Content and Format of an Initial IND Submission

21 CFR 312.23

REdI Fall Conference 2017

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Poll Question 

- **How many commercial and research INDs* combined did CDER receive during the 2016 calendar year?**
  - **960**
  - **1,669**
  - **501**
  - **2,185**

***Excludes Biosimilar Biologic INDs, Expanded Access INDs, and Unknown INDs. Unknown refers to those INDs where the designation of Commercial or Research had not been made at the end of the calendar year.**

How many INDs?

Commercial	+	Research	=	Total
777	+	892	=	1669*

*https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/UCM540616.pdf

21 CFR 312 - INDs

Subpart A:

- §312.1: Scope
- §312.2: Applicability
- §312.3: Definitions and interpretations

Subpart B:

- §312.20: Requirement for an IND
- §312.21: Phases of an investigation
- §312.22: General principles of the IND submission
- **§312.23: IND Content and Format**

Overview

IND Content and Format

§312.23

- Cover Letter
- Regulatory Forms
  - FDA 1571 (Cover sheet)
  - FDA 1572 (Statement of Investigator)
  - FDA 3674 (clinical trials certification)
- Table of Contents

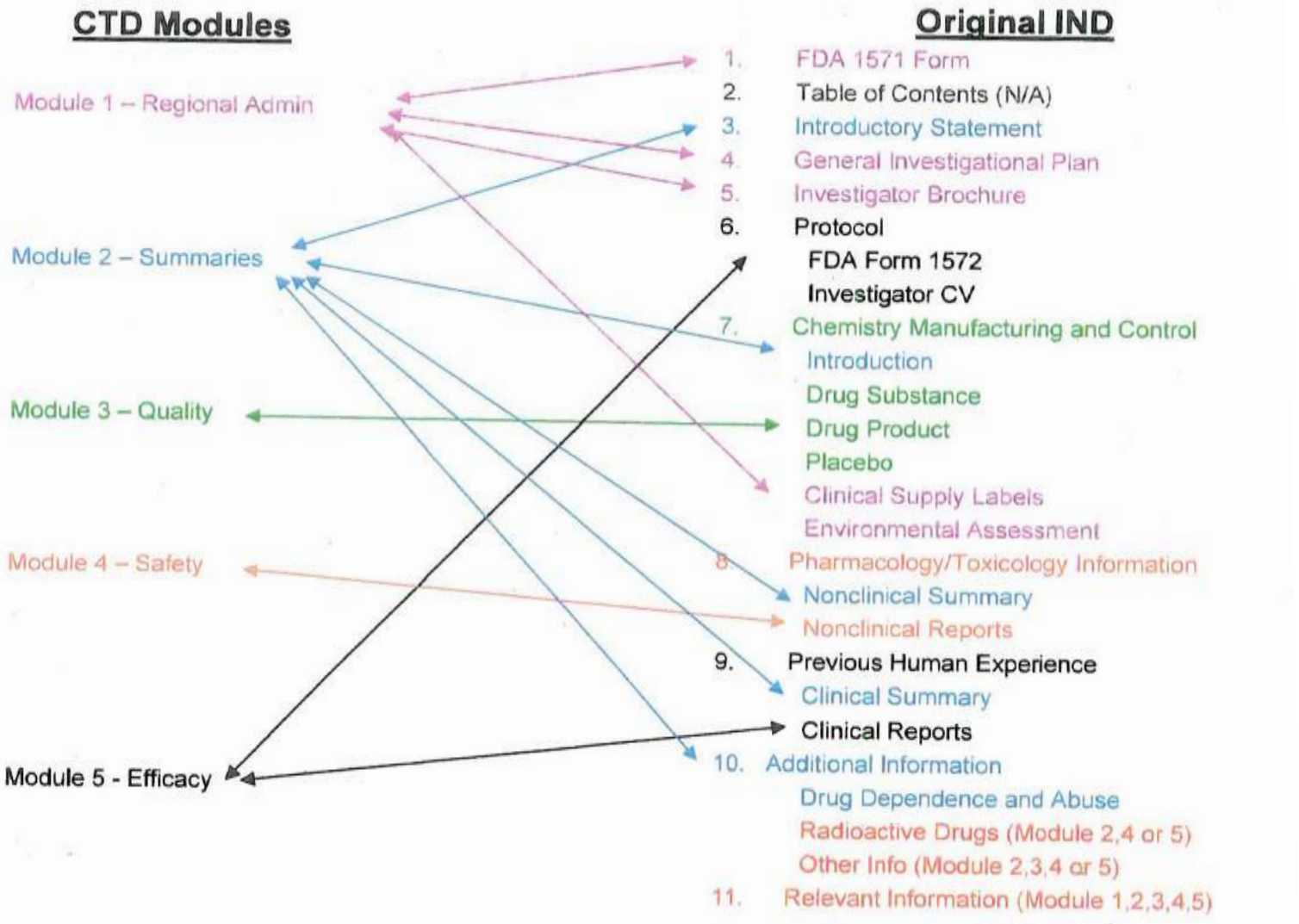
IND Content and Format

- Introductory statement
- General Investigational plan
- Investigator's brochure
- Protocol(s) - Clinical
- Chemistry, manufacturing and control data

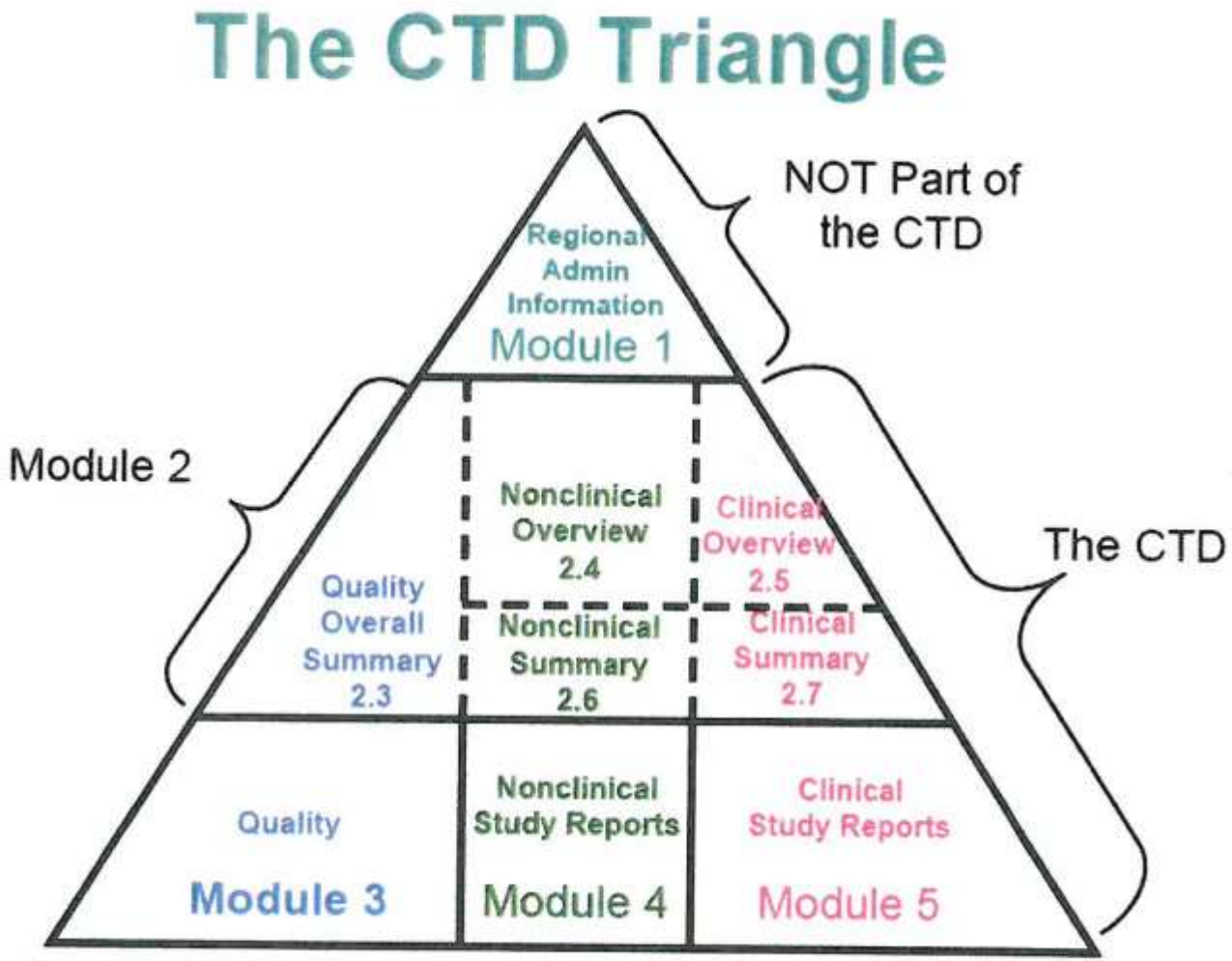
IND Content and Format

- Pharmacology and toxicology information
- Previous human experience
- Additional Information (drug dependence, abuse potential, radioactive, pediatric studies)
- Relevant information (foreign, previously submitted)

Mapping the IND to the CTD



Common Technical Document



Module Contents

CTD Modules	IND Items	
Module 1 – Regional Admin	IND Item 1. FDA 1571 Form	☐
	IND Item 2. Table of Contents (N/A)	
	Item 7. Environmental Assessment	☐
	Item 7. Clinical Supply Labels	☐
	IND Item 4 General Investigational Plan	☐
	IND Item 5. Investigator Brochure	☐
Module 2 – Summaries	IND Item 3 Introductory Statement	☐
	IND Item 7 CM&C Introduction	☐
	IND Item 8 Nonclinical Summary	☐
	IND Item 9 Previous Human Experience – Clinical Summary	☐
	IND Item 10 Additional Information	☐
	Drug Dependence and Abuse	☐
Module 3 – Quality	IND Item 7 Chemistry Manufacturing and Control	☐
	IND Item 7 Drug Substance	☐
	IND Item 7 Drug Product	☐
	IND Item 7 Placebo	☐
Module 4 – NonClinical Safety	IND Item 8 Pharmacology/Toxicology Information	☐
	IND Item 8 Nonclinical Reports	☐
Module 5 – Clinical Efficacy	IND Item 6. Protocol	☐
	FDA Form 1572	☐
	Investigator CV	☐
	Sponsor's CV	☐
	Item 9. Previous Human Experience Clinical Reports	☐

CTD – Sample Hierarchy

Module 1 Regional

- 1.1 Forms
  - 1.1.1. Form FDA 1571: Investigational New Drug Application
- 1.2 Cover Letters
  - Cover Letter
  - Certificate of Compliance: FDA Form 3674
- 1.3 Administrative Information
  - 1.3.1. Contact/sponsor/applicant Information
- 1.4 References
  - 1.4.1 Letter of authorization
  - 1.4.2 Statement of right of references
- 1.12 Other Correspondence
  - 1.12.1. Pre IND correspondence
  - 1.12.14 Environmental analysis
- 1.14 Labeling
  - 1.14.4. Investigational drug labeling
    - 1.14.4.1. Investigational brochure
    - 1.14.4.2. Investigational drug labeling
- 1.20 General investigational plan for initial IND

Module 2 Summaries

- 2.2 Introduction to summary
- 2.3 Quality overall summary
- 2.4 Nonclinical overview
- 2.5 Clinical overview
- 2.6 Nonclinical written and tabulated Summaries

Module Contents

Module 1 – Administrative Information

Module 2 – Summaries

Module 3 – Quality

Module 4 – Nonclinical Study Reports

Module 5 – Clinical Study Reports

IND Content and Format
Module 1 –Administrative

- Form 1571 – Investigational New Drug Application
- Cover Letter
- Guide to Reviewer/Reviewers Guide
- Clinical Trials Certification (Form FDA 3674)
- References [letters of authorization/cross-references]
- Fast Track or other designation requests
- Other Correspondence [meetings/waivers/environmental analysis]
- Annual Report / General Investigational Plan
- Investigator's Brochure
- Labeling

Form FDA 1571

- Format - Fill-in-the-blanks/check boxes

  Form FDA 1571 – Instructions:

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571

- Administrative / Application Information
- Sponsor Address
  - Responsible Agent
  - Contents of application

Key - Form FDA 1571

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor

2. Date of Submission *(mm/dd/yyyy)*

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

4. Telephone Number *(Include country code if applicable and area code)*

5. Name(s) of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*

Continuation Page for #5

6. IND Number *(If previously assigned)*

Key - Form FDA 1571

17. Name of Sponsor or Sponsor's Authorized Representative		
18. Telephone Number *(Include country code if applicable and area code)*	19. Facsimile (FAX) Number *(Include country code if applicable and area code)*	
20. Address		21. Email Address
Address 1 *(Street address, P.O. box, company name c/o)*		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		22. Date of Sponsor's Signature *(mm/dd/yyyy)*
City	State/Province/Region	
Country	ZIP or Postal Code	
23. Name of Countersigner		
24. Address of Countersigner		
Address 1 *(Street address, P.O. box, company name c/o)*		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		
City	State/Province/Region	**WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).**
Country United States of America	ZIP or Postal Code	

Cover Letter

- Typically 1-2 pages
- Addressed to the Division Director
- Submission identifier-Initial Investigational New Drug Application; reference to existing IND (if applicable)
- Brief explanation of the intended investigation (type/title of the study); protocol; mode of action
- Investigational product name and proposed formulation
- Disease or condition to be studied
- IND manufacturer's name and contact information
- Meetings held; specific requests

Reviewers Guide

- Identifies type of submission/material (media) submitted
- Provides an outline and summary of the contents in the IND submission
- Provided to assist the reviewers in navigating the application.
- Commercial IND applications (for products distributed commercially)

Form FDA 3674
Clinical Trials Certification

- Certification of Compliance
- Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. 282(j)) – Title VIII of FDAAA
- Registration and submission of trial results
- Applies to drugs, biologics and devices
- Register by date -NLT 21 days after the first patient is enrolled in any non-Phase 1 study

Module 1 – Administrative Information

- Other Correspondence
  - Meetings (pre-IND)
  - Environmental Analysis General
- Investigational Plan
- Investigators Brochure
- Labeling
  - Clinical Supply labels
  - Labeling

Investigational Plan
§312.23(a)(3)

- Brief description of the overall plan for investigation
- Summary of rationale to support trial
- Dose, Dosing Schedule, Patient Population
- Indication(s)
- Trial Duration/Number of Subjects
- Known risks (based on toxicology)

Investigator's Brochure
§312.23(a)(5)

- Description of drug substance, structural formula (if known) and formulation
- Summary of:
  - pharmacological and toxicological effects in animals, and if known, in humans
  - pharmacokinetics and biological disposition in animals, and if known, in humans
  - the safety and effectiveness information in humans
- Description of possible risks and side effects to be anticipated; special montoring

Module Contents

Module 1 – Administrative Information

Module 2 – Summaries

Module 3 – Quality

Module 4 – Nonclinical Study Reports

Module 5 – Clinical Study Reports

Module 2 –Summaries

Common Technical Document (CTD)

- Introduction to summary [2.2]
- Quality overall summary [2.3]
- Nonclinical overview [2.4]
- Clinical overview [2.5]
- Nonclinical written and tabulated summaries [2.6](pharmacology/PK/toxicology)
- Clinical summary [2.7](clinical pharmacology/ Efficacy/Safety/References)

Module 2 – Summaries

Introduction to Summary

- Usually several pages
- Name of the drug, all active ingredients, drug pharmacologic class, structural formula, dosage form, route of administration
- Clinical trial objectives and planned investigations
- Regulatory History / Summary of information

Module 2 – Summaries

- **Quality Overall Summary**
  - Drug Substance
  - Drug Product
- **Nonclinical Overview**
  - Overview of nonclinical testing
- **Nonclinical Written & Tabulated Summaries**
  - Pharmacology/Pharmacokinetics/Toxicology Summary

Module 2 – Summaries

- **Clinical Overview**
  - Brief description of the overall plan for investigation
  - Summary of rationale to support trial
  - Dose, Dosing Schedule, Patient Population
  - Indication(s)
  - Trial Duration/Number of Subjects
  - Known risks (based on toxicology)
- **Clinical Summary**
  - Biopharmaceutics/biopharmaceutical analytical methods
  - Clinical pharmacology
  - Clinical efficacy and safety data

Module Contents

Module 1 – Administrative Information

Module 2 – Summaries

Module 3 – Quality

Module 4 – Nonclinical Study Reports

Module 5 – Clinical Study Reports

Module 3 – Quality

Chemistry, Manufacturing, and Controls §312.23(a)(7)

- Drug Substance
- Drug Product
- Certificates of Analysis (COA)
- Placebo Formulation, if applicable
- Description of drug product/drug substance from non-IND foreign clinical studies

IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362283.htm

Module Contents

Module 1 – Regional and Administrative Information

Module 2 – Overview and Summaries

Module 3 – Quality

Module 4 – Nonclinical Study Reports

Module 5 – Clinical Study Reports

Module 4 – NonClinical Study Reports §312.23(a)(8)

- Adequate information about the drug's pharmacology and toxicology (in vitro or animal studies) to support use in humans
- Pharmacological effects and Drug Disposition study reports
- Pharmacodynamics (primary/drug interactions)
- Pharmacokinetics (ADME/analytical methods/validation)
- Toxicology
  - Summary of toxicological effects in animals & in vitro
  - Results of acute/subacute /chronic toxicity tests
  - Carcinogenicity
  - Reproduction / developmental toxicity/ fetal effects
  - Special toxicity tests due to mode of administration
- Literature References

Module Contents

Module 1 – Regional and Administrative Information

Module 2 – Overview and Summaries

Module 3 – Quality

Module 4 – Nonclinical Study Reports

Module 5 – Clinical Study Reports

Module 5 – Clinical

- Human Clinical study reports and related information/ components
- Protocols
- FDA Form 1572
- Investigator CVs
- Previous Human Experience (clinical study reports)*
- Other Clinical Reports [Human PK and PD Studies, Efficacy and Safety Studies, Antibacterial Microbiology/Special Pathogens, Literature References]

*Clinical Summary (Module 2)

Protocol(s) – Clinical
§312.23(a)(6)

- Components:
  - Clinical Protocol(s) / Phase of development
  - Qualifications of clinical investigator/sub-investigator(s)
  - Research facilities and Institutional Review Board
  - Previous human experience/ ex-US trials /PK data
  - Measures to monitor risk

Clinical Protocol
§312.23(a)(6)

- Phase 1
  - Outline of investigation
  - Estimate of patient numbers
  - Safety exclusions/Safety monitoring
  - Dosing plan with duration or method to determine dose

Clinical Protocol
§312.23(a)(6)

- Phase 2/3
  - Detailed complete protocol(s)
  - Statement of objectives and purpose
  - Proposed dosing and patient numbers
  - Inclusion / Exclusion criteria
  - Safety monitoring parameters / Stopping rules
  - Well designed studies

Form FDA 1572 – Statement of Investigator

- Requirement to have investigator(s) sign before participation
- Clinical Investigator qualifications
- Agreements:
  - conduct of protocol
  - obtain informed consent
  - Institutional Review Board (IRB) review
  - recordkeeping, adverse drug reactions

Regulatory Form

- Form FDA 1572-Statement of the Investigator conducting clinical research under IND
  - Form

    https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf
  - Instructions

    https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm223432.pdf
  - Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs – FAQ – Statement of Investigator (Form FDA 1572)

    http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

Previous Human Experience
§312.23(a)(9)

- Provide summary of previous experience
- Ex-US Marketing (information/labeling)
- Letter(s) of Authorization/Right of Reference
- State if no previous human experience

Additional and Relevant Information*

§312.23(a)(10) and §312.23(a)(11)

- **Drug Dependence and Abuse Potential**
  - Provide relevant clinical and/or animal study data
- **Radioactive Drug(s)**
  - Provide data from animal or human studies to calculate radiation-absorbed dose
- **Pediatric studies**
  - Provide plans
- **Information Previously submitted**
  - Incorporate by reference or include authorization
- **Material in a foreign language**
  - Original and translated versions

***as needed – use appropriate sections**

IND Application-Format

- **Paper**
  - Common Technical Document (CTD) format
  - Regulatory Content (21 CFR 312.23)
  - No longer accepted for commercial after 5/5/18
- **Electronic**
  - Must use CTD format
  - Physical media
  - Electronic Submission Gateway (ESG)

Submission of the IND

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Note: Effective May 5, 2018, all commercial INDs must be in electronic Common Technical Document (eCTD) format

Application Resources

- How Drugs are Developed and Approved

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm

- IND application (includes links to all IND Guidances)

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

- IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362283.htm

Application Resources

- Small Business Assistance
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069898.htm
- Investigator-Initiated Investigational New Drug Application
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm
- CTD/ Comprehensive Table of Contents Headings and Hierachy
  https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm270304.pdf

Additional Resources

- Electronic Common Technical Document (eCTD)

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- Electronic Submissions Gateway

  http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm
  - Preparation/Registration/Policy Questions: esgprep@fda.hhs.gov
  - Technical Issues: ESGHelpDesk@fda.hhs.gov
  - Secure e-mail account contact: SecureEmail@fda.hhs.gov
  - CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.
- Pre-assigned application number
  - Send one email per application number request to cderappnumrequest@fda.hhs.gov
- Electronic Common Technical Document (eCTD)

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Please complete the session survey:

surveymonkey.com/r/DRG-D1S03

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