pharmaceutical products:

1. Apply for IEC number.
2. Get the customers means contact the countries interested in importing the drug.
3. Register the drug product in the country where you are going to export.
4. Get the DCGI approval for exporting.
5. Finalize the shipping method.
6. Receive the purchase order from the country which is importing and send invoice with complete product details.
7. Sign the contract with the agency of the importing country.
8. Pre-shipment inspection.
9. Export of the product.

Requirements to apply for IEC:

- Current bank account
- Pan card
- IEC Application fee receipt (Rs.250)

✓ IEC number given to an applicant will be remain same for all the branches/ division.

✓ When exporting to Overseas markets one should be carefully manufacture the products and comply with all the standards of the importing country without fail in production, packaging, labelling instructions as approved by the importing country.

✓ Inspection is done at various stages of the manufacturing. The exporter should register his/ her facility/ unit as "Export worthy".

✓ Inspection will be done the approved and notified export inspection agency time to time and Inspection reports should be maintained carefully.

Once the applicant get order copy and confirmed invoice the product is ready to export but before that an important stage has to pass that is Quality control pre-shipment inspection. Once the product is ready for dispatch it has to be inspected by the Assistant Drug Controller (ADC) and should get ADC clearance certificate. ADC will verify all commercial documents such as,

- Copy of commercial invoice.
- Copy of letter of credit.
- Details of packaging specifications.
- Copy of contract order.
- License.
- Certificate of Pharmaceutical Product (COPP)
- Certificate of Analysis (COA).
- Pre-shipment sample.

On the time of export, ADC will verify all the necessary documents and check the Samples given. Usually the ADC sample will be 5. If he gets ant doubt he may asks for consignment sample and he will check and reseal it and issue ADC clearance certificate and customs clearance certificate. Thereby ready for export.

Technical Documentation

Documentation is the Essential and crucial part in any of the company. In pharma we can say ***"If it is not documented, it has not done"***. Documentation is an evidence to show or to prove that the things have done accordingly. Quality assurance documents are the heart of the company.

Technical documents are

- Master Formula Record (MFR).
- Batch Manufacturing Record (BMR).
- Batch Packaging Record (BPR).
- Certificate of Analysis (COA).
- Certificate of Pharmaceutical Product (COPP).
- Product specifications.

While registering the Indian product in overseas market RA team should be carefully check, verify all the documents for the genuinity, quality and uniformity from batch to batch and to avoid delay in the approval process.

Documentation flow chart:

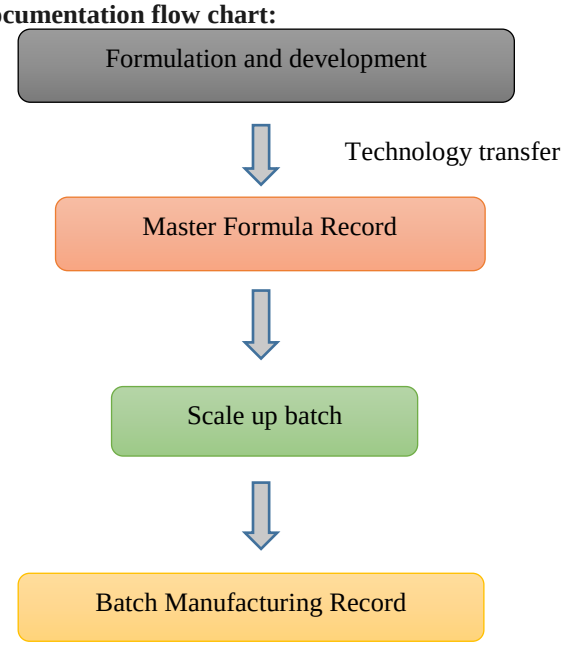


FIGURE 2. Documentation Process-Flowchart.

Master Formula Record (MFR):

MFR is a master document which contains detailed information about the product, process etc. MFR is prepared by the Formulation and Development team which is called technology transfer. By this master document BMR and BPR prepared.

Contents of MFR:

1. **Product details:**
   - Name, address, logo of the manufacturing company.
   - Product name.
   - Dosage form.
   - Brand name.
   - Generic name.

- Product code.
- Product description.
- Label claim of all ingredients used.
- Batch size.
- Pack size.
- Shelf life.
- Storage conditions.
- MFR number and date.
- Supersede number of MFR and date.
- Effective batch number.
- Checked, verified and authorized by production and QA head [8].

2. **Flow chart:**
   - Steps involved in the manufacturing process and flow chart representing the material movement from dispensing to the finished product to packaging and to the store.
3. **Equipment:**
   - List of equipment required for the manufacture of the product with the capacity
4. **Special instructions:**
   - Warnings and precautions related to manufacturing process should be clearly mentioned.
   - Quantity to be added should be mentioned.
   - Time interval and overages to be added to be mentioned clearly.
   - Name of the ingredient with tests and specification limit as per IP, BP and USP.
5. **Calculations:**
   - Quantity to be added to get 100% final product.
   - It can be done by using water content or LOD to get 100% potency.
6. **Manufacturing process:**
   - It should include all the steps involved the manufacturing process like sifting, milling, granulation, mixing, blending, lubricating, compression, coating, filling, if necessary filtration with environmental conditions such as temperature, humidity, storage to be maintained with time.
7. **Packaging process:**
   - Details of packaging materials used.
   - Line clearance, batch reconciliation of the packing material.
8. **Yield:**
   - It includes theoretical yield, Practical yield and acceptance limit of the batch [9].

Batch Manufacturing Record (BMR): Once the Master formula is prepared, pilot batch will be started to validation and BA/BE studies, upon getting the report from the pilot batch BMR will be prepared which will be used for commercial batch manufacturing.

Contents of BMR:

- Name of the product, Batch number, revision number, effective date.
- Product details like Type of the product, dosage, shape of the drug.
- Batch size and Total number of tablets or capsules.
- Pack size and packaging Instructions.
- Storage instructions.
- Production batch record issuance.
- Reference documents i.e., SOP's such as Dispensing of the product, temperature and humidity monitoring, material weighing, cleaning procedure, use, operation and cleaning of the equipment.
- List of raw material along with quantity required.
- Equipment description, calibration certificate etc.
- Area clearance- step by step cleaning of the equipment and area.
- Production procedure- Instruction for each step of the production from dispensing to dispatch.
- Calculation of yield.

$$\text{Yield} = \frac{\text{Weight of tablets}}{\text{Weight of raw materials}} \times 100$$

$$\text{Finished product yield} = \frac{\text{No. of goods produced in process+Rejects+Samples+Returned}}{\text{No. of goods received at the start of procedure}} \times 100$$

- Post production review- Complete batch has been reviewed for the completeness and accuracy in the entries for Good Documentation Practices.
- Product release- the product should comply with the finished goods specifications and released to market [10].

Certificate of Analysis (COA):

COA will be issued to prove the purity of the product. The Laboratory where the testing will be done should be approved by the WHO and should comply with the Good Laboratory Practices. COA will be issued to each batch to show that the product is uniform from batch to batch. Here the received products will be tested or analyzed for the presence of impurities.

Contents of COA:

- Name and address of the laboratory where the analysis will be carried out.
- Registration number of COA.
- Name and description of the product (quantity received, grade, batch number etc.)
- Batch for which certificate is issued-manufacturing date and expiry date.
- Name of the tests performed and the acceptance limit.
- Results of tests performed.
- Date on which certificate issued.
- Signature of the person or authorized person.

Model COA [11]:

Certificate of Analysis for API, Drug product, Excipients.

Registration number of sample or certificate:

Name and address of laboratory testing the sample:

Sample information

Name of product (INN, brand name(s), etc.):

Dosage form (if applicable):

Marketing authorization number (if applicable):

Description (appearance of container and contents):

Batch number(s):

Required storage conditions:

Date received:

Date of manufacture:

Expiry date (for medicinal products) or retest date (for starting materials or excipients):

Name and address of original manufacturer:

Telephone: Fax:

Name and address of repacker and/or trader (if applicable):

Telephone: Fax:

Test procedure (reference Result (numerical Acceptance criteria to test procedure) result) (limits) (if applicable) (if applicable)

A. Tests performed on samples from batch for which certificate is issued

B. Tests performed as part of periodic statistically based testing program

Conclusions: Compliance with acceptance criteria: yes No

Date of test performed/finalized:

Name and address of head of laboratory/authorized person:

Telephone: Fax: Signature:

Explanatory notes:

1. Statement of expected conditions of shipping, packaging, storage and distribution, deviation from which could render the certificate invalid.
2. Indicate if the results were obtained from periodic statistically based testing.

References:

Important note: The product is highly costly and effective but when it is not certified for its purity, it is valueless [12].

FIGURE 3. Model COA.

Certificate of pharmaceutical Product (COPP):

COPP is a certificate issued in the format of WHO by the National Health Authorities. COPP will be issued by the Exporting country upon request from the applicant.

It will be issued for each product for each country. Same COPP cannot be used for all the markets.

When the proprietor wishes to commercialize his/ her product in overseas markets, he/ she has to apply for COPP. Upon requisition the National Health Authority of that country will come and inspect the facility according to the WHO norms there by issue COPP [13].

Model COPP:

CERTIFICATE OF PHARMACEUTICALS PRODUCT 1

Certificate No: Valid Up to:

This certificate conforms to the format recommended by the World Health Organization
No. of Certificate:
Exporting (Certifying) country:
Importing (requesting) country
1-Name and dosages form of product:
1-1Active ingredient(s) 2 and amount (s) per unit dose :
Composition4:
Ingredients: Starch] micro crystalline cellulose, lactose, methyl paraben, talc, magnesium stearate, sodium starch glycoate, sillicon dioxie, isopropyl alcohol, PVPK-30 and purified water.
1.2 Is this Product licensed to be placed on the market for use in the exporting country?5
1.3 Is this Product actually on the market in the exporting country?

2A
A.1 Number of product licensed7 and date of issue:
A.2 Product-license holder:
A.3 Status of product-license holder:8

(A) (B) (C)
A.3 1 For Category B and C the name and address of the Manufacturer producing the dosage form are:9
A.4 Is summary basis of Approval appended ? 10
A.5 Is the attached, officially approved product
In formation complete and consonant with the licence?

3.0 Does the certify Authority arrange for periodic inspection of the manufacturing plant in which the dosages form is product.
If no or not applicable proceed to question 4.
3.1 Periodicity of routine inspection: At least once in a year:
3.2 Has the manufacturer of this type dosage form been inspected?
3.3 Do the facilities and operation conform to GMP as recommended by the World Health Organization? 15
4.0 Does the information submitted by the applicant satisfy the certifying authority on all manufacture of the Product. If no, explain :
Address of certifying authority:
Drugs Licensing Cum controlling authority,
Directorate General of Medical Health Service,
107 Chandar Nagar. Dehradun (Uttrakhand)

Telephone Number: Name of Authorized Person

FIGURE 4. Model COPP.

Drug Master File (DMF)
DMF is a confidential document for API (Active Pharmaceutical Ingredient) submitted to the regulatory body for the approval process. In fact there is no regulations to file a DMF. It is not reviewed on receipt as like dossier and DMF's are neither approved nor disapproved.
It has divided into 2 parts

1. **Open part (Applicant's part):** Contains all the required information related to method of manufacture and brief outline of method of manufacture, potential impurities, manufacturing system etc.
2. **Closed Part (Restricted part):** Contains Confidential information on the manufacture of API like Extraction, validation, process, solvents

used, reactions, temperature, conditions, critical steps in manufacture etc. [14].

Apart from this DMF is divided into 5 types

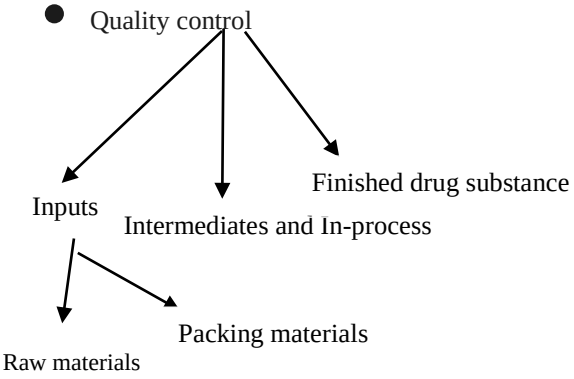
1. Type I: Plant information (No more a part of DMF)
2. Type II: Drug substance, drug products, intermediates and materials used in manufacturing.
3. Type III: Packaging materials.
4. Type IV: Excipients or additives.
5. Type V: FDA accepted reference information [15].

✓ **Type I DMF:** It contains information about the plant information like

- Manufacturing site.
- Equipment capabilities.
- Operational layout.
- Corporate headquarters.
- Site Address.

✓ **Type II DMF:** It includes information about all the significant steps in manufacturing and control of drug substance and intermediates.

- Manufacturing sections.
- Quality control



- Validations.
- Stability data.
- Impurities.
- Packaging and labelling.

✓ **Type III DMF:** It contains detailed information of the packaging material used. i.e.,

- Intended use of the packing material.
- Composition of the packing material.
- Name of the suppliers.
- Specifications.
- Toxicological data on the packing material.

✓ **Type IV DMF:**

- Excipients used in the manufacture of the product.
- Compendia excipients usually not reviewed so DMF is not required.

Differences between the Application (Dossier) and DMF [16]:

TABLE 2- Differences between Dossier and DMF.

SL.NO	Application (Dossier)	DMF
01	Must be filed by applicant	Not mandatory to file DMF
02	Comes under regulatory status	No such regulations
03	Each applications and their supplements are entered in common database	DMF's are entered in separate database as per the type
04	Submitted to intended review division	Submitted to Regulatory body
05	Review procedure is different than that of DMF	Reviewed only when referenced with NDA/ ANDA applications
06	Approval timeline is there	No approval timeline

DMF Filing System:

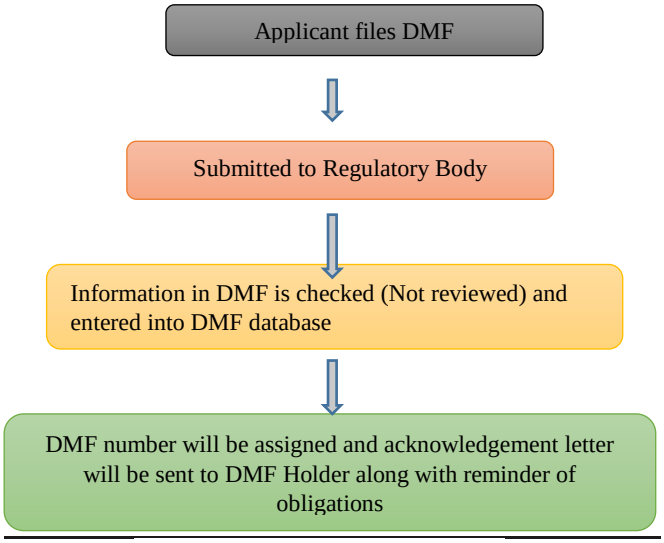


FIGURE 5. DMF Filing Process.

DMF Reviewing System:

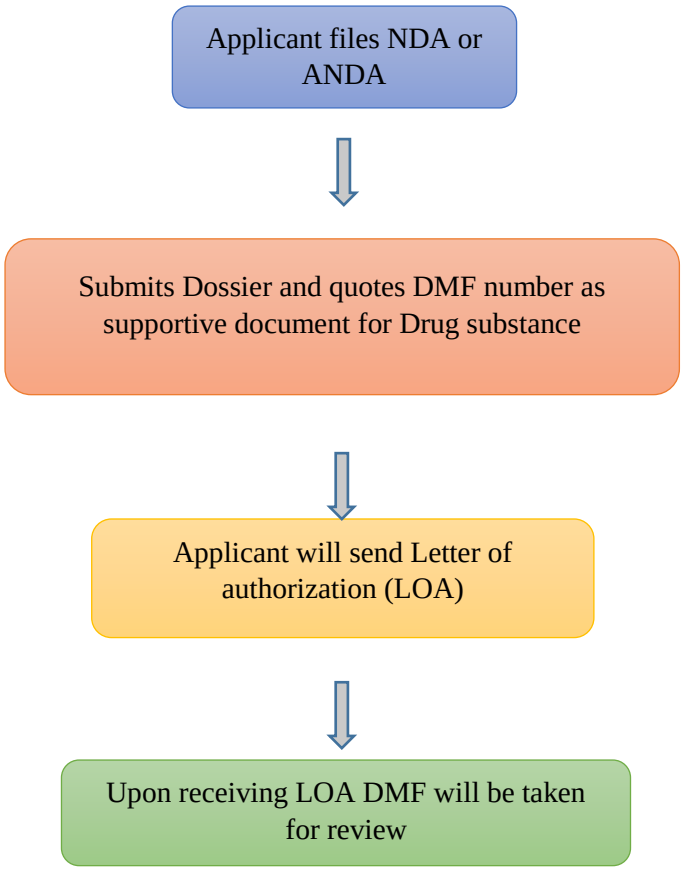


FIGURE 6. DMF Reviewing Process.

Important points to be noted in DMF

- **Holder:** The person who submits a DMF.
- **Agent:** The person or company who represents the DMF holder.
- **Applicant:** The person or company who use the DMF for referencing in the NDA or ANDA submission.
- Agent will be appointed by the DMF holder to file DMF and to communicate with the regulatory body.
- Major contents of DMF are, Transmittal letter, Administrative information of DMF holder, Technical information of the product.
- **Reason to file DMF:** DMF filed for API's which acts as supportive document while submitting NDA or ANDA.
- **Obligations of DMF Holder:**
  - Should submit any changes as amendments.
  - Should notify regulatory body of change in holder name or address.
  - Should notify regulatory body of change in agent or representative.
  - Issue LOA to each applicant who intends to use that API.
  - Should submit annual report to regulatory body on the anniversary date of DMF filing.
- Symbols used in finding the status of DMF
  - **"A"-** Active, (DMF is acceptable and up to date)
  - **"I"-** Inactive
  - **"N"-** Not assigned DMF number
  - **"P"-** Pending filing review
- DMF for OTC drugs and compendia excipients are never reviewed.
- DMF cannot be registered or approved, it just entered in DMF database.
- Letter of Authorization (LOA) shall be send by DMF holder to regulatory body (2 copies) and NDA/ANDA applicant (1 copy).
- DMF number will be assigned only when the regulatory body receives 2 copies of DMF along with the cover letter.
- If any deficiencies found in DMF it shall be communicated with the holder and the applicant will be just notified.
- DMF shall be registered immediately but not reviewed.
- Regulatory body will issue termination letter to DMF holder when there is no communication for 3 consecutive years (i.e., no annual report) regarding the DMF.
- If annual report is not send, it causes delay in the review process of the filed NDA and ANDA.
- Regulatory body shall send a reminder letter called overdue notice letter (ONL) to DMF holder, if there is no response from the holder within 90 days, one copy will be send to federal center and the other will be destroyed [17].
- Now a days DMF filing also become electronic submission and can convert existing Paper MF's to eCTD [18].

COMMON TECHNICAL DOCUMENT (CTD).

Common Technical Document is an essential document to be submitted to regulatory body as a supportive list of leaflets attached with the registration applications for pharmaceuticals to get market authorization. Mainly CTD tells about the format for the data.

Some of the overseas countries with their regulatory bodies are as follows: [19, 20]

TABLE 3- List of Countries with Regulatory Bodies.

Sl. No	Country Name	Regulatory Body
01	India	Central Drug Standard Control Organization (CDSCO)
02	USA	Food and Drug Administration (USFDA)
03	European Union	European Medicines Agency (EMA)
04	Canada	Health Canada
05	Australia	Therapeutic Goods Administration (TGA)
06	Japan	Pharmaceutical and Medical Device Agency (PMDA)
07	China	National Medical Products Administration (NMPA)
08	South Africa	South African Health Products Regulatory Authority (SAHPRA)
09	Singapore	Health Science Authority (HAS)
10	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)
11	Brazil	Agencia National De Vigilancia Sanitoria (ANVISA)
12	Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
13	Thailand	Thai FDA
14	Russia	Ministry of Health (MOH)
15	Cambodia	Department of Drugs and Food
16	South Korea	Ministry of Food and Drug Safety (MFDS)
17	Philippines	Food and Drug Administration (FDA)
18	Indonesia	National Agency of Drug and Food Control (NADFC)
19	Saudi Arabia	Saudi Food and Drug Authority (SFDA)
20	Myanmar	Food and Drug Administration (FDA)

CTD Triangle [21]**:**

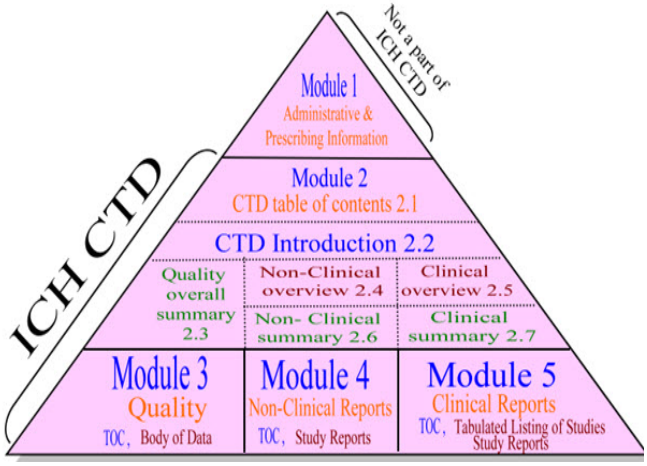


FIGURE 7. CTD Triangle

It is common that RA expert knows the documents to be submitted while getting approval for any drug product. But CTD mainly tells about the organization of the information in order. CTD documents should be clear, unambiguous and transparent. Accordingly it is having 5 modules.

1. Module 1: Administrative and prescribing information
2. Module 2: Common Technical Document Summaries (Quality Overall summary)
3. Module 3: Quality Data
4. Module 4: Non- Clinical study reports
5. Module 5: Clinical Study reports

- Module 2 is Question based summary- This should not exceed 40 pages if it is biotech product or product containing more complex process information can be longer but should not exceed 80 pages of text excluding tables and figures.
- Module 3 documents should be as described in M4Q.
- Module 4 documents should be as described in M4S.
- Module 5 documents should be as described in M4E.

The Format should be clear in such a way that it should be clearly readable and understandable

- Font size: 12.
- Font: Times New Roman.
- Page layout: For EU and Japan – A4 paper
  For U.S.A – 8.5 × 11
- The left hand margin should be large enough so that the information should not be hidden or unclear after binding.
- Acronyms and abbreviations should be defined at the first time they used in each module [22].

Note:

- **CTD** dossier should be detailed and easily acceptable by the regulatory authority.
- The documents should be arranged in such a way that it can be easily reviewed by the reviewer.
- Documents submitted should be signed and dated.
- Labelling should be clearly mentioned as per the country regulatory guidelines.
- Required documents should be submitted according to the checklist to avoid rejection of the application or queries which in turn speed up the review process and approval.
- The justification for certain tests should be clearly mentioned and supportive documents should be attached.
- Once dossier is prepared before sending it has to checked and verified for any mistakes.

- While in clinical study report (Module 5) CRF, all study reports should be attached.
- BMR is required not MFR.
- Some countries asks for validation certificates that should be up date.
- Changes done in any batches should be notified and justified.
- Amendments, supplements should be submitted to regulatory body.
- Annual reports should be submitted.

ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD)

eCTD is electronic Common Technical Document, an electronic format where the information and document is submitted to regulatory body electronically by using a software. Some of the eCTD software are Pharm ready, Edios etc.

eCTD submission is for applications, amendments, variations, supplements, reports, Master formulae etc.

Understanding the eCTD format and applying successfully in submission is the biggest hurdle. While sponsor or the applicant may face problem when the documents does not fit into the format because the application or submission shall be bounced back known as technical rejection [23]. Here the main thing to be noted is the software used should be validated.

Requirements of eCTD:

1. Copy and paste.
2. Verifying and printing documents.
3. Document Annotation.
4. Export of information to databases.

Modular Structure of eCTD:

Overall structure of submission is defined by XML eCTD DTD (Document Type Definition). The XML file is the backbone for eCTD submission. The purpose of XML backbone is,

1. To manage meta-data of the entire submission like information about submitting and receiving organization, manufacturer, ID etc. and documents.
2. To form Comprehensive table of contents and provide corresponding navigation aids.

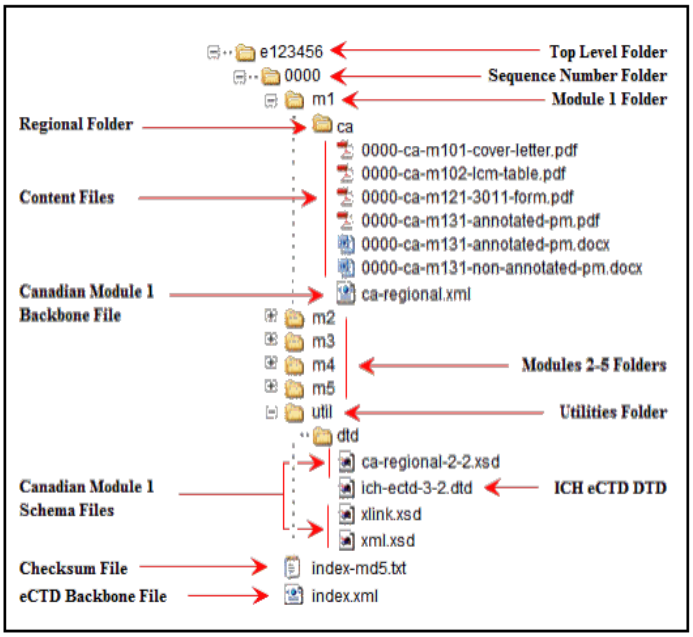
Common Formats of eCTD:

1. Narrative: Portable Document Format (PDF) [Calibri 12]
2. Structure: Extensible Markup Language (XML)
3. Graphic: Use PDF, whenever PDF is not supporting, use Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG) and Graphic Interchange Format (GIF).
4. Font size 9 and 10 are suggested for tables.

Folder and File Naming Conventions:

- The maximum length of name of a single folder or file is 64 characters.
- Folder name should be written in lower case only. For example: Study Report 1 should be written as *study-report-1.pdf* [24].
- File should not exceed more than 2 GB
- Hyperlink- "Insert cross- Reference" feature in MS word is known as Hyperlinking
- Hyperlink improves overall quality and accuracy of the complete file.

- eCTD will be submitted in Electronic Submission Gateway (ESG)
- All documents should be scanned properly which will help to recognize the file clearly.
- Scanning will be done by using OCR software (Optical Character Recognition).



Screenshot of the folder structure [25]:

FIGURE 8. eCTD Folder Structure.

Advantages of eCTD:

A. Reduced cost in producing, checking and storage of paper documents.
B. Easy to Review
C. Faster process.
D. Greater search functionality
E. Easy to manage dossier life cycle
F. Can reuse the documents
G. Easy to do any amendments
H. Reviewer friendly in comparing the dossier with amendments.
I. Several people can read the documents at the same time.
J. More predictable format
K. More convenient for exchange of information.
L. Time saving process [26].

ASEAN Common Technical Document (ACTD)

ASEAN (Association of South East Asian Nations) Common Technical Document (ACTD) is a structured document for the registration of pharmaceuticals in ASEAN countries.

ASEAN countries and their regulatory bodies,

1. Indonesia- National Agency of Drug and Food Control (NADFC).

2. Vietnam- Drug Administration of Vietnam.
3. Thailand- Thai FDA.
4. Singapore- Health Science Authority (HAS).
5. Malaysia- National pharmaceutical Regulatory Agency (NPRA).
6. Philippines- Food and Drug Administration (FDA).
7. Brunei- Ministry of Health.
8. Cambodia- Department of Drugs and Food.
9. Myanmar- Food and Drug Administration (FDA).
10. Laos- Food and Drug Department [27].

ACTD includes 4 parts

1. Part 1: Table of Contents, Administrative data and Product information.
2. Part 2: Quality Document.
3. Part 3: Non- clinical Document.
4. Part 4: Clinical document.

Organization of ACTD:

1. **Part 1: Table of Contents, Administrative data and Product information.**
   Section A: Introduction.
   Section B: Overall ASEAN CTD Table of contents.
   Section C: Documents like registration application, product data sheet, prescribing information and labelling.
2. **Part 2: Quality Document**
   Section A: Table of Contents.
   Section B: Quality Overall summary.
   Section C: Body of Data.
3. **Part 3: Non- clinical Document**
   Section A: Table of Contents.
   Section B: Non- clinical Overview.
   Section C: Non-clinical written and tabulated summaries.
   - Table of Contents.
   - Pharmacology.
   - Pharmacokinetics.
   - Toxicology.

   Section D: Non- clinical Study Reports,
   - Table of Contents.
   - Pharmacology.
   - Pharmacokinetics.
   - Toxicology.
4. **Part 4: Clinical document**.
   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 References.

The registration fee will differ from country to country. The documents shall be submitted to the particular regulatory authority. The documents related to drug substance and drug products and new chemical entity will be according to the country requirements [28].

Differences between CTD/ eCTD/ ACTD [29]:

TABLE 4- Differences Between CTD, eCTD and ACTD.

SL.NO.	**CTD**	**eCTD**	**ACTD**
01	Common Technical Document	Electronic Common Technical Document	ASEAN Common Technical Document
02	Paper submission	Electronic (Using Software)	Paper or Electronic
03	Tedious and Difficult Review process	Faster review process	Depends upon the country
04	Bulk and Large documents	XML files storage will be in GB	Large documents
05	Includes 5 modules	5 modules	Includes 4 parts
06	Cross references include CTD section number	Cross references include hyperlink and book mark	Cross references include CTD section number
07	CTD navigation through TOC and Volumes	eCTD navigation by XML backbone	CTD navigation through TOC and Volumes
08	Paper volume- A4	Layout shall be A4 or US letter size	Paper volume- A4
09	Submitted in Binders or boxes	Submitted on CD or DVD or e-mail or Portal.	Submitted in Binders or boxes
10	Compiled electronically with volumes, tabs and slip sheets and then printed to paper.	Compiled electronically with documents in folders	Compiled electronically with volumes, tabs and slip sheets and then printed to paper.

CONCLUSION:

Registration and approval phase is very crucial part in commercialization of the pharmaceutical products. As per the regulatory point of view, one has to prepare and compile the documents as per CTD module. But other requiremets like import export code, Drug master file, technical documentation are the supportive documents to be submitted to the regulatory body for review and approval. In this article we have covered all the certification process suach as COA and COPP also actual process like DMF filing and revieing system, arangements of floders in eCTD structure and differences between the CTD, eCTD and ACTD module for better understanding in regulatory point of view.

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