# "Regulatory Framework for Electronic Submissions eCTD"

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**ABSTRACT**

The pharmaceutical industry operates under detailed regulatory systems that aim to guarantee the safety, effectiveness, and superior quality of medicines. The shift from traditional paper submissions to the electronic Common Technical Document (eCTD) format has completely transformed the global process of compiling, reviewing, and exchanging regulatory information. This review explores the roles of key regulatory authorities CDSCO (India), USFDA (USA), EMA (Europe), and others and highlights the modular eCTD structure (Modules 1–5) for administrative, quality, non-clinical, and clinical information. Drug Master Files (DMFs) enable secure sharing of proprietary manufacturing data, while harmonized submission standards accelerate drug approvals across countries. The article also outlines streamlined drug approval processes, from preclinical studies and IND applications to clinical trials, NDA/ANDA submissions, and post-marketing surveillance. By integrating global regulatory strategies with modern electronic submission systems, this review presents a comprehensive roadmap for efficient, standardized, and safe drug development worldwide.

Keywords: Regulatory Affairs, eCTD, CTD, Drug Master File, Drug Approval, Clinical Trials, CDSCO, USFDA, EMA

## INTRODUCTION

Regulatory Affairs (RA) also known as Government Affairs plays a vital role in highly regulated sectors such as pharmaceuticals, medical devices, and biotechnology. The main responsibility of RA professionals is to collect, analyze, and communicate information about the benefits and potential risks of medical products to both regulatory authorities and the public worldwide. This field focuses on developing scientific approaches, standards, and tools to assess the safety, quality, performance, and effectiveness of regulated products. Every medicinal product must meet strict requirements to ensure that it is safe, effective, and of high quality, with all regulatory decisions grounded in solid scientific evidence. In healthcare, regulatory affairs hold particular importance across pharmaceuticals, biologics, medical devices, and functional foods. Effective interpretation, implementation, and communication of regulations both within an organization and externally are essential for achieving successful regulatory outcomes. [1]

Establishment of Regulatory Authorities: To address such events and similar challenges, several countries created dedicated regulatory agencies to oversee and control the pharmaceutical sector. [2]

**Examples of Key Regulatory Authorities:**

1. CDSCO (Central Drugs Standard Control Organization) – India's primary regulatory body responsible for overseeing drug approvals, safety, and quality control.

2. FDA (Food and Drug Administration) – The U.S. agency tasked with evaluating and approving new drugs before they can be made available to the public.

3. EMA (European Medicines Agency) – Established to accelerate the drug approval process within the European Union. [3]

4. Health Canada – Oversees the regulation of drugs, biologics, medical devices, and other health-related products. Different directorates within Health Canada, such as the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate, manage specific product types. [4]

5. PMDA (Pharmaceuticals and Medical Devices Agency, Japan) – The Japanese authority responsible for the review, approval, and regulation of

pharmaceuticals, medical devices, and regenerative medicine products. [5]

**CTD**

Earlier regulatory submissions relied on paper-based applications, often delivered physically (sometimes even shipped on pallets), requiring manual collation and review. Over time, with initiatives such as the ICH CTD and later eCTD, regulatory authorities globally have shifted toward electronic submissions to improve efficiency, consistency, and speed. (e.g., Ahluwalia et al. 2025; Structured Content and Data Management, AAPS Open; Journal of Pharmaceutical Sciences, 2022) [6]

In 2000, representatives from the FDA, the European Medicines Agency, and Japan's Ministry of Health, Labor, and Welfare developed a set of guidelines for structuring and presenting a new medicine application dossier. These guidelines were intended to ensure that all three authorities followed a consistent approach. The principles were later incorporated into the International Conference on Harmonisation (ICH) recommendations. The creation of the Common Technical Document (CTD) introduced a standardized format for technical data, facilitating electronic submissions and streamlining the process of applying for human medicine registration. Using a single, harmonized document allows regulatory authorities to conduct reviews more efficiently, improves communication with applicants, and accelerates the sharing of regulatory information globally. [7,8]

The Common Technical Document (CTD) is supported by four ICH guidelines, in addition to several publications containing questions and answers. The first set of ICH CTD guidelines was issued in 2002. Although the CTD was developed by the ICH, it has been adopted by other countries including Canada, Australia, and India. In 2003, the use of the CTD became mandatory for NDA submissions in Europe and Japan. While the FDA has not yet made it compulsory, it strongly recommends the use of the CTD for regulatory submissions. [9]

The CTD has proven highly effective by eliminating the need to reformat and reorganize data for different regulatory authorities, thereby saving organizations significant time and resources. By providing a uniform format for NDA submissions, the CTD enables simultaneous applications across multiple regions. The FDA described the CTD as "a compilation of scientific, manufacturing, clinical, and non-clinical data presented in a standardized format with consistent content," aiming to streamline the approval process for new drugs in the US, EU, and Japan. [10]

**eCTD**

The main justifications for switching to electronic submissions are to enhance the submission and review procedure, improve submission accuracy, and reduce overall expenses. [11]

Regulatory bodies and the pharmaceutical sector can exchange information through the eCTD [12]

In the pharmaceutical industry, the electronic Common Technical Document (eCTD) serves as a platform for sharing regulatory information with authorities. The eCTD is built upon the structure of the Common Technical Document (CTD), which provides the framework for its core content. The CTD was developed by the Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG) under the International Conference on Harmonization (ICH). [13]

By using the eCTD standards for documentation, businesses can give agencies information in more portable electronic formats instead of in several bound paper volumes. [14]

The eCTD relies on open standards such as the widely recognized Extensible Markup Language (XML) and Portable Document Format (PDF). The overall structure of an eCTD submission is defined by the XML eCTD DTD (Document Type Definition), which enables the management of metadata and allows the dossier's table of contents (TOC) to be properly viewed and navigated in a compatible web browser. [15]

Because the eCTD dossier serves as the single official administrative record, it removes the need to prepare and maintain paper-based dossiers, reducing associated costs. It also enhances the ability to plan, schedule, and manage submissions efficiently. The eCTD provides opportunities to accelerate the approval process, improve communication with reviewers, and shorten response times to regulatory queries. Additionally, it facilitates collaboration among regulatory authorities, reviewers, document authors, and external partners. [16]

Benefits of eCTD Implementation: Establishing standards for electronic submissions encourages increased uniformity for businesses and regulators. The primary benefits consist of: effective Reviews

can be completed more quickly with tools that let you search, copy, and paste text. More procedures when several reviewers are involved. Improved the process for sponsors to reuse documents across various areas. Improved capacity to plan, prepare, and oversee submission materials. Reduced expenses for storage compared to paper dossiers. Enhanced cooperation and streamlined processes throughout the marketing, regulatory, and development departments. [17]

**File Format and Organization FOR eCTD:**

Document ready for e-CTD authoring documents using eCTD-compliant templates is essential to creating eCTD-ready documents. If this is not done, reformatting documents takes up a significant portion of the "publishing time." Below are guidelines for creating papers that are ready for eCTD.

**Guidelines for Submission Formats**

In general, documents included in the different modules should adhere to the ICH Common Technical Document (CTD) format. This section explains how files should be prepared for inclusion in the eCTD. It also outlines the specifications for each document. The eCTD submission consists of the following components:

**Directory Structure**

An eCTD submission consists of:

- XML eCTD instance
- Content files
- Folder hierarchy

The directory structure is composed of files and folders, with each folder containing a limited, suitable number of items (both subfolders and files). The structure should follow established guidelines to ensure consistency and proper organization. Files can be stored in various approved formats. Folder and file names act as identifiers and should be concise. It is helpful if the names indicate their content in a meaningful way, but they are not intended to serve as metadata.

**XML eCTD Instance**

The XML eCTD instance is the initial file that an XML (Extensible Markup Language) processor reads. Rather than creating a single XML document containing the entire eCTD (Electronic Common Technical Document) submission, the instance is designed to include links from its leaf elements to the individual files within the submission. It also contains metadata at the leaf level to provide additional information about the linked content. [18]

**eCTD Template**

To demonstrate the structure of an eCTD (Electronic Common Technical Document) submission folder, the ICH (International Conference on Harmonization) website (http://estri.ich.org/eCTD) provides a blank eCTD folder template. This template, shown in Appendix 4, includes all the potential Module 2–5 folders that could be used in a submission. Applicants can add or remove folders as necessary to accommodate their application data. A valid eCTD submission still requires the creation of XML (Extensible Markup Language) index files, the inclusion of relevant regional Module 1 folders and content, and the addition of required utility folders and supporting information. This section also outlines the commonly used file formats for electronic submissions.

**File Naming**

File names, including their extensions, must not exceed 64 characters. Similarly, folder names are limited to 64 characters, and the full path of a file within the folder structure cannot exceed 180 characters. In sequence number folders, numbering starts with the first digit of the folder's assigned sequence.

**PDF**

For documents specified in this specification, PDF is recognized as the industry standard. Adobe produced the publication format known as Adobe Portable Document Format (PDF). To create PDF documents, you do not have to utilize a software from Adobe or any other company. For documents specified in this specification, PDF is recognized as the industry standard.

**Version**

All PDF files should be readable by agencies using Acrobat Reader version 4.0 or later. To read and use the PDF files, agencies shouldn't require any further software. [19]

**Fonts**

In the pharmaceutical industry, eCTD is primarily used for regulatory submissions. This is achieved by standardizing the module-based structure and format for pharmaceutical applications, ensuring that submissions can be prepared and filed efficiently. To

enhance usability, the ICH regularly updates the eCTD guidelines. For instance, in February 2015, the ICH M8 Expert Working Group (EWG) released a draft implementation guide for eCTD version 4.0. This marked the first major update since the release of version 3.0 in 2003. [20]

**MODULES**

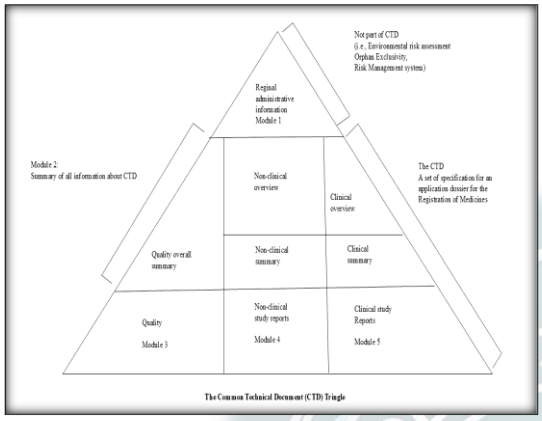


**Fig No. 1. The Common Technical Document (CTD) Triangle**

**INTRODUCTION TO CDSCO**

The Central Drugs Standard Control Organization (CDSCO) serves as India's national regulatory authority (NRA) and operates under the Directorate General of Health Services within the Ministry of Health and Family Welfare. CDSCO is responsible for approving drugs, overseeing clinical trials, setting drug standards, monitoring the quality of imported medicines, and guiding state drug control authorities to ensure uniform implementation of the Drugs and Cosmetics Act, 1940. [21]

The CDSCO headquarters manages regulatory oversight of drug imports, approval of new drugs and clinical trials, convenes meetings of the Drugs Consultative Committee (DCC) and the Drugs Technical Advisory Board (DTAB), and functions as the Central License Approving Authority for granting specific licenses.[22]

**Drug Master File (DMF):**

To streamline the drug approval process, the USFDA issued guidelines for Drug Master Files (DMFs) in 1989. A DMF is not a substitute for other applications such as ANDA, NDA, IND, or export applications, and it is neither approved nor rejected on its own. DMFs contain detailed, confidential information regarding the drug's formulation and manufacturing process, and they are reviewed only when referenced in other regulatory submissions.[23]

A DMF has two sections. The first section, known as the applicant's part, is non-confidential and provides information about the quality requirements of the drug product that the licensee must submit in a license or amendment application. The second section, called the restricted part, is confidential and accessible only to regulatory authorities. It includes detailed information about the drug's manufacturing process, safeguarding proprietary production data.

DMFs are not mandatory filings, are stored in a separate database, and are evaluated only when referenced in NDA or ANDA submissions. This is what distinguishes DMFs from other types of regulatory applications. [24]

**Drug Approval Process:**

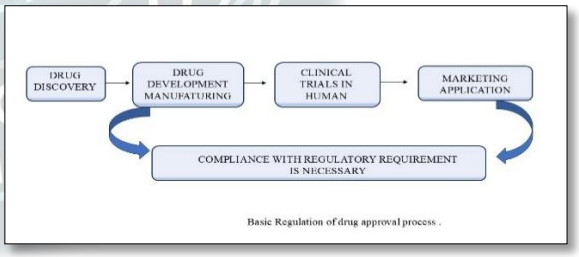


**Fig No. 2. Drug Approval Process**

**CDSCO DRUG APPROVAL PROCESS: STEP-BY-STEP** [25]

1. **Determine the Product Category**
   Identify whether the product is a biologic, Fixed-Dose Combination (FDC), or a novel drug. New drugs must obtain CDSCO approval before entering the market.
2. **Prepare the Application**

| Form | Purpose |
|---|---|

| | |
|---|---|
| Form 44 | Submission of new drug applications |
| Form CT-04 | Request for clinical trial permission |
| Form 10 | License to import a drug |
| Form 11 | Permission for testing and research (non-commercial) |

**Table No. 1. Prepare the Application**

**3.Dossier Submission (CTD/eCTD)**

Submissions must follow the Common Technical Document (CTD) format:

- Module 1: Regional information (India-specific)
- Module 2: Summaries and overviews
- Module 3: Quality data
- Module 4: Non-clinical studies
- Module 5: Clinical study reports

**4.Review by Subject Expert Committee (SEC)**

Expert panels within the SEC conduct scientific evaluations to verify data integrity, safety, and efficacy of the submission.

**5.Approval or Query Letter**

If all requirements are met, CDSCO issues Form 46 to grant approval. If additional information is needed, a query letter is sent requesting clarification.


**Fig No. 3. CDSCO Drug Approval Process**

## INTRODUCTION TO USFDA

Before the 20th century, the United States had very few federal laws regulating the composition and distribution of food and medicines, with the exception of the brief Vaccine Act of 1813. Various state laws provided limited protection against deceptive practices, such as mislabeling food products or medicines. The U.S. Food and Drug Administration (USFDA) traces its roots to the Division of Chemistry (later the Bureau of Chemistry) within the U.S. Department of Agriculture in the late 1800s. Under the leadership of Harvey Washington Wiley, who became chief chemist in 1883, the Division began investigating food and drug adulteration and misbranding in the American market. [26,27]

## DRUG MASTER FILE (DMF)

A Drug Master File (DMF) is a submission to the U.S. Food and Drug Administration (FDA) that provides confidential, detailed information about the facilities, processes, materials, or equipment used in the manufacture, processing, packaging, and storage of one or more human-use pharmaceutical products. [28]

Starting from May 5, 2018, all submissions to both existing and new Drug Master Files (DMFs) must be made using the electronic Common Technical Document (eCTD) format. Any DMF submissions submitted after this date that do not follow the eCTD format will be considered ineligible. [29]

## USFDA DRUG APPROVAL PROCESS

The drug approval process with the USFDA involves five key steps:

1. Discovery and Preclinical Research
2. Investigational New Drug (IND) Application
3. Clinical Trials (Phase I–III)
4. New Drug Application (NDA) Submission and Review
5. Post-Marketing Surveillance (Phase IV)

**1.Discovery and Preclinical Study**

Before a new drug is tested in humans, it undergoes preclinical testing in laboratory animals. During this stage, the focus is on:

- Identifying potential drug candidates
- Assessing pharmacological activity
- Evaluating toxicity, bioavailability, and pharmacokinetics

Key preclinical studies include:

- In vitro tests using cell cultures
- In vivo studies in animals to assess safety and biological effects
- Toxicology studies to detect possible adverse effects

The results from these preclinical studies form the basis for submitting an Investigational New Drug (IND) application, which is the next essential step in the drug approval process.

**2.Investigational New Drug (IND) Application**

An IND application is submitted to the FDA to obtain permission to begin testing a drug in humans. The application must include preclinical study results, details of the drug's composition, manufacturing information, pharmacological and safety data, investigator details, and the proposed plan for clinical trials. The FDA reviews the IND application within 30 days. If the FDA does not issue a clinical hold within this period, the sponsor may proceed with human trials.

It is important to note that IND approval is not a marketing authorization. Instead, it grants permission to conduct clinical studies, ensuring that preclinical data have been properly evaluated and that participants are not exposed to unnecessary risks.

**3.Clinical Trials: Phases I–III**

Once the IND is approved by the FDA, the investigational drug enters the three main phases of clinical trials.

**Phase I: Safety and Dosage**

Phase I typically lasts several months and involves 20–100 healthy volunteers or patients. The primary objective is to assess the drug's safety, tolerability, and pharmacokinetics.

**Phase II: Efficacy and Side Effects**

Phase II focuses on determining the optimal dose and evaluating preliminary efficacy. This phase is conducted with 100–300 patients who have the target condition and usually takes a few months to two years to complete.

**Phase III: Large-Scale Efficacy and Safety Monitoring**

In Phase III, the drug is tested in 1,000–3,000 patients to confirm effectiveness, monitor side effects, and compare it with existing treatments. This phase generally lasts one to four years and provides the critical data needed for regulatory approval.

**4.New Drug Application (NDA) Submission and Review**

A New Drug Application (NDA) is a formal request submitted to the FDA seeking permission to market a new drug in the United States. The NDA must include comprehensive clinical trial data, manufacturing information, proposed labeling, risk-benefit analysis, and updates on safety.

The FDA provides 60 days for initial review of submissions, while a standard review typically takes 10 months, and a priority review takes 6 months. During this period, the FDA inspects manufacturing facilities, evaluates clinical and statistical data, and reviews the company's labeling and promotional materials. After completing the review, the FDA either issues an approval letter, allowing the drug to be marketed, or a complete response letter, highlighting deficiencies that must be addressed before approval.

**5.Post-Marketing Surveillance (Phase IV)**

The drug approval process continues even after FDA authorization. Phase IV studies, also known as post-marketing surveillance, monitor the drug after it has been released to the market. This phase focuses on evaluating long-term safety, identifying rare side effects, studying drug interactions, and assessing use in specific populations, such as the elderly and pregnant women. [30]

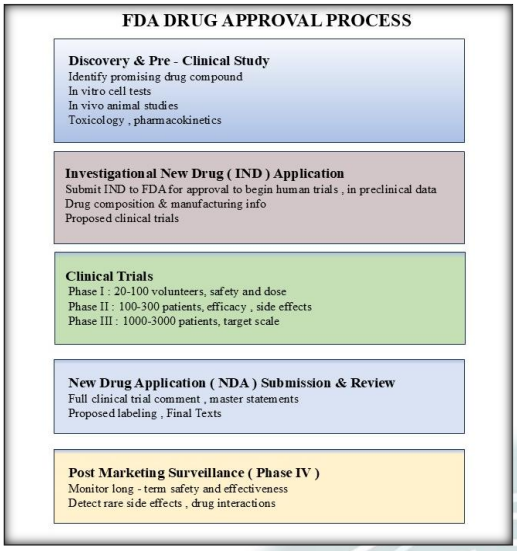


Fig. **No. 4. FDA Drug Approval Process**

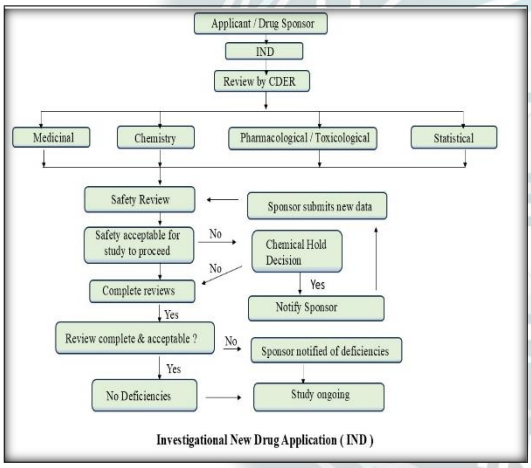


**Fig No. 5. Investigational New Drug Application (IND)**

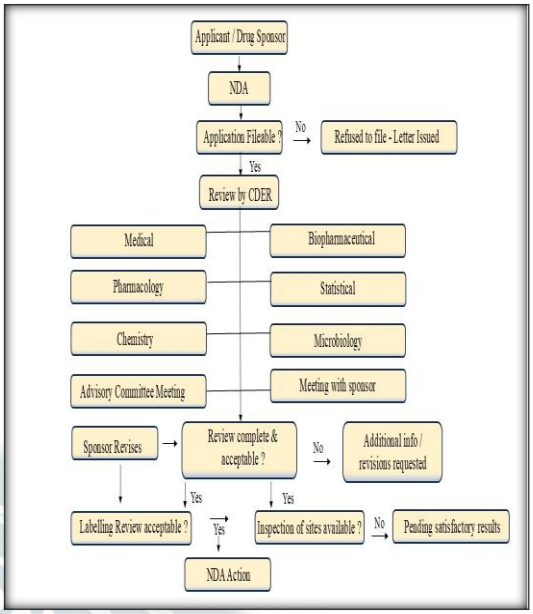


**Fig No. 6. New Drug Application (NDA)**

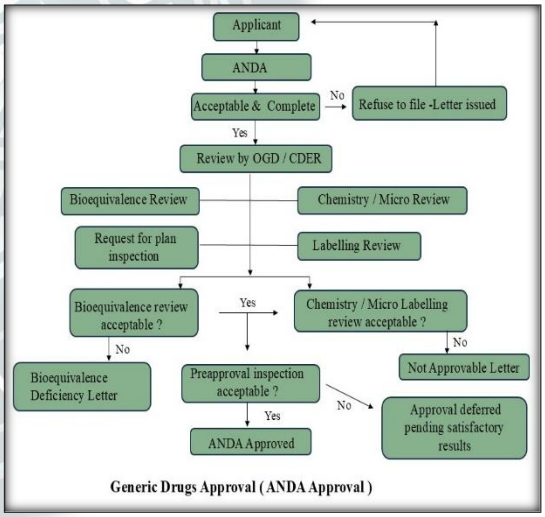


**Fig No. 7. Generic Drug Approval (ANDA Approval)**

## INTRODUCTION TO EMA

The European Medicines Agency (EMA) was founded in 1995 to protect human and animal health within and beyond the European Union (EU). The agency evaluates medicines following rigorous scientific standards and provides unbiased, science-based information about medications to its partners and stakeholders. [31]

The scientific activities of the European Medicines Agency (EMA) are conducted by seven specialized scientific committees, along

with several working groups and related expert panels. [32]

**DMF: European Drug Master File (DMF) / Active Substance Master File (ASMF)**

In cases where the manufacturer of the active ingredient is not the same as the applicant for a marketing authorization, the European Commission (EC) procedure enables confidential sharing of information with both the applicant and regulatory authorities to protect proprietary manufacturing knowledge. The European DMF system was established between 1989 and 1991. After the implementation of the CTD in the EU, the document was updated in 2005 and renamed as the Active Substance Master File (ASMF).

The ASMF is divided into two parts that apply specifically to active substances: the applicant's part and the ASM Restricted Part. The Active Substance Manufacturer (ASM) provides the applicant with their section of the DMF, which is then included in the marketing authorization application. Regulatory authorities receive both the applicant's section and the ASM Restricted Part for review. [33]

**EMA DRUG APPROVAL PROCESS:**

**European Drug Approval**

In Europe, drug approval involves two main regulatory pathways: the Clinical Trial Application (CTA) and the Marketing Authorization Application (MAA). While MAAs can be submitted at either the centralized or member state level, CTAs are approved solely at the member state level. [34]

**Centralized Procedure:**

Through the centralized procedure, a single marketing authorization is issued that is valid across the EU, Norway, Iceland, and Liechtenstein. The application is assessed by a designated rapporteur and submitted to the European Commission along with the EMA's opinion within approximately 210 days. This pathway is mandatory for orphan drugs, treatments for HIV/AIDS, diabetes, neurodegenerative or autoimmune disorders, and medicines derived from biotechnology. [35]

**Mutual Recognition Procedure (MRP):**

The Mutual Recognition Procedure, which typically takes around 390 days, allows a drug that has been approved by one Reference Member State (RMS) to obtain marketing authorization in other Concerned Member States (CMS). [36]

**National Procedure:**

This procedure allows the marketing of new active substances that are not included under the centralized procedure in a single EU member state. The process generally takes around 210 days. [37]

**Decentralized Procedure:**

The decentralized procedure is used to authorize products that have not yet been approved in multiple EU countries. It involves a review by the Reference Member State (RMS) and consideration of comments from the Concerned Member States (CMS), with a typical timeline of 210 days. [38]

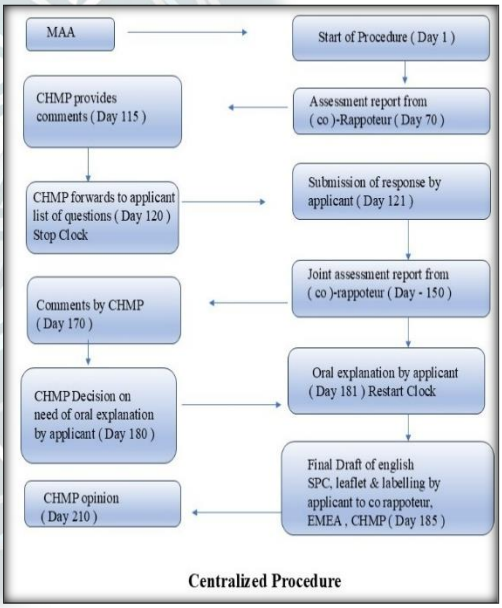


**Fig No. 8. Centralized Procedure**

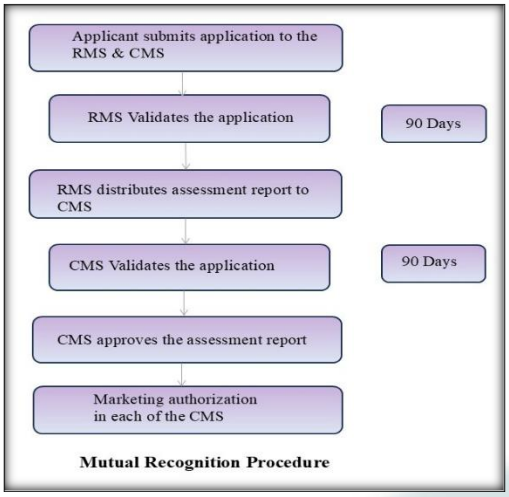


**Fig No. 9. Mutual Recognition Procedure**

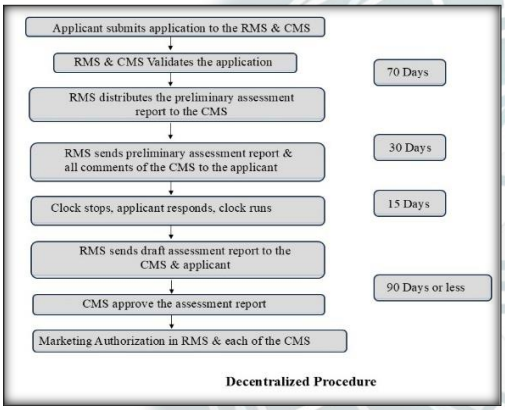


**Fig No. 10. Decentralized Procedure**

**COUNTRY-SPECIFIC VARIATIONS IN THE FORMAT AND REQUIREMENTS FOR DRUG MASTER FILES** [39]

| **Requirement** | **India** | **US** | **Europe** |
|---|---|---|---|
| Regulatory Body | CDSCO | USFDA | EMA |
| Purpose of Filing | Not applicable | Used when relevant information is missing in the CMC section of an application | Used when the marketing authorization applicant is different from the active substance manufacturer |
| Use of DMF in Support of Applications | MAA | IND, NDA, ANDA | MAA |
| Information Provided | API, drug products, flavors, colorants, etc. | Drug intermediate, drug substance, drug products, flavors, etc. | Active substance |
| DMF Number Assignment | No DMF number assigned | DMF number assigned | No DMF number assigned |

**Table No. 2. Country-specific variations in the format and requirements for drug master files**

**Common Abbreviations in Regulatory Affairs:**

- USFDA – United States Food and Drug Administration
- EMA – European Medicines Agency
- CDSCO – Central Drugs Standard Control Organization (India)
- IND – Investigational New Drug
- NDA – New Drug Application
- ANDA – Abbreviated New Drug Application
- MAA – Marketing Authorization Application
- API – Active Pharmaceutical Ingredient
- DMF – Drug Master File

### 3.1 MODULAR STRUCTURE OF THE eCTD

The Common Technical Document (CTD) is organized in a modular format, consisting of Modules 1 to 5:

- Module 1: Regional administrative information, which varies for each ICH region
- Module 2: Summaries of the overall submission
- Module 3: Quality-related information
- Module 4: Nonclinical study reports

- Module 5: Clinical study reports [40]

The following topics are covered in Module 1:

**Module 1: Administrative and Prescribing Information**

Overview:

Module 1 of the eCTD contains documents specific to each region, such as application forms or proposed product labeling for that region. The format and content of this module may be defined by the respective regulatory authorities. Guidelines for creating the electronic Common Technical Document (eCTD) are provided to ensure standardization.

**Backbone File Structure for Module 1 (eCTD):**

- Start of the Module 1 eCTD Backbone File
- Admin Elements

The admin element, part of the FDA regional element, includes administrative information divided into three main components:

1. Admin Applicant-info
2. Product-description
3. Application-information

These components should be arranged in the order listed above.

**1.Applicant-applicant-info element**

This element contains applicant information, such as the company name and submission date, which are included within the application-info elements.

**2.Company-name element**

The company-name element specifies the name of the sponsor or applicant. For example, a sample entry could be "Top Pharmaceutical Company". This element should be included in every submission.

**3.Date-of-submission element**

Indicates the date on which the application is submitted.

**4.Prod-name element**

This element provides the product name. Multiple types of product names can be included, with an attribute specifying the type of name used in the submission.

In the prod-name element, up to four types of product names can be included in a single submission. Each prod-name element must have an attribute called "type" to indicate which category of product name is being used. The four allowed values for the type attribute are summarized in the table below.

| Type Attribute | Value / Description |
|---|---|
| type = "established" | Established name (proper or generic name) |
| type = "proprietary" | Proprietary name (brand name or trade name) |
| type = "chemical" | Chemical name (Greek letters spelled fully; no superscripts or subscripts) |
| type = "code" | Internal code used by the application sponsor |

**Table 3: Product Name Types and Corresponding Type Attributes**

**5.Application-information Element**

The application-information element includes details about the submission. Each element must have an attribute called "application-type" to indicate the type of application being submitted. You should select one of the allowed values for the application-type attribute. The permitted application types and their meanings are summarized in the table below.

| Application-Type Attribute | Application Type (Meaning) |
|---|---|
| application-type = "nda" | New Drug Application |
| application-type = "anda" | Abbreviated New Drug Application |
| application-type = "bla" | Biologics License Application |
| application-type = "ind" | Investigational New Drug Application |
| application-type = "dmf" | Drug Master File |

**Table 3: Application Types and Corresponding Attribute Values**

**Leaf Element**

The leaf element contains information specific to an individual document, along with its attributes and associated title element. In eCTD submissions, the leaf element is frequently used in the backbone files to provide unique details for each submitted document. Detailed explanations of all components of the leaf element and guidance on their usage can be found in the eCTD Backbone File Specifications for Modules 2 through 5.

**Heading Elements for Module 1**

The heading elements in Module 1 are similar to those defined in the eCTD Backbone File Specifications for Modules 2 through 5. This section outlines the heading elements that are specifically applicable to Module 1.

V. Document Type Definition (DTD) The DTD defines the different types of documents that can be included in the eCTD submission.[41]

**Topics Covered in Module 1:**

- Section 1.2: Cover letter, Statement of Commitment, and Generic Drug User Fee Cover Sheet (Form 3794), if applicable.
- Section 1.3: Administrative information relevant to the submission.
- Section 1.4: Reference section, which includes:
    - 1.4.1 Letter of Authorization (LOA): Provided by the DMF holder to allow another party to reference the data.
    - 1.4.2 Statement of Right of Reference: Completed by the authorized person referencing the DMF, accompanied by a copy of the LOA granting access.
    - 1.4.3 List of Persons Authorized to Include by Reference: Lists companies whose LOAs have been submitted to the DMF and must be reported in the annual report.
- Section 1.5: Application status, including withdrawal of unauthorized BLA, NDA, ANDA, or supplement, requests for reactivation, and DMF closure.
- Section 1.6: Meetings related to the submission process.
- Section 1.11: Information amendments covering data not included in Modules 2 and 5, such as quality updates, nonclinical, and clinical amendments.
- Section 1.12: Other communications, including requests for comments, guidance, and environmental assessments.
- Section 1.13: Annual report summarizing any manufacturing changes.
- Section 1.14: Labeling, which may include the final version of the product label. [42,43]

**MODULE 2: SUMMARIES**

Module 2 provides a general overview of the drug, including its pharmacologic class, mechanism of action, and proposed clinical use. The introduction is usually concise, ideally no longer than one page. It should include the drug's proprietary, non-proprietary, or common name, company name, dosage form, strength, route of administration, and intended indications.

The contents of Module 2 are organized into the following sections:

2.1 Table of Contents
- A comprehensive listing of all documents and sections included in Module 2.

2.2 Introduction
- A general introduction to the drug, including its pharmacologic class, mechanism of action, and suggested clinical use.

2.3 Quality Overall Summary (QOS)
- Provides an overview of the data contained in Module 3. The QOS should not include information already detailed in Module 3 or other CTD sections.
- The summary must offer sufficient information from each section to give the reviewer a clear understanding of Module 3. Key product characteristics, deviations from standard guidelines, and explanations should be highlighted.
- Important issues from Module 3 and relevant supplementary data (e.g., toxicological studies supporting impurity qualification) should be included, with

cross-references to volumes and page numbers in other modules.

2.3.S Drug Substance
- 2.3.S1 General Information
- 2.3.S2 Manufacturing
- 2.3.S3 Characterization
- 2.3.S4 Control of Drug Substance
- 2.3.S5 Reference Standards or Materials
- 2.3.S6 Container Closure System
- 2.3.S7 Stability

2.3.P Drug Product
- Details of the finished product, including formulation and control measures.

2.3.A Appendices
- 2.3.A1 Facilities and Equipment
- 2.3.A2 Adventitious Agent Safety Evaluation
- 2.3.A3 Excipients

2.3.R Regional Information
- Region-specific regulatory information.

2.4 Non-Clinical Overview
- Summary of non-clinical data supporting the application.

2.5 Clinical Overview
- Summary of clinical data and findings.

2.6 Non-Clinical Written and Tabulated Summaries
- Detailed non-clinical data presented in narrative and tabular formats.

2.7 Clinical Summaries
- Summaries of clinical trials, outcomes, and safety information.

**MODULE 3: QUALITY**

Module 3 describes the structure and format for submitting information about drug substances and their corresponding drug products in a registration application. This format may also be applicable to other product categories; however, applicants are advised to consult the appropriate regulatory authorities to confirm whether this structure is suitable for their specific product type.

The contents of Module 3 are organized as follows:

3.1 Table of Contents
- A detailed listing of all sections and documents included in this module.

3.2 Body of Data

3.2.S Drug Substance
- 3.2.S1 General Information
  - Nomenclature
  - Structure
  - General properties
- 3.2.S2 Manufacture
  - Manufacturer details
  - Description of the manufacturing process and process controls
  - Control of materials
  - Control of critical steps and intermediates
  - Process validation and evaluation
  - Manufacturing process development
- 3.2.S3 Characterization
- 3.2.S4 Control of Drug Substance
- 3.2.S5 Reference Standards and Materials
- 3.2.S6 Container Closure System
- 3.2.S7 Stability

3.2.P Drug Product
- 3.2.P1 Description and Composition of Drug Product
- 3.2.P2 Pharmaceutical Development
- 3.2.P3 Manufacture
- 3.2.P4 Control of Excipients
- 3.2.P5 Control of Drug Product
- 3.2.P6 Reference Standards and Materials
- 3.2.P7 Container Closure System
- 3.2.P8 Stability

3.2.A Appendices
- Supporting documentation or additional technical data.

3.2.R Regional Information / Requirements
- Region-specific or authority-specific information.

3.2 List of Literature References
- Includes bibliographic references supporting data and justifications provided in the

**MODULE 4: NON-CLINICAL STUDY REPORTS**

Each study report included in Module 4 should generally be submitted as an independent document. However, if a study report is extensive—such as in the case of carcinogenicity studies—the applicant may divide it into multiple parts. In such instances, the main report should remain in one document, while supplementary materials or appendices can be submitted as separate files.

When deciding how to organize these reports, the applicant should consider that any time key information is updated during the product's lifecycle, revised versions of the affected documents must be provided.

The structure and content of Module 4 are divided into the following sections:

4.1 Table of Contents

4.2 Study Reports

4.2.1 Pharmacology

- 4.2.1.1 Primary pharmacodynamics
- 4.2.1.2 Secondary pharmacodynamics
- 4.2.1.3 Safety pharmacology
- 4.2.1.4 Pharmacodynamic drug interactions

4.2.2 Pharmacokinetics

- 4.2.2.1 Methods of analysis
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic drug interactions (non-clinical)
- 4.2.2.7 Other pharmacokinetic studies

4.2.3 Toxicology

- 4.2.3.1 Single-dose toxicity (by species and route)
- 4.2.3.2 Repeat-dose toxicity (by species, route, and duration, including toxicokinetic evaluations)
- 4.2.3.3 Genotoxicity
  - 4.2.3.3.1 In vitro studies
  - 4.2.3.3.2 In vivo studies (including toxicokinetic evaluations)
- 4.2.3.4 Carcinogenicity (including toxicokinetic support)
  - 4.2.3.4.1 Long-term studies (by species; includes range-finding studies not suitable for repeat-dose sections)
  - 4.2.3.4.2 Short- or medium-term studies (includes range-finding studies)
  - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and developmental toxicity
  - 4.2.3.5.1 Fertility and early embryonic development
  - 4.2.3.5.2 Embryo-fetal development
  - 4.2.3.5.3 Prenatal and postnatal development (including maternal function)
  - 4.2.3.5.4 Studies on offspring (juvenile animals)
- 4.2.3.6 Local tolerance
- 4.2.3.7 Other toxicity studies (if available)
  - 4.2.3.7.1 Antigenicity
  - 4.2.3.7.2 Immunotoxicity
  - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
  - 4.2.3.7.4 Dependence
  - 4.2.3.7.5 Metabolites
  - 4.2.3.7.6 Impurities
  - 4.2.3.7.7 Other

4.2 Literature References

Includes published scientific studies and supporting references used in the preparation of Module 4.

**MODULE 5: CLINICAL STUDY REPORTS**

Module 5 of the Common Technical Document (CTD) focuses on the presentation of clinical study reports and related data that support the safety, efficacy, and pharmacological properties of a medicinal product. The structure of this module ensures that all essential information is systematically arranged for efficient review by regulatory authorities.

To clearly identify all vital elements of the submission—such as placebo-controlled trials (5.3.5.1.1)—the Table of Contents for Module 5 must include all the numerical subsections specified in CTD guidelines. The contents should be detailed enough to list every clinical study report individually. Either the overall table of contents for Module 5 or the specific table of contents of each clinical report may be used to identify individual study sections as per the ICH E3 guidance.

**Structure and Contents of Module 5**

**5.1 Table of Contents**

This section provides a detailed listing of all subsections and documents included in Module 5, ensuring traceability and logical flow.

**5.2 Tabular Listing of All Clinical Studies**

This section presents all clinical trials and associated studies in a tabular format. The table should typically include the information outlined in the CTD guidance (Table 5.1), such as study type, design, indication, population, and investigational drug details. Applicants may include additional data if it provides further clarity. The order of studies should follow the same sequence described in Section 5.3; if a different order is used, it must be clearly justified in the introduction to the tabular listing.

**5.3 Clinical Study Reports**

This section compiles detailed reports of all clinical studies performed to evaluate the drug. The subsections include:

- Reports of biopharmaceutics studies
- Bioavailability (BA) study reports
- Comparative bioavailability and bioequivalence (BE) study reports
- In vitro–in vivo correlation (IVIVC) study reports
- Reports of bioanalytical and analytical methods used in human studies
- Reports of studies related to pharmacokinetics using human biological materials
- Plasma protein binding study reports
- Reports on hepatic metabolism and drug interaction studies
- Reports of studies involving other human biomaterials
- Reports of human pharmacokinetic (PK) studies
- Reports of human pharmacodynamic (PD) studies
- Reports of efficacy and safety clinical trials
- Reports on post-marketing experience, summarizing adverse events and safety findings
- Case report forms (CRFs) and individual patient listings, when applicable Conclusion [41]

**CONCLUSION**

The development of pharmaceutical regulatory frameworks in India, the United States, and Europe demonstrates a unified global effort to ensure the safety, efficacy, and quality of medicines while embracing technological advancements. Regulatory authorities such as the CDSCO, USFDA, and EMA play vital roles in the evaluation, monitoring, and approval of medicinal products, each reflecting both common objectives and region-specific priorities.

The introduction of the Common Technical Document (CTD) and its digital version, the electronic Common Technical Document (eCTD), has brought uniformity to submission formats worldwide. This shift has minimized duplication, enhanced efficiency, and shortened review timelines. Although all three regions follow the modular eCTD structure (Modules 1 - 5), each maintains unique characteristics India focuses on administrative and regional documentation in Module 1, the United States emphasizes detailed clinical and non-clinical data for New Drug Applications (NDAs), and Europe incorporates centralized, decentralized, and mutual recognition procedures to address multi-country approvals.

Drug Master Files (DMFs) continue to be essential for maintaining the confidentiality of proprietary manufacturing data while supporting regulatory transparency. The USFDA issues DMF numbers, while India and Europe follow their own procedural systems. Despite these regional differences, all aim to protect sensitive data and streamline the drug approval process.

When comparing regulatory pathways from preclinical evaluation and Investigational New Drug (IND) applications to clinical trials, NDA submissions, and post-marketing surveillance each region exhibits distinct timelines and processes. For instance, the EMA utilizes centralized and mutual recognition routes to harmonize approvals across member states, whereas CDSCO and USFDA rely on nationally governed review mechanisms and regulatory committees.

In summary, the worldwide implementation of eCTD-based submissions, modular documentation, and harmonized DMF practices has strengthened the transparency and consistency of the global drug approval landscape. This alignment among international regulatory agencies promotes faster drug

development and approval while maintaining the highest standards of safety, efficacy, and quality.

## REFERENCES


1. https://www.researchgate.net/profile/Jitendra-Badjatya/publication/326576082_OVERVIEW_OF_DRUG_REGULATORY_AFFAIRS_AND_REGULATORY_PROFESSION/links/5f887f51a6fdccfd7b654692/OVERVIEW-OF-DRUG-REGULATORY-AFFAIRS-AND-REGULATORY-PROFESSION.pdf?origin=journalDetail&_tp=eyJwYWdlIjoiam91cm5hbERldGFpbCJ9
2. H. Broughton, A Global History of Regulatory Affairs How Regulation Shaped the Modern Pharmaceutical Industry, Journal of Regulatory Affairs, 2020:11(4):123-145.
3. https://ijprdjournal.com/myapp/uploads/355-TOMBOLI%20TOHIF%202447-2460.pdf
4. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html?utm_source
5. https://www.jpharmsci.org/article/S0022-3549%2817%2930779-7/abstract?utm_source
6. https://aapsopen.springeropen.com/articles/10.1186/s41120-025-00113-7?utm_source
7. Carl MA. Regulatory Streamlining and Improvement. Interstate Oil and Gas Compact Commission. Technical Report; 2006 Jul 11.
8. Ahluwalia K, Abernathy MJ, Beierle J, Cauchon NS, Cronin D, Gaiki S, et al. The future of CMC regulatory submissions: Streamlining activities using structured content and data management. J Pharm Sci. 2022 May 1;111(5):1232-44.
9. Challa SS, Chawda AD, Benke AP, Tilala M. Streamlining change control processes in regulatory affairs: Best practices and case studies. Integr J Res Arts Human. 2024 Jul 18;4(4):67-75.
10. Alquier L, Richmond FJ. Streamlining processes-the WHO collaborative procedure for accelerated registration in Africa. Regul Rapporteur. 2021;18(9):4-7.
11. https://web.archive.org/web/20180423215550id_/http://ijtpls.com/wp-content/uploads/2015/09/IJTPLS-2015-Vol-12-p-RA2-sruthi-225-231.pdf
12. Sama R, Latha KS, Sathish M, Krishna MG, Santhosh P. Electronic common technical document (eCTD): A review of history, benefits of implementing, challenges, modules, risks involved in eCTD publishing and quality control. Int J Pharm Chem Biol Sci. 2016;6(2):133-49.
13. Wikipedia. http://en.wikipedia.org/wiki/electronic_common_technical_document.
14. https://link.springer.com/article/10.2165/00124363-200620030-00001
15. https://www.ecv.de/ecv/catalog/ecv-rs/dra/upload/0057-0063_PI0110_Thormeyer.pdf
16. Pansare SD, Chavanke P. Review on CTD and eCTD submission criteria. International Research Journal of Modernization in Engineering, Technology and Science. 2024;6(1):869-873.
17. https://kronika.ac/wp-content/uploads/13-KKJ2367.pdf
18. www.ivowen.com/regulatory-affairs-common-abbreviations acronyms/
19. ICH M2 EWG – eCTD specifications ICH M2 EWG Electronic Common Technical Document Specification version 3.2.2." (PDF). ICH. Retrieved 29 October 2015.
20. www.fda.gov/RegulatoryInformation/Guidances/ucm126959 .htm
21. Janjal VS, Dhamodkar SR, Jadhao YP, Manmode SB, Pawar AK, Khandelwal H. Recent drug regulatory affair and CTD module progress review for submission of pharmaceutical products. GSC Biological and Pharmaceutical Sciences. 2021;16(3):200-221.
22. https://cdsco.gov.in/opencms/opencms/en/About-us/Introduction/
23. Drug Master Files Guidance for Industry. [[Last accessed on 2023 Mar 31]]. Available from: https://www.fda.gov/media/131861/download .
24. Sravanti VK, Bandla R, Juturi RK. Filing of DMF in the US, EU, and India, and its comparative review. Int J Drug Regul Aff. 2021;9:22–32. [Google Scholar]
25. CDSCO Drug Approval Process – Step-by-Step Drug Registration Guide in India
26. ICH M2 technical specification, Electronic Common Technical Document

Specification (accessible at http://estri.ich.org/eCTD/index.htm).
27. FDA technical specification, eCTD Backbone Files Specification for Module 1 (accessible athttp://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm).
28. FDA guidance for industry, ICH M4 Granularity Annex, Granularity Document — Annex to M4: Organization of the CTD (accessible athttp://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm).
29. FDA technical specification, FDA eCTD Table of Contents Headings and Hierarchy (accessibleathttp://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm).
30. https://www.pharmaguideline.com/2025/05/understanding-us-fda-drug-approval-process.html [30]
31. https://www.ema.europa.eu/en/about-us/history-ema
32. https://www.ema.europa.eu/en/committees/how-committees-work
33. https://www.jgtps.com/admin/uploads/tmvf0T.pdf
34. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 48
35. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 212-14
36. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 215-17
37. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 49
38. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 51
39. https://pmc.ncbi.nlm.nih.gov/articles/PMC11698287/table/ijp_297_23-t001/#R6
40. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised common technical document. Adopted 2000 Nov [online]. Available from URL: http://www.ich.org/cache/compo/1325-272-1.html [Accessed 2006 Jun 12]
41. https://www.researchgate.net/profile/N-Vishal-Gupta/publication/224937610_Documentation_in_the_process_of_obtaining_US_FDA_approval_for_a_tablet_manufacturing_industry/links/55dc96f208aeb38e8a8d2235/Documentation-in-the-process-of-obtaining-US-FDA-approval-for-a-tablet-manufacturing-industry.pdf
42. CDER SBIA Webinar Series. New Requirement for Electronic Submission of Drug Master Files ( DMFs ): What You Need to Know New Requirement for Electronic Submission of DMFs [Internet]. USA: USFDA; 2016. Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM485449.pdf
43. USFDA. The eCTD Backbone Files Specification for USFDA; 2014. Module 1. USA: Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf