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# BP804ET

## PHARMACEUTICAL REGULATORY SCIENCE

B.Pharm 8th Semester

# UNIT - III

## REGISTRATION OF INDIAN DRUG PRODUCT IN OVERSEAS MARKET

Procedure for Export | Technical Documentation | DMF | CTD | eCTD | ACTD

## SYLLABUS COVERAGE — UNIT III

**Topics: Registration of Indian drug product in overseas market**
Procedure for export of pharmaceutical products, Technical documentation, Drug Master Files (DMF), Common Technical Document (CTD), electronic Common Technical Document (eCTD), ASEAN Common Technical Document (ACTD)research.

# Introduction — Indian Pharma in the Global Market

India is recognized as the 'Pharmacy of the World', supplying approximately 20% of global generic medicine volumes by quantity. India exports pharmaceutical products to over 200 countries, with export revenue of approximately USD 27.9 billion in 2023-24. To register and market drug products in overseas markets, Indian manufacturers must navigate complex, country-specific regulatory requirements and prepare technical documentation in standardized formats.

> *Registering an Indian drug product overseas requires mastery of technical documentation (CTD/eCTD/ACTD), Drug Master Files (DMFs), and country-specific regulatory procedures, while maintaining GMP compliance recognized by the target market.*

| India Pharma Export —Facts | Details |
|---|---|
| Export Value (2023-24) | Approximately USD 27.9 billion; target USD 65 billion by 2030 |
| Export Destinations | USA (~31%), UK, Russia, South Africa, Canada, Brazil, Germany, Australia, ASEAN countries, Africa |
| Products Exported | Formulations (~70%), APIs/Bulk drugs (~30%), Biologics, Biosimilars, Vaccines |
| Regulatory Compliance Required | USFDA (21 CFR), EMA (EU GMP), WHO-GMP (WHO-PQ), TGA (Australia), Health Canada, ANVISA (Brazil) |
| Export Promotion | PLI Scheme, PharmExcil (Pharmacy Export Promotion Council), EEPC, APEDA (herbal products) |
| GMP Standards | Schedule M (India), WHO-GMP, EU-GMP, US cGMP (21 CFR 210/211) depending on target market |

# Procedure for Export of Pharmaceutical Products

The export of pharmaceutical products from India is governed by the Drugs and Cosmetics Act, 1940 (Sections 12, 12A), Foreign Trade Policy, and Customs Act, 1962. Indian manufacturers must also comply with the importing country's regulatory requirements.

## Governing Laws for Pharma Export from India

- Drugs and Cosmetics Act, 1940 — Section 12 and Rules 68-78 govern export of drugs
- Foreign Trade (Development and Regulation) Act, 1992 and Foreign Trade Policy (FTP 2023)
- Customs Act, 1962 — Export procedures at ports
- FEMA (Foreign Exchange Management Act) — Repatriation of export proceeds
- DGFT (Directorate General of Foreign Trade) — IEC (Import Export Code) mandatory for all exporters
- PharmExcil — Apex export promotion council for pharmaceutical and allied products

## Types of Drug Export from India

| Type of Export | Requirements |
|---|---|
| **Export per Indian Standards** | Drugs conforming to Indian standards (IP/BP/USP); Section 12 D&C Act; Certificate from Licensing Authority; Labeling per importing country |
| **Export per Importing Country Standards (not standard in India)** | DCGI approval required; Different standards/excipients may be used; Special manufacturing license endorsement needed |
| **WHO-Certified Exports (WHO-PQ)** | Certificate of Pharmaceutical Product (CPP) from CDSCO in WHO format; for LMIC countries and UN procurement agencies |
| **Export of Narcotic/Psychotropic Substances** | NCB (Narcotics Control Bureau) permit under NDPS Act; additional INCB (International Narcotics Control Board) authorization |
| **Re-export of Imported Drugs** | Permitted with customs clearance and DGFT permission; drugs imported for re-processing then re-exported |

## Step-by-Step Export Procedure

### PHASE 1: PRE-EXPORT PREPARATION

### Step 1 — Market Research and Regulatory Strategy

- Identify target market: regulatory framework, market size, competition, IP status
- Assess required dossier format: CTD (ICH markets), ACTD (ASEAN), WHO PQ dossier
- Identify and appoint local regulatory representative (mandatory in most countries)
- Assess patent status in target country — freedom to operate analysis
- Gap analysis: what additional studies (BE, stability, bridging) are needed

### Step 2 — GMP Compliance and Certification

- Manufacturing under Schedule M (Indian GMP) — minimum requirement for all exports
- WHO-GMP Certificate from CDSCO — required for WHO-PQ and most developing country markets
- EU-GMP Certificate — for export to EU/EEA; site must be registered with EMA and inspected by EU NCA
- USFDA Drug Establishment Registration (21 CFR 207) — for US market; annual renewal required
- PIC/S GMP — for markets requiring PIC/S compliance (Singapore, Australia, Canada)

### Step 3 — Technical Documentation and Dossier Preparation

- Prepare regulatory dossier in appropriate format: CTD/eCTD (ICH), ACTD (ASEAN), WHO PQ format
- Conduct stability studies per ICH Q1A (Zones I-IVb as applicable to target market)
- Conduct Bioequivalence (BE) study if required by target regulatory authority
- File Drug Master File (DMF) for API if required (US: Type II DMF; EU: ASMF/CEP)
- Prepare labeling compliant with target country requirements

### Step 4 — Submit Registration Application in Target Country

- File marketing authorization application (MAA/NDA/ANDA/ANDS) through local agent
- Pay regulatory fees; respond to queries; attend meetings if required
- Timeline varies: USA ANDA ~10 months; EU generic ~1.5-2 years; ASEAN varies by country

## PHASE 2: EXPORT DOCUMENTATION (PER SHIPMENT)

### Export Documents Required

| Document | Issuing Authority / Purpose |
|---|---|
| **Import Export Code (IEC)** | DGFT — Mandatory 10-digit code for all exporters; one-time registration |
| **Manufacturing/Marketing License** | State Licensing Authority — Form 25/25A/28/28A under D&C Rules |
| **Certificate of Pharmaceutical Product (CPP)** | CDSCO (DCGI) — WHO-format certificate; confirms product is licensed and manufactured per GMP; required by most importing countries |
| **WHO-GMP / EU-GMP Certificate** | CDSCO / EU NCA — Confirms GMP compliance of manufacturing site |
| **Free Sale Certificate (FSC)** | CDSCO/DGFT — Confirms product is freely sold in India (not banned) |
| **Certificate of Analysis (CoA)** | Manufacturer's QC Department — Batch-specific quality certificate |
| **Commercial Invoice** | Exporter — Product details, quantity, price, consignee/consignor |
| **Packing List** | Exporter — Detailed list of items in shipment |
| **Shipping Bill / Bill of Export** | Customs — Filed via ICEGATE portal; LEO (Let Export Order) generated |
| **Bill of Lading / Airway Bill** | Carrier — Contract of carriage and receipt of goods |
| **Drug Export Permit (NDPS)** | NCB (Narcotics Control Bureau) — For narcotic/psychotropic substances |
| **Country of Origin Certificate** | Chamber of Commerce / FIEO — For preferential tariff/FTA benefits |
| **Insurance Certificate** | Insurance Company — Marine/air cargo insurance |
| **Marketing Authorization from Target Country** | Target country regulatory authority — After registration approval |

## PHASE 3: POST-EXPORT REGULATORY OBLIGATIONS

### Post-Marketing Requirements in Target Country

- Pharmacovigilance (PV): ADR reporting per local requirements of target country

- Periodic Safety Update Reports (PSURs): submitted at defined intervals
- License renewal: Marketing authorizations require periodic renewal (typically every 5 years)
- Variation management: Report and obtain approval for all post-approval changes
- Annual product reviews and quality monitoring
- Product recall capability for overseas markets

### WHO Prequalification Programme (WHO-PQ)

- **Purpose:** Assess whether medicines meet unified quality, safety, efficacy standards for WHO member countries lacking strong national regulatory systems
- **Products:** HIV/AIDS, malaria, TB, reproductive health, NCD medicines; vaccines; IVDs
- **Process:** Pre-submission meeting → Dossier (CTD format) → Product assessment → WHO-GMP site inspection → WHO PQ Listing
- **Timeline:** Approximately 12-18 months for new applicants
- **India's Share:** India supplies more than 40% of WHO Prequalified generic medicines globally

**Companies:** Cipla, Sun Pharma, Dr. Reddy's Laboratories, Aurobindo Pharma, Lupin, Mylan India, Strides Pharma are major WHO-PQ holders from India.

## Drug Master Files (DMF)

A Drug Master File (DMF) is a submission to a regulatory authority providing confidential, detailed information about the facilities, processes, or articles used in the manufacture, processing, packaging, and storage of a drug substance, drug product, or packaging material. The DMF allows sensitive technical information to be reviewed by the regulatory authority while protecting trade secrets from disclosure to third parties (e.g., drug product manufacturers referencing the API).

> *A DMF is NOT an application for regulatory approval. It is a voluntary, confidential reference document submitted to support another party's drug application (IND/NDA/ANDA). FDA reviews a DMF only when referenced by an active application.*

### Purpose and Importance

- **Confidentiality:** API manufacturers share detailed manufacturing data with regulatory authority without disclosing trade secrets to drug product manufacturers (ANDA filers)
- **Efficiency:** Multiple ANDA filers can reference the same DMF — avoids repetition of API data in each dossier
- **Regulatory Access:** Regulatory authority sees complete API manufacturing picture while maintaining confidentiality between commercial parties
- **Global Acceptance:** US (DMF), EU (ASMF/CEP), Japan (MF), Canada (Drug Substance Information — DSI), India (evolving)

## Types of DMF — US FDA Classification (21 CFR 314.420)

| Type | Subject | Contents / Current Status |
|---|---|---|
| Type I | Manufacturing Site, Facilities, Personnel | Discontinued by FDA since 2000; was for facility/GMP information; now incorporated into Type II or separate site master files |
| Type II | Drug Substance / Drug Substance Intermediate / Drug Product | MOST COMMON; Complete pharmaceutical, chemical, biological information for API; includes synthesis, characterization, controls, impurities, stability; filed by Indian API manufacturers |
| Type III | Packaging Material | Composition, manufacture, controls, specifications for container/closure systems; extractables and leachables; plastic, glass, rubber components |
| Type IV | Excipient, Colorant, Flavor, Essence | Manufacture, controls, specifications, safety data for excipients; increasingly replaced by GRAS submissions or Excipient Information Package (EIP) |
| Type V | FDA-Accepted Reference Information | For information frequently referenced but not covered by other types; cross-references to published literature or FDA guidances; rarely used |

**Most Important:** Type II DMF for Drug Substance (API) is by far the most common DMF type. Indian API manufacturers (e.g., Dr. Reddy's, Aurobindo, Laurus Labs) file Type II DMFs with USFDA to support US generic ANDA applications.

## Contents of Type II DMF (Drug Substance/API) — CTD Section 3.2.S

| CTD Section | Information in DMF |
|---|---|
| **3.2.S.1 General Information** | INN/chemical name/CAS number, structural formula, molecular formula and weight, physicochemical properties (solubility, pKa, partition coefficient, polymorphic forms, hygroscopicity, particle size distribution) |
| **3.2.S.2 Manufacture** | Manufacturer name/address, manufacturing process (reaction scheme/flow chart, reagents, solvents), in-process controls, batch formula, process validation/evaluation, scale-up data, discussion of critical steps |
| **3.2.S.3 Characterization** | Structural elucidation (IR, NMR, MS, UV, X-ray crystallography, elemental analysis), stereochemistry, confirmation of proposed structure, physicochemical characterization |
| **3.2.S.4 Control of Drug Substance** | Specification (tests, methods, acceptance criteria), analytical method validation per ICH Q2(R1), batch analysis of min. 3 production batches, impurity profiling per ICH Q3A (identification/qualification thresholds) |
| **3.2.S.5 Reference Standards** | Source, characterization, CoA of primary and working reference standards used for testing; for compendial APIs: reference to official reference standard |

| | |
|---|---|
| **3.2.S.6 Container Closure System** | Description of storage container and closure (material, grade, specifications); compatibility with drug substance; container qualification data |
| **3.2.S.7 Stability** | Summary of all stability studies, post-approval stability protocol; ICH Q1A conditions: accelerated (40 deg C/75% RH, 6 months), intermediate (30 deg C/65% RH, 12 months), long-term (25 deg C/60% RH, 12+ months); photostability per ICH Q1B; retest period/shelf life with proposed storage conditions; degradation product characterization |

## DMF Submission Process — USFDA

1. DMF holder prepares the Type II DMF in eCTD or paper/PDF format (eCTD strongly preferred)
2. DMF submitted electronically to FDA via Electronic Submissions Gateway (ESG) or CDER Direct portal
3. FDA assigns unique DMF Number and issues Acknowledgment Letter within 30 days
4. Administrative review (completeness check) within 30 days — not a scientific review
5. NO scientific review at time of filing — DMF reviewed ONLY when referenced by an active application
6. DMF holder issues Letter of Authorization (LOA) to each authorized applicant (ANDA filer)
7. ANDA/NDA applicant references the DMF number + LOA in their application dossier
8. FDA reviews DMF as part of ANDA/NDA review; issues DMF Deficiency Letters if issues found
9. DMF holder must respond to deficiency letters (separate from applicant's responses)
10. Annual Report to FDA required within 60 days of DMF anniversary date

## Letter of Authorization (LOA)

A Letter of Authorization is a formal written document from the DMF holder authorizing the FDA to reference the DMF in connection with a specific drug application from a named applicant.

- Must state: DMF number, name and address of authorized applicant (ANDA filer), specific application number being supported (if known)
- Without LOA: FDA cannot review the DMF content in context of the applicant's submission
- LOA is NOT a transfer of ownership or responsibility — DMF holder retains full accountability
- LOA can be revoked by DMF holder at any time (with written notice to FDA and applicant)
- Multiple LOAs can be issued from the same DMF to different ANDA filers

## EU Equivalent — ASMF (Active Substance Master File)

| Feature | Details |
|---|---|
| **Full Name** | Active Substance Master File (ASMF) — also called European Drug Master File (EDMF) |
| **Regulatory Basis** | Volume 6A of Rules Governing Medicinal Products in EU; Directive 2001/83/EC; EMEA/CHMP/QWP/227/02 |

| | |
|---|---|
| **Structure** | Open Part (Applicant's Part — AP): non-confidential, shared with MAA applicant; Restricted Part (Applicant's Holder's Part — AHP): confidential, submitted directly by ASMF holder to regulatory authority |
| **Review** | ASMF assessed as integral part of MAA/generic application; ASMF holder responds directly to assessor's questions on restricted part |
| **EDQM CEP/COS** | Certificate of Suitability (CEP) from European Directorate for the Quality of Medicines (EDQM): confirms API compliance with Ph. Eur. monograph; accepted in EU+36 countries as alternative to ASMF; simplifies multiple country submissions |
| **Advantage of CEP** | One CEP supports applications in all 36+ EDQM member states; no separate ASMF needed; reduces regulatory burden for Indian API exporters |

**EDQM CEP:** A Certificate of Suitability (CEP/COS) from EDQM is highly valuable for Indian API manufacturers. It allows the API to be referenced in any MAA across EU member states and several non-EU countries without filing a separate ASMF for each country.

## DMF in India (iDMF)

- CDSCO does not yet have a fully formalized DMF system equivalent to the US Type II DMF
- API/excipient information is typically included directly within the drug product dossier (Form 44 submission)
- Site Master File (SMF): manufacturers prepare facility-level GMP documentation for CDSCO inspections
- CDSCO draft guideline on DMF is being developed; formal iDMF system expected in near future
- For export dossiers: API Module 3.2.S is fully included in the eCTD/CTD for overseas regulatory submissions

## Annual DMF Update Requirements

- Annual DMF Report (ADR) must be submitted within 60 days of the DMF anniversary date
- Contents of ADR: list of all authorized applicants (LOA holders), summary of all changes made during the year, statement if no changes were made
- Significant changes to manufacturing process, specifications, or site must be reported promptly (not just annually)
- Failure to submit annual updates: FDA may place DMF on Inactive status — prevents referencing by applicants
- Active DMFs: listed in FDA's online DMF database at https://www.fda.gov/drugs/drug-master-files-dmfs

# Common Technical Document (CTD)

The Common Technical Document (CTD) is a harmonized international format for preparing regulatory applications (new drug, generic, biologic) for submission to regulatory authorities in ICH member regions. Developed by the International Council for Harmonisation (ICH) under guideline ICH M4, the CTD standardizes the structure and format of regulatory dossiers, significantly reducing the effort required for multi-regional submissions.

> *The CTD does not harmonize the actual approval requirements or data standards — it harmonizes the STRUCTURE and FORMAT of how data is presented, enabling the same core scientific data (Modules 2-5) to be used across multiple ICH regions with only Module 1 being region-specific.*

| Feature | Details |
|---|---|
| Developed by | ICH (International Council for Harmonisation); Working Groups M4Q (quality), M4S (safety), M4E (efficacy) |
| ICH Guidelines | ICH M4: overall structure; ICH M4Q: Module 3 (quality); ICH M4S: Module 4 (non-clinical); ICH M4E: Module 5 (clinical) |
| Adopted Regions | USA (since 2003), EU (since 2003), Japan (2003); now: Canada, Australia, Brazil (ANVISA), Korea, Singapore, CDSCO India (preferred format) |
| Mandatory eCTD | Electronic CTD (eCTD per ICH M8) is mandatory for US, EU, Japan, Canada; strongly recommended in all ICH regions |
| Benefits | Eliminates duplication of data for multiple-country submissions; faster review; standardized review by agencies; industry efficiency |
| NOT Harmonized | Module 1 (administrative, region-specific); labeling requirements; some regional clinical data expectations |

## CTD Structure — Five Modules

The CTD is organized into 5 modules. Modules 2-5 are harmonized (same content regardless of region). Module 1 is region-specific.

### MODULE 1 | Administrative and Prescribing Information — REGION-SPECIFIC

Module 1 is NOT harmonized — its content differs between regulatory regions (FDA, EMA, PMDA, Health Canada, TGA, CDSCO). It contains:

- 1.1: Table of Contents (Module 1)
- 1.2: Application Forms — FDA Form 356h/1571; EMA Application Form; CDSCO Form 44
- 1.3: Product Information — Prescribing Information (PI/Package Insert), SmPC (EU), Patient Information Leaflet (PIL), labeling artwork
- 1.4: Expert Information — Qualifications of experts who prepared Module 2 summaries
- 1.5: Region-specific requirements — Patent certifications (US Para I-IV), orphan drug designation, pediatric plan (PDCO), risk management plan (EU)
- 1.6: Environmental Risk Assessment (ERA) — Required in EU for new active substances

- 1.7: GMP Certificates — Site-specific GMP certificates (WHO-GMP, EU-GMP, USFDA compliance)
- 1.8: Information on related applications (cross-references)
- 1.9: Declarations of compliance, debarment certifications

## MODULE 2 | CTD Summaries and Overviews — HARMONIZED

Module 2 provides concise summaries of the detailed data in Modules 3, 4, and 5. It is the most critical module for regulatory reviewers — it provides the strategic narrative of the entire submission.

| Section | Content |
|---|---|
| **2.1 — CTD Table of Contents** | Overall table of contents for Modules 1-5 of the entire CTD submission |
| **2.2 — Introduction** | Brief introduction to drug substance and drug product; general description of the application |
| **2.3 — Quality Overall Summary (QOS)** | Summary of Module 3 data; narrative of drug substance (manufacture, characterization, controls, stability) and drug product (formulation, manufacture, controls, stability); highlights critical quality attributes; written by CMC expert |
| **2.4 — Non-clinical Overview** | Integrated discussion of pharmacology, pharmacokinetics, and toxicology; risk-benefit assessment of non-clinical data; written by non-clinical expert |
| **2.5 — Clinical Overview** | Critical analysis of clinical data; benefit-risk evaluation; proposed prescribing information rationale; written by clinical expert |
| **2.6 — Non-clinical Written and Tabulated Summaries** | Detailed written summaries and data tables for pharmacology, PK/TK, toxicology organized by study type; must be consistent with Module 4 study reports |
| **2.7 — Clinical Summary** | Summary of biopharmaceutic studies (BA/BE), clinical pharmacology, clinical efficacy, clinical safety; synopsis of each clinical study; tabular listing of all clinical studies |

## MODULE 3 | Quality — Chemistry, Manufacturing and Controls (CMC) — HARMONIZED

Module 3 contains all quality (CMC) information and is the most complex module for generic drug submissions. It is organized into Drug Substance (3.2.S) and Drug Product (3.2.P) sections.

### Module 3 — Drug Substance (3.2.S)

| Sub-section | Content |
|---|---|
| **3.2.S.1 General Information** | Nomenclature (INN, IUPAC, CAS No.), structural formula, mol. formula, mol. weight; physicochemical properties including solubility profile, pKa, partition coefficient (LogP), polymorphism, hygroscopicity, BCS classification |
| **3.2.S.2 Manufacture** | Name/address of manufacturer, complete manufacturing process description with reaction scheme, reagents, solvents, in-process |

| | |
|---|---|
| | controls, process validation data, discussion of critical steps and intermediates |
| **3.2.S.3 Characterization** | Elucidation of structure by spectroscopy (IR, 1H/13C NMR, MS, UV), elemental analysis, X-ray powder diffraction (XRPD), stereochemistry confirmation, physicochemical properties |
| **3.2.S.4 Control of Drug Substance** | Specification table (test, analytical procedure, acceptance criterion), analytical method validation per ICH Q2(R1), batch analysis data (min. 3 batches), impurity profiling per ICH Q3A (identification threshold 0.05%, qualification threshold 0.10%/1.0 mg/day) |
| **3.2.S.5 Reference Standards** | Description, source, characterization, CoA of primary and working reference standards; certificate of analysis |
| **3.2.S.6 Container Closure System** | Storage container specification (material, grade, color, dimensions), compatibility with API, environmental stress considerations |
| **3.2.S.7 Stability** | Stability protocol (storage conditions, time points, tests), results of accelerated and long-term studies, stress degradation studies, photostability (ICH Q1B), forced degradation; proposed retest period with statistical evaluation |

## Module 3 — Drug Product (3.2.P)

| Sub-section | Content |
|---|---|
| **3.2.P.1 Description and Composition** | Description of dosage form (appearance, color, size, weight), full composition table with all components (API and excipients), quantity per unit, function, compendial grade, manufacturer |
| **3.2.P.2 Pharmaceutical Development** | Development rationale, selection of drug substance form (polymorph, salt, hydrate), excipient selection and compatibility studies, formulation optimization, manufacturing process development, container closure selection; QbD elements (QTPP, CQA, CMA, CPP, design space) if applicable |
| **3.2.P.3 Manufacture** | Manufacturing site details, batch formula, step-by-step manufacturing process with flow chart, in-process controls with limits, batch size, scale-up data |
| **3.2.P.4 Control of Excipients** | Specifications for each excipient per pharmacopoeia or in-house; non-compendial excipients: full characterization; novel excipients: full safety data (Module 4 equivalent) |
| **3.2.P.5 Control of Drug Product** | Release and shelf-life specifications (tests, methods, limits), analytical method validation, batch analysis results (min. 2 pilot-scale + 1 additional batch), characterization of degradation products per ICH Q3B |
| **3.2.P.6 Reference Standards** | Description and characterization of drug product reference standards used for testing |
| **3.2.P.7 Container Closure System** | Primary packaging description and specifications; suitability for the intended use; extractables and leachables studies (for parenteral, ophthalmic, inhalation products) |
| **3.2.P.8 Stability** | Stability protocol (ICH Q1A conditions per climate zone), results for primary and commitment batches (3 primary + 2 commitment for |

| | |
|---|---|
| | each strength), photostability, proposed shelf life and storage conditions |

## MODULE 4 | Non-clinical Study Reports — HARMONIZED

Module 4 contains full study reports for all non-clinical (pre-clinical) studies. For generic drugs (ANDA), Module 4 is generally not required if the drug is bioequivalent to the RLD and non-clinical toxicology data are published/available in literature.

- 4.2.1 Pharmacology: Primary PD, secondary PD, safety pharmacology (cardiovascular/CNS/respiratory)
- 4.2.2 Pharmacokinetics: Analytical methods, absorption, distribution, metabolism, excretion (ADME), PK drug interactions, other PK studies
- 4.2.3 Toxicology: Single-dose toxicity, repeat-dose toxicity (sub-acute 28d, sub-chronic 90d, chronic 180d/360d), genotoxicity, carcinogenicity, reproductive/developmental toxicity, local tolerance, special toxicity studies

## MODULE 5 | Clinical Study Reports — HARMONIZED

Module 5 contains all clinical study reports. For generic products (ANDA/ANDS), Module 5 primarily contains Bioequivalence (BE) study reports. For new drugs, all Phase I-III clinical study reports are required.

| Section | Content |
|---|---|
| **5.2 Tabular Listing** | Master list of all clinical studies submitted (study ID, title, design, population, drug, dose, duration, enrollment numbers, status) |
| **5.3.1 Biopharmaceutic Studies** | Bioavailability studies (absolute, relative), comparative BA/BE studies, in vitro-in vivo correlation (IVIVC), bioanalytical methods and validation reports |
| **5.3.2 Clinical Pharmacology** | PK studies in healthy subjects and patients, PK in special populations (hepatic/renal impaired, elderly, pediatric), PK drug-drug interaction studies, pharmacodynamic studies |
| **5.3.3 Clinical Efficacy Reports** | Phase II/III controlled clinical trial reports, population PK/PD analyses, uncontrolled studies, support data from more than one study (integrated analyses) |
| **5.3.4 Clinical Safety Reports** | Integrated safety data, post-marketing experience, case report forms, individual patient data listings |
| **5.3.5 Literature References** | Published literature referenced in the application (bibliographic applications, 505(b)(2) NDA) |

# Electronic Common Technical Document (eCTD)

The Electronic Common Technical Document (eCTD) is the standard electronic format for submitting pharmaceutical regulatory applications. It uses the same content structure as the paper CTD (ICH M4) but adds a specific electronic file format with an XML backbone for document management, structured directory, and life cycle tracking. eCTD enables electronic submission, review, and management of regulatory dossiers throughout the product lifecycle.

> *eCTD is MANDATORY for all NDA/BLA submissions to USFDA since May 2017 and for all ANDA submissions since May 2018. EMA, Health Canada, PMDA Japan, TGA Australia also require or strongly recommend eCTD format.*

## ICH M8 — eCTD Guideline

- ICH M8 provides the technical specifications for eCTD format and implementation
- Current eCTD version: v3.2.2 (most widely used); eCTD v4.0 (XML-based; newer; being adopted)
- ICH M8(R1): latest revision covering eCTD version 4.0 technical specifications
- Validation criteria ensure compliance before agency will accept the submission for review

## eCTD Architecture —Components

### Directory Structure

- Root folder: named with application number (e.g., 'anda078432', 'nda012345')
- Sequence folders: each submission increment is a 4-digit numbered sequence
- Sequence 0000: original application (complete dossier)
- Sequence 0001, 0002...: amendments, supplements, responses, annual reports
- Each sequence contains: index.xml (backbone), util/ folder (stylesheet), m1/ through m5/ (module folders)
- Document files: stored in appropriate module subdirectories; PDF is primary format

### XML Backbone (index.xml)

- The index.xml is the heart of the eCTD — it defines the complete structure of the submission
- Contains metadata: applicant name, application number, submission type, date of submission, sequence number
- Leaf elements: each document represented by a leaf element with attributes — title, href (file path), operation, modified-date, checksum
- Operation attribute (CRITICAL): defines how each document relates to previous submissions
- Validation: index.xml must be well-formed XML, valid against the eCTD DTD/schema, with correct namespace declarations

## Accepted File Formats in eCTD

| File Type | Accepted Format(s) |
|---|---|
| **Narrative documents (reports, summaries)** | PDF/A-1b (preferred); minimum PDF version 1.4; must have embedded fonts, bookmarks, hyperlinks; no security/password protection; no JavaScript |
| **Clinical datasets** | SAS Transport Files (.xpt) per CDISC SDTM (study data) and ADaM (analysis data) standards; Define.xml with controlled terminology |
| **XML backbone files** | Well-formed XML per ICH eCTD DTD/schema; validated before submission |
| **Study data reviewer guides** | PDF format; SDRG (Study Data Reviewer Guide), ADRG (Analysis Data Reviewer Guide) |
| **Specifications / SOPs** | PDF format (no executable files) |
| **Images** | Embedded within PDF documents; standalone TIFF/PNG for high-resolution figures if required |

## eCTD Life Cycle Management

One of the most powerful features of eCTD is life cycle management — the ability to track the complete history of all submitted documents across multiple sequences throughout the entire lifecycle of a drug application.

| Operation Attribute | Meaning | When Used | Effect |
|---|---|---|---|
| new | Document submitted for first time | Seq 0000 (original application) or first occurrence of a section | Creates new document in active dossier |
| replace | Supersedes a previous document; old doc becomes inactive | Updated stability report, revised specification, amended protocol | Old document archived; new is current |
| append | Adds to existing doc; both remain active | Additional batch data, supplementary clinical data | Both old and new documents are current |
| delete | Removes document from active dossier | Withdrawal of erroneous submission, removal of withdrawn study | Document removed from active dossier (still in archive) |

**Benefit:** Life cycle management means the agency always has a complete, current picture of the active dossier. All history is preserved in the archive, and changes are tracked electronically — no paper correspondence needed.

## eCTD Submission Types

| Submission Type | eCTD Sequence |
|---|---|

| | |
|---|---|
| **Original Application** | Sequence 0000; complete dossier with all modules/parts; Modules 1-5 fully populated |
| **Amendment (pre-approval)** | Sequences 0001+; adds new studies, responds to information requests; new or replace operations |
| **Complete Response (CR)** | Response to CRL (Complete Response Letter); addresses all deficiencies cited by FDA |
| **Prior Approval Supplement (PAS)** | New sequence; major post-approval change; requires FDA approval before implementation |
| **CBE-30 Supplement** | New sequence; moderate change; implemented 30 days after submission unless FDA objects |
| **CBE-0 Supplement** | New sequence; minor change; implemented immediately upon submission |
| **Annual Report (AR)** | Annual update; lifecycle document updates, stability updates, minor changes |
| **Information Request (IR) Response** | Response to specific FDA query; usually within 30-60 days |

## Technical Validation of eCTD

- Submissions must pass technical validation checks before substantive review begins
- FDA uses automated validation tools; checks include:
  - XML backbone: well-formed, valid DTD/schema, correct namespace, proper leaf element attributes
  - File naming: lowercase only, no spaces, max 64 characters, only alphanumeric + hyphens/underscores allowed
  - PDF compliance: embedded fonts, no encryption, no security restrictions, no JavaScript, correct PDF version
  - Hyperlinks: all cross-references functional within submission; no broken links
  - Checksums (MD5): verified for each document file listed in backbone
- Refuse to Receive (RTR): FDA may refuse a submission for technical non-compliance before scientific review

## CDISC Standards for Clinical Data in eCTD

- **SDTM (Study Data Tabulation Model):** Standard format for organizing and tabulating clinical trial data; required for all new NDAs/BLAs and most ANDAs; 30+ domain-specific datasets (AE, LB, VS, EG, DM, CM, EX, etc.)
- **ADaM (Analysis Data Model):** Standard format for analysis-ready datasets directly linked to statistical results in clinical study reports
- **Define.xml:** Metadata file describing all datasets, variables, controlled terminology, value-level metadata; required alongside SDTM and ADaM
- **SDRG/ADRG:** Study/Analysis Data Reviewer Guides — PDF documents explaining dataset organization and how to use data for review

## eCTD vs Paper CTD —Differences

| Parameter | Paper CTD | eCTD |
|---|---|---|

| | | |
|---|---|---|
| Format | Physical paper or simple PDF files in folders | Structured XML backbone + PDF/SAS XPT files in defined directory |
| Document Management | Manual tracking; paper amendments and supplements | Automated lifecycle via operation attributes (N/R/A/D) |
| Life Cycle Tracking | Difficult; requires manual cross-referencing | Automated; complete history maintained electronically |
| Mandatory? | No (phased out for major submissions) | Yes — FDA mandatory since 2017 (NDA) / 2018 (ANDA) |
| Agency Review | Physical review of paper; slower process | Electronic review tools; faster search and navigation |
| Version Control | Challenging — requires numbering systems | Built-in via sequences and operation attributes |
| Cost | High (printing, shipping, physical storage) | Lower (electronic; cloud/server storage) |
| Searchability | Limited (index-based) | Full text search within PDFs; electronic navigation |
| Data Submission | Printed tables and listings | SAS XPT datasets per CDISC standards; Define.xml |
| Common in | Legacy submissions; some developing countries | All ICH regions; WHO-PQ; increasingly global standard |

# ASEAN Common Technical Document (ACTD)

The ASEAN Common Technical Document (ACTD) is a harmonized format for regulatory dossier preparation adopted by all 10 ASEAN (Association of Southeast Asian Nations) member countries for registration of pharmaceutical products. It was developed by the ASEAN Pharmaceutical Product Working Group (PPWG) under ACCSQ, and is analogous to the ICH CTD but tailored to the regulatory environment of ASEAN member states.

## ASEAN Region — Pharmaceutical Market Overview

| ASEAN Country | Regulatory Authority | Features |
|---|---|---|
| Indonesia | BPOM (Badan Pengawas Obat dan Makanan) | Largest ASEAN pharma market; 280 million population; local BE studies may be required; longest timelines (3-5 years) |
| Malaysia | NPRA (National Pharmaceutical Regulatory Agency), MOH | Well-developed framework; MRC (Malaysia) participates in ACCSQ; ACTD fully accepted; ~1-2 year timelines |
| Philippines | FDA Philippines | ACTD accepted; local clinical data may be required; some WHO-PQ products get expedited review; ~2-3 years |
| Singapore | HSA (Health Sciences Authority) | Most developed ASEAN regulatory framework; MRA with Australia; CTD/eCTD accepted; fastest in ASEAN (~9-12 months) |
| Thailand | FDA Thailand (TFDA) | ACTD accepted; bridging studies may be required; some local manufacture preference; ~2-3 years |
| Vietnam | Drug Administration of Vietnam (DAV), MOH | ACTD used; WHO-PQ products get streamlined review; improving timelines (~2-3 years) |
| Brunei Darussalam | BAFRA | Small market; aligned with ASEAN guidelines; imports most pharmaceuticals |
| Cambodia | Dept. of Drugs and Food (DDF), MOH | Developing regulatory system; ACTD format recommended; shorter review for WHO-PQ products |
| Lao PDR | Food and Drug Department (FDD), MOH | Developing system; accepts WHO-PQ products with simplified review |
| Myanmar | Myanmar FDA (MoHS) | Developing; ACTD format; WHO-PQ products preferred; improving infrastructure |

## ACTD Structure — Four Parts

The ACTD is divided into four Parts. Part I is region/country-specific (not harmonized). Parts II, III, and IV are harmonized across all ASEAN member states.

**PART I**

### ADMINISTRATIVE INFORMATION — COUNTRY-SPECIFIC (Not Harmonized)

- 1A: Table of Contents for the entire ACTD dossier
- 1B: Application Form — country-specific format; applicant details, product name, dosage form, strength, indication
- 1C: Summary of Product Characteristics (SmPC) / Package Insert / Product Information — adapted per country's format
- 1D: Labeling — outer carton, inner label, patient information leaflet (PIL) artwork per importing country language and format
- 1E: Expert Reports — some ASEAN countries require expert opinions on quality, safety, and efficacy summaries
- 1F: Country-Specific Requirements — GMP certificates (WHO-GMP or equivalent), Certificate of Pharmaceutical Product (CPP) from country of origin, Free Sale Certificate, marketing authorization in country of origin, patent information, pricing data, local agent letter of authorization

**PART II**

### QUALITY (CMC INFORMATION) — HARMONIZED ACROSS ASEAN

- 2A: Table of Contents for Part II
- 2B: Quality Overall Summary — Equivalent to CTD Module 2.3 (QOS); concise narrative summary of all quality data for drug substance and drug product
- 2C: Drug Substance Information — Equivalent to CTD 3.2.S; nomenclature, structure, manufacture (synthesis), characterization, controls (specifications, methods, validation, batch analysis), reference standards, container-closure system, stability (ICH Q1A conditions per climate zone)
- 2D: Drug Product Information — Equivalent to CTD 3.2.P; description and composition, pharmaceutical development, manufacture (process, batch formula, controls), control of excipients, control of drug product (specification, methods, batch analysis), reference standards, container-closure system, stability
- 2E: Appendices — Facilities and equipment list (site master file), adventitious agents safety evaluation (for biological-derived excipients), novel excipients safety data, analytical method validation data appendices
- 2F: Regional Information — GMP compliance documentation, country-specific manufacturing requirements, additional quality information requested by individual ASEAN member states

**PART III**

### NON-CLINICAL (SAFETY) INFORMATION — HARMONIZED ACROSS ASEAN

- 3A: Table of Contents for Part III
- 3B: Non-clinical Overview — Equivalent to CTD Module 2.4; integrated written summary discussing pharmacology, pharmacokinetics, and toxicology; risk-benefit assessment for non-clinical data

- 3C: Non-clinical Written and Tabulated Summaries — Equivalent to CTD Module 2.6; organized written summaries of pharmacology (primary PD, secondary PD, safety pharmacology), pharmacokinetics (ADME), toxicology (all types); data tabulations
- 3D: Non-clinical Study Reports — Equivalent to CTD Module 4; full reports for all pharmacology, PK, toxicology studies conducted for the product
- NOTE FOR GENERICS: For generic drug products that are bioequivalent to a reference medicinal product, Part III data is generally limited or waived. Cross-references to published literature or the originator's data (when publicly available) are acceptable in most ASEAN countries.
- NOTE: Safety pharmacology studies must demonstrate acceptable cardiovascular, CNS, and respiratory safety; GLP compliance statements required for pivotal toxicology studies

**PART IV**

**CLINICAL INFORMATION — HARMONIZED ACROSS ASEAN**

- 4A: Table of Contents for Part IV
- 4B: Clinical Overview — Equivalent to CTD Module 2.5; critical integrated assessment and discussion of clinical data from clinical pharmacology, efficacy, and safety studies; benefit-risk evaluation; proposed prescribing information rationale
- 4C: Clinical Summary — Equivalent to CTD Module 2.7; summary of biopharmaceutic studies (BA/BE studies, IVIVC), clinical pharmacology studies (PK/PD), clinical efficacy studies (Phase II/III), clinical safety data; synopsis of each clinical study; tabular listing of all studies
- 4D: Clinical Study Reports — Equivalent to CTD Module 5; tabular listing of all studies; biopharmaceutic study reports (in vivo BE studies — most critical for generics); clinical pharmacology reports; Phase II/III efficacy/safety study reports; literature references
- FOR GENERIC PRODUCTS (Most Common Indian Export Scenario): Part IV primarily contains the in vivo Bioequivalence Study Report per ASEAN BE Guidelines; BE acceptance: 90% CI for AUC and Cmax within 80.00-125.00%; Tmax (informational); may also include food effect BE study if applicable
- BIOWAIVER: BCS-based biowaiver available for BCS Class I and Class III drugs with rapidly dissolving formulations per ASEAN/WHO BE guidelines; dissolution profile comparison at pH 1.2, 4.5, 6.8 using f2 similarity factor (f2 >= 50)

## ACTD vs ICH CTD — Module Mapping

| CTD Module (ICH) | ICH CTD Content | ACTD Part (ASEAN) |
|---|---|---|
| Module 1 | Administrative (Region-specific) | Part I (Country-specific Admin) |
| Module 2 Sec 2.3 (QOS) | Quality Overall Summary | Part II — Section 2B |
| Module 2 Sec 2.4 (NCO) | Non-clinical Overview | Part III — Section 3B |
| Module 2 Sec 2.5 (CO) | Clinical Overview | Part IV — Section 4B |
| Module 2 Sec 2.6 (NCS) | Non-clinical Summaries | Part III — Section 3C |
| Module 2 Sec 2.7 (CS) | Clinical Summary | Part IV — Section 4C |

| | | |
|---|---|---|
| Module 3 (3.2.S) | Drug Substance Data (CMC) | Part II — Section 2C |
| Module 3 (3.2.P) | Drug Product Data (CMC) | Part II — Section 2D |
| Module 3 (3.2.A) | Appendices (facilities, adventitious agents) | Part II — Section 2E |
| Module 4 | Non-clinical Study Reports | Part III — Section 3D |
| Module 5 (BE Studies) | Biopharmaceutic Study Reports | Part IV — Section 4D |

## Practical Registration of Indian Drug in ASEAN Countries

| Step | Details |
|---|---|
| **1. Market Selection** | Choose target ASEAN country based on: market size, regulatory timeline, competition, IP situation; Singapore is fastest (~9-12 months); Indonesia is slowest (~3-5 years) |
| **2. Local Agent/MAH** | Most ASEAN countries require a local marketing authorization holder (MAH) or local agent; Indian company acts as manufacturer; agent manages local registration |
| **3. Dossier Preparation (ACTD)** | Prepare ACTD dossier: Part I is country-specific; Parts II, III, IV are common across ASEAN (with minor country-specific variations) |
| **4. CPP from CDSCO** | CDSCO-issued Certificate of Pharmaceutical Product (WHO format) is mandatory for ASEAN registration; certifies Indian marketing authorization and GMP compliance |
| **5. GMP Certificate** | WHO-GMP certificate from CDSCO; Singapore/Malaysia may require independent GMP inspection of Indian manufacturing site |
| **6. BE Study** | Conduct in vivo BE study per ASEAN BE Guidelines; BE may be conducted in India (CDSCO-approved BE center) or in an ASEAN country; 90% CI of AUC and Cmax must be within 80-125% |
| **7. Stability Studies** | ICH Q1A studies per climate zone: most ASEAN countries = ICH Zone IVb (30 deg C/75% RH, 12 months long-term; 40 deg C/75% RH, 6 months accelerated) |
| **8. Submit ACTD dossier** | Submit through local agent to ASEAN country's regulatory authority; pay regulatory fees; respond to queries |
| **9. Approval and Post-marketing** | After approval: pharmacovigilance reporting, license renewal (every 3-5 years), variation management, local language labeling compliance |

## Comparative: CTD vs eCTD vs ACTD

| Feature | CTD (Paper) | eCTD | ACTD |
|---|---|---|---|
| Full Form | Common Technical Document | Electronic Common Technical Document | ASEAN Common Technical Document |
| Developed by | ICH (M4 guideline) | ICH (M8 guideline) | ACCSQ/PPWG under ASEAN |

| | | | |
|---|---|---|---|
| Format | Paper or unstructured PDF | XML backbone + structured PDFs + SAS data | Paper or PDF (no mandatory eCTD for most ASEAN) |
| Structure | 5 Modules (M1-M5) | 5 Modules (same as CTD) + XML backbone | 4 Parts (Part I-IV) |
| Admin/Regional | Module 1 (Region-specific) | Module 1 in eCTD format | Part I (Country-specific) |
| Quality (CMC) | Module 3 | Module 3 in eCTD | Part II |
| Non-clinical | Module 4 | Module 4 in eCTD | Part III |
| Clinical | Module 5 | Module 5 in eCTD | Part IV |
| Summaries | Module 2 (2.3-2.7) | Module 2 in eCTD | Part II (2B), Part III (3B/3C), Part IV (4B/4C) |
| Mandatory in | Phasing out; still used in some countries | FDA (mandatory); EU/Japan/Canada (mandatory/required); TGA (required) | 10 ASEAN member countries |
| Lifecycle Mgmt | Manual (paper amendments) | Automated (N/R/A/D operation attributes) | Manual/semi-electronic per country |
| Clinical Data | Printed tables/listings | CDISC SDTM + ADaM datasets + Define.xml | Tabular listings in PDF format |
| GMP Standard | ICH/WHO/EU/US cGMP | ICH/WHO/EU/US cGMP | WHO-GMP or ASEAN GMP (PIC/S for SGP/MYS) |
| BE Criteria | 80-125% (ICH standard) | 80-125% (ICH standard) | 80-125% (ASEAN harmonized with WHO/ICH) |
| Stability Zones | ICH Q1A Zones I-IVb | ICH Q1A Zones I-IVb | Primarily Zone IVb (30 deg C/75% RH) for most ASEAN |



**— Best Of Luck For Your Exam —**

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