Content and Format of an Initial IND Submission 21 CFR 312.23

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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

Which fields were recently added to the Investigational New Drug Application [FDA Form 1571]?

A. Field 6B
B. Field 7B
C. Field 12
D. All the Above

Answer – All the Above

FDA

Field 6B = IND TYPE

Field 7B = SNOMED CT INDICATION DISEASE TERM(S)

Field 12 = COMBINATION PRODUCTS

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf

Regulatory & Administrative Components

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 of Presentation

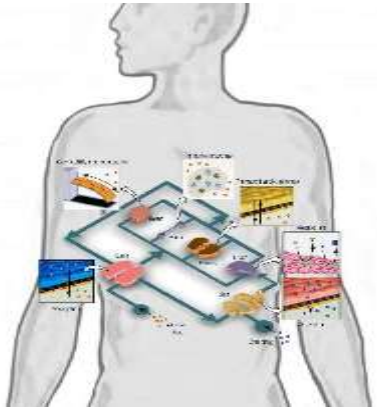
IND Content and Format

§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

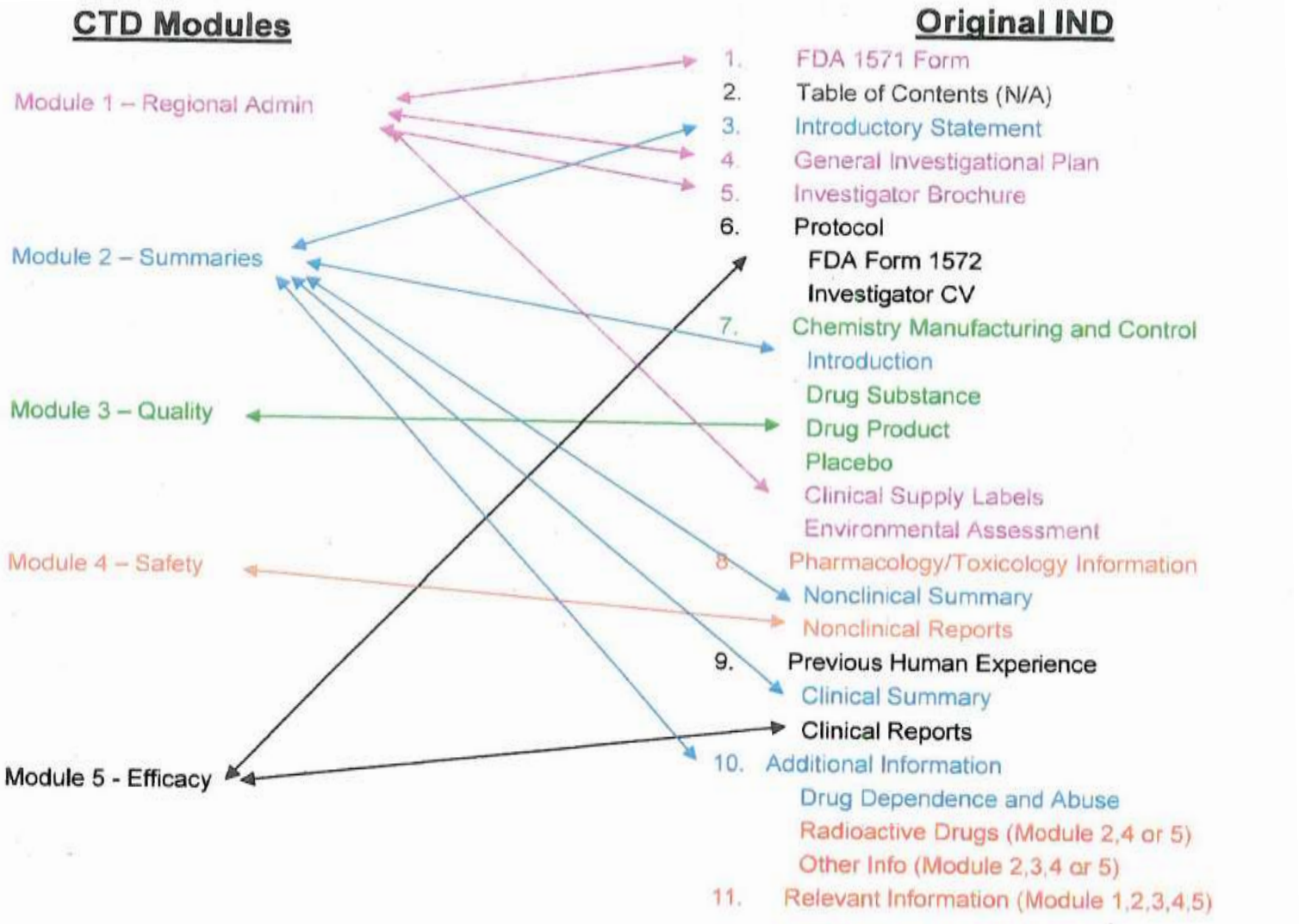
- Introductory statement
- General Investigational plan
- Investigator's brochure
- Protocol(s) - Clinical
- Chemistry, manufacturing and control data



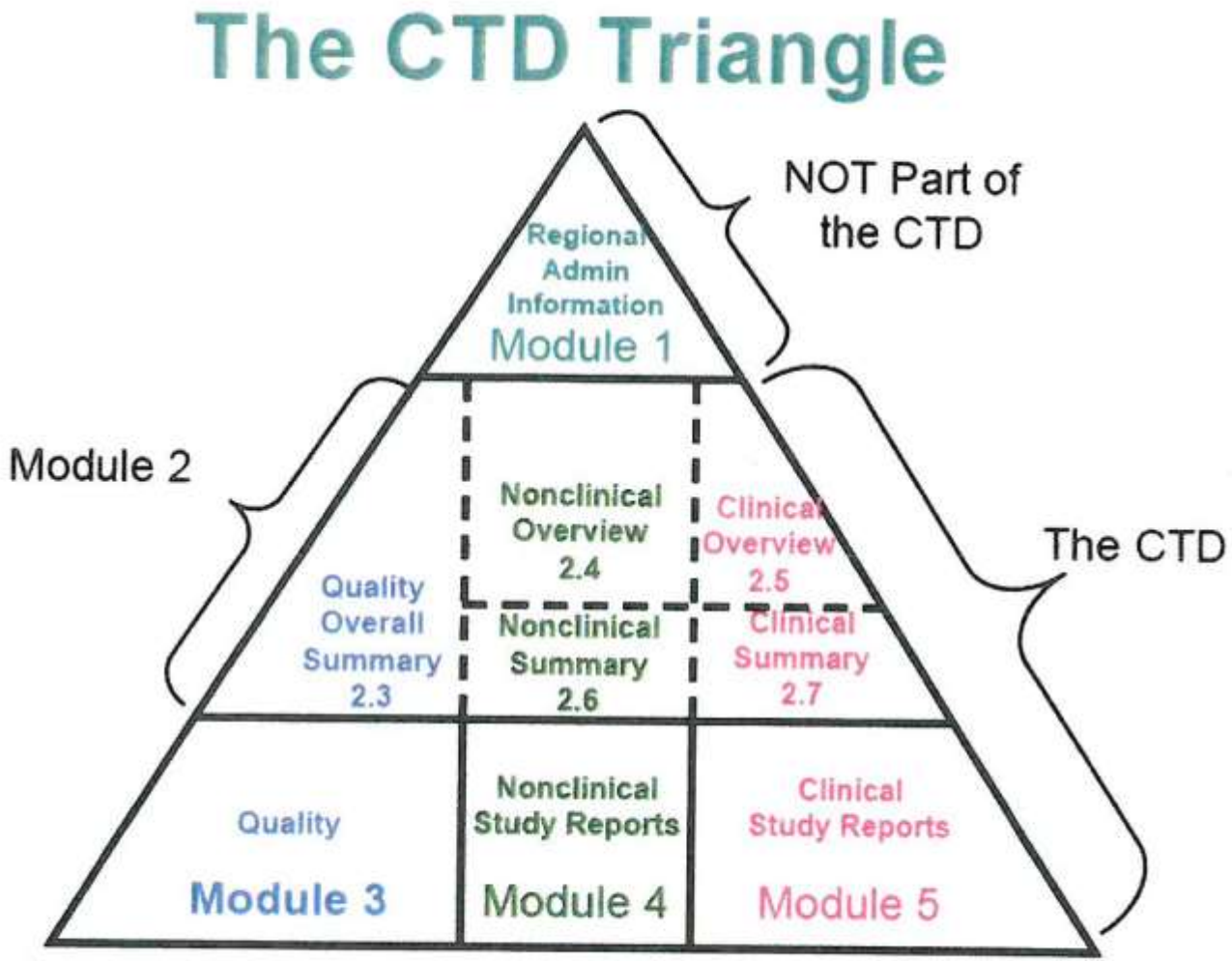
IND Content and Format

- 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



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

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

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

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

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)*

6A. IND Number *(If previously assigned)*

6B. Select One: ☐ Commercial ☐ Research

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

Continuation Page for #5

7A. (Proposed) Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

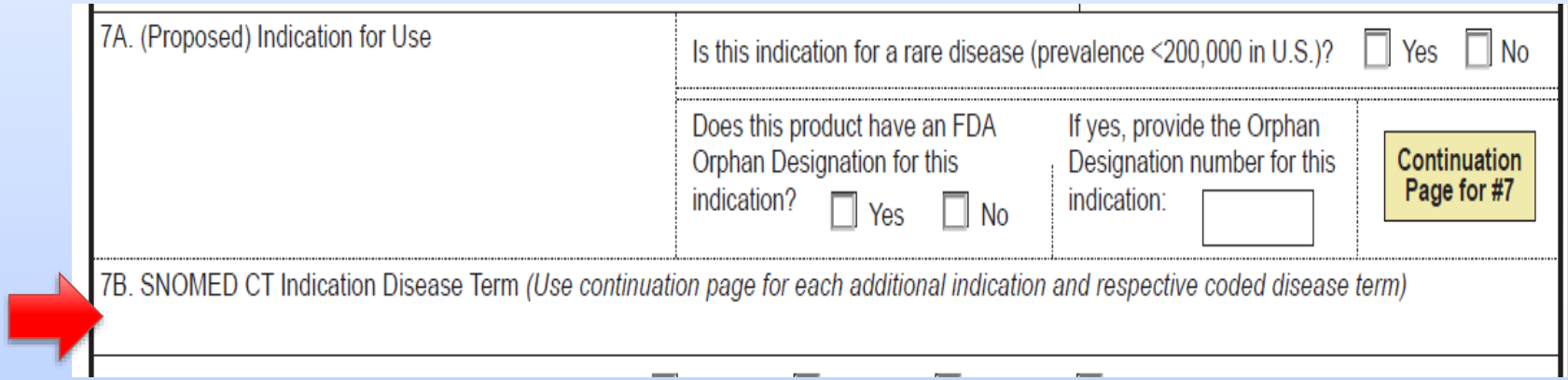
Field 6B

3. Sponsor Address			4. Telephone Number *(Include country code if applicable and area code)*
Address 1 *(Street address, P.O. box, company name c/o)*			
Address 2 *(Apartment, suite, unit, building, floor, etc.)*			6A. IND Number *(If previously assigned)*
City	State/Province/Region		
Country	ZIP or Postal Code		6B. Select One: ☐ Commercial ☐ Research
5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)* **Continuation Page for #5**			

Field 6B –IND Type Defined

- Select Commercial IND if the product under investigation is intended to be commercialized at a later date. (21 CFR 312.320)
- Select Research IND if the product under investigation is not intended to be commercialized at a later date.
- Research INDs are generally sponsored by individual investigators, academic institutions and non-profit
- entities. May include INDs for emergency use and expanded access. (21 CFR 312.305 and 312.310)

Field 7B


7A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
7B. SNOMED CT Indication Disease Term (Use continuation page for each additional indication and respective coded disease term)

Field 7B-SNOMED CLINICAL TERMS (CT) CODED DISEASE TERM(S) DEFINED

- For each original IND submission(including resubmissions to this submission type), provide the SNOMED CT coded disease term (e.g., 38341003 | Hypertensive disorder, systemic arterial (disorder) |) for the indication provided in Field 7A. To look up the indication's SNOMED CT coded disease term:
- Navigate to http://browser.ihtsdotools.org/
- Under Local Extensions, select 'Go Browsing United States edition'.
- Select 'Search' tab located in the upper left hand of page.
- Enter the disease term in the search field.
- Check the box 'Group by concept'.
- Select the single most appropriate term for the indication.
- Select the 'Expression' tab located in the upper right hand of page.
- Copy the entire text that appears under the heading 'Pre-coordinated Expression.'
- Paste the copied SNOMED CT disease term into Field 7B of Form FDA 1571.
- For additional indications, use the continuation page for #7 and repeat these steps.

Form FDA 1571 – Submission Contents

8. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other *(Specify)*: _____

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.. | Serial Number ___ ___ ___ ___

11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Response to Clinical Hold
☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement
☐ Annual Report
☐ General Correspondence
☐ Development Safety Update Report (DSUR)
☐ Other *(Specify)*: _____

Protocol Amendment
☐ New Protocol
☐ Change in Protocol
☐ New Investigator
☐ PMR/PMC Protocol
☐ Human Factors Protocol

Information Amendment
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☐ Clinical/Safety
☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report
☐ Initial Written Report
☐ Follow-up to a Written Report

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No | Combination Product Type *(See instructions)* | Request for Designation (RFD) Number

13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8

Expanded Access Use, 21 CFR 312.300

☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Treatment IND or Protocol, 21 CFR 312.320

Field 12 – Combination Products Defined

- For original submissions (i.e., the Initial Investigational New Drug Application (IND)), indicate if the product proposed within the application is a combination product (e.g., drug-device, drug-biological product, drug- device-biological product, see 21 CFR 3.2(e)) by selecting 'Yes' and entering the number below that identifies the type:
  - 1: Convenience Kit or Co-Package
  - 2: Prefilled Drug Delivery Device/System
  - 3: Prefilled Biologic Delivery Device/System
  - 4: Device Coated/Impregnated/Otherwise Combined with Drug
  - 5: Device Coated or Otherwise Combined with Biologic
  - 6: Drug/Biologic Combination
  - 7: Separate Products Requiring Cross Labeling
  - 8: Possible Combination Based on Cross Labeling of Separate Products
  - 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)
- If the product is not a combination product, select 'No' and leave the Combination Product Type blank.
- If this is the initial submission for a product for which a Request for Designation (RFD) was submitted, provide the six-digit RFD number.

FDA 1571- Application Contents

14. Contents of Application – This application contains the following items *(Select all that apply)*

- ☐ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- ☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
- ☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
- ☐ 4. General Investigational plan *(21 CFR 312.23(a)(3))*
- ☐ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- ☐ 6. Protocol *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
- ☐ 6. Protocol *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - ☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- ☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- ☐ 9. Previous human experience *(21 CFR 312.23(a)(9))*
- ☐ 10. Additional information *(21 CFR 312.23(a)(10))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

15. Is any part of the clinical study to be conducted by a contract research organization? ☐ Yes ☐ No

If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☐ No

If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*.

Continuation Page for #15

16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug

Form FDA 1571 - Contacts

18. Name of Sponsor or Sponsor's Authorized Representative

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

20. Facsimile (FAX) Number *(Include country code if applicable and area code)*

21. 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

22. Email Address

23. Date of Sponsor's Signature *(mm/dd/yyyy)*

24. Name of Countersigner

25. 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

Country

United States of America

ZIP or Postal Code

26. Email Address

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

27. Signature of Sponsor or Sponsor's Authorized Representative

28. Signature of Countersigner

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

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

Electronic Common Technical Document (eCTD)

- 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 – Introduction

- 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

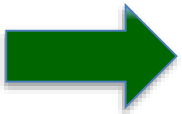
- **Clinical Overview**
  - Brief description of the overall plan for investigation
  - Summary of rationale to support trial
  - Dose, Dosing Schedule, Patient Population
  - Indication(s)
  - Trial Duration/Number of Subjects
  - Known risks (based on toxicology)

- **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

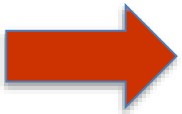
IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362283.htm

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
- 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
- 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

- Form FDA 1572-Statement of the Investigator conducting clinical research under IND
- Requirement to have investigator(s) sign before participation
- Provides Clinical Investigator qualifications
- Agreements:
  - conduct of protocol
  - obtain informed consent
  - Institutional Review Board (IRB) review
  - recordkeeping, adverse drug reactions

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 (Research applications only)**
  - Common Technical Document (CTD) format
  - Regulatory Format (21 CFR 312.23)
- **Electronic**
  - Must use eCTD format
  - Physical media
  - Electronic Submission Gateway (ESG)

Submission of the IND

For Paper - Research Only

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

Submission of IND - Commercial

- 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

Pre-Assigned App #/ Secure Email

- To request a Pre-assigned application number:
  - Send one email per application number request to cderappnumrequest@fda.hhs.gov

- Before you request a pre-assigned eCTD application number, you need to apply for a secure email address with the FDA by contacting SecureEmail@fda.hhs.gov

FDA site- Requesting a pre-assigned application number:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

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

- Electronic Common Technical Document (eCTD)

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

Application Resources

- Forms FDA 1571 and 1572
  - Forms

1571 –https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm083533.pdf

1572 -https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

  - Instructions

1571- https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm182850.pdf

1572-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 1571 and 1572)

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

Initial IND Submission
First 30 Days

Judit Milstein

Chief, Project Management Staff

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

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301-796-0763

FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

IND initial submission
The first 30 days

- FDA's work once your IND submission is received
- Safe to proceed or clinical hold
- Clinical Hold
  - Imposing, responding, and removal

IND submission-requirements

- May 5, 2018
- Commercial INDs
  - Must be in eCTD format
  - Less than 10 GB, must use the gateway
  - Larger than 10 GB must use physical media
  - Fillable forms (FDA Form 1571) are required
- Research INDs
  - Can be submitted in paper although electronic submission is encouraged

IND submission: the first 30 days

- IND arrives to CDER
  - Data entered into DARRTS (Document Archiving, Reporting, and Regulatory Tracking System
  - IND assigned to Division by indication (endpoints)
- IND forwarded to CPMS (Chief, Project Management Staff)
- RPM (Regulatory Project Manager) assigned
  - Point of contact with the review division
  - Issues acknowledgment letter
  - Tracks/manages IND review process

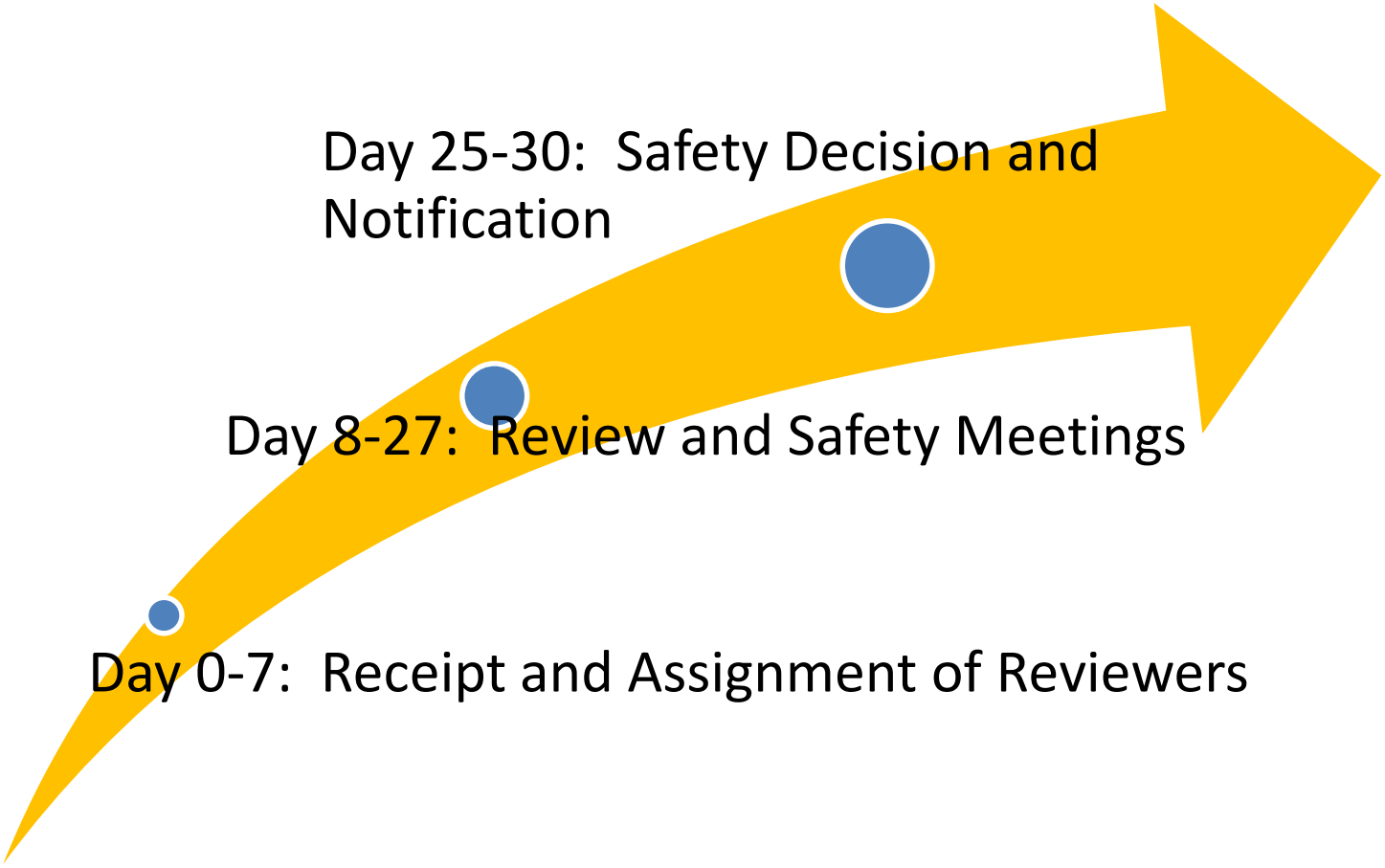
IND submission: the first 30 days

- Review Team assigned
  - Clinical
  - Non-Clinical Pharmacology and Toxicology
  - CMC (Chemistry, Manufacturing and Controls)
  - Clinical Pharmacology
  - Biostatistics
  - Clinical Microbiology (Antimicrobial and antiviral drugs)
  - Microbiology-Sterility (as needed)
  - Consults

IND submission: the first 30 days

- The Review team will determine within 30 days of receipt of your IND whether your study is
  - "safe to proceed"- IND "goes into effect" (active) or
  - IND is placed on clinical hold
- INDs are not approved
- Some Divisions issue a "safe to proceed letter"; Otherwise, "no news is good news"
- MaPP 6030.9 Good Review Management Principles and Practices for Effective IND Development and Review
  - https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm349907.pdf

IND Process from Day 1-30



Safety Review Parameters

- Are all adverse events observed from nonclinical data addressed in the clinical protocol and Investigator's Brochure?

- Are risk/benefits/safety discussed and supported for the proposed dosing regimen/clinical trial?

- Are stopping criteria (individual, cohort, study) well thought out?

Safety Review Objectives

- Primary Objective: To determine if a trial can be conducted without unreasonable risk to the subjects/patients.
- Phase 1
  - Assure the safety and rights of subjects
- Phases 2 and 3
  - Assure quality of scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety

Clinical Hold definitions

- **Clinical Hold**: An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation

  - **Full Clinical Hold**: A delay or suspension of all clinical study under an IND.

  - **Partial Clinical Hold**: A delay or suspension of only part of the clinical study under an IND (e.g., a specific protocol or part of a protocol is allowed to proceed).

Grounds for Imposing a Clinical Hold: (1) Phase 1 Trials

21 CFR 312.42(b)(1)

- Human subjects would be exposed to an unreasonable and significant risk of illness or injury
- Clinical investigators are not qualified
- Investigator Brochure is misleading, erroneous, or materially incomplete
- Insufficient information to assess risks to subjects
- Exclusion by gender for life-threatening disease or condition [unless justified/special circumstances]

Grounds for Imposing Clinical Hold: (2) Phase 2/3 Trials

21 CFR 312.42(b)(2)

- Any of the reasons listed above for Phase 1 trials
- The protocol is deficient in design to meet its stated objectives

What to do when you have a Potential Clinical Hold

21 CFR 312.42(c)

- If deficiency(ies) is identified that may be grounds for imposing a clinical hold:
  - FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor first
  - Many potential holds can be resolved through such discussion (e.g., inadequate patient monitoring)

Imposing a Clinical Hold

21 CFR 312.42 (d)

- Division Director (DD) or person with responsibility for review of the IND acting on behalf of the DD makes the final decision to impose a clinical hold

Imposing a Clinical Hold

- Commercial Sponsor:
  - DD and RPM notify sponsor by telephone
  - Reasons for hold are discussed
- Sponsor-Investigator:
  - RPM notifies sponsor by telephone and briefly explains reasons for hold
  - Teleconference with DD is offered if desired by sponsor
- Clinical Hold letter is issued within 30 days of the date of the teleconference
- See details in MaPP 6030.1
  - https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm082022.pdf

Sponsor Responds to Clinical Hold

- RPM consults with review team to determine whether the sponsor's submission is a **complete response** (i.e., addresses all the issues identified in the clinical hold letter)
  - If not complete response, RPM notifies sponsor
  - If complete response, RPM sends acknowledgment letter and another 30-day cycle begins

Resumption of Clinical Investigations [21 CFR 312.42(e)]

- The reviewers evaluate the submission to determine if the response addresses adequately the deficiencies.
- Depending on the issues, a team meeting may take place to discuss lifting of the hold.
- FDA either allows study to proceed (remove hold) or implements a continuation of the hold (unresolved safety issues).
- Sponsor informed either way and a letter issued.

Appeal

21 CFR 312.42(f)

If a Sponsor disagrees with the reasons cited for a hold they can:

- Request reconsideration of the decision in accordance with 21 CFR 312.48
- Dispute resolution procedure(s) 21 CFR 312.48
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm343101.pdf

Best Practices

- Although not required, a cover letter is extremely useful
  - Contact phone #
  - Alternate name and phone #
  - E-mail addresses
- The initial IND submission (and each subsequent submission to the IND) should be accompanied by a Form FDA 1571
  - If paper, must be submitted in triplicate (1 original and two copies)

Best Practices

- Clear and well organized (if paper)
- Provide assurance on subject safety
- Provide assurance on the adequacy of scientific information to evaluate the drug's safety and effectiveness (Phase 2 and Phase 3 protocols)
- E-mail Communications- Set up secure email with the Agency

More Best Practices

- Initial IND submission with one protocol
- Effectively communicate with the FDA RPM assigned to the IND
- Be available for any discussion during the first 30 days
- If you do not get funding, withdraw the IND
- Consider Pre-IND Consultation before submitting IND

Frequently Asked Questions

- Should I submit a pre-IND before IND?
  - A pre-IND is a consultative mechanism to receive early feedback.
  - It fosters early communications between sponsors and drug review divisions to provide guidance on the information necessary for a complete IND submission.
  - The review divisions are organized generally along therapeutic class
  - Pre-IND meetings can be in the format of a Face-to-face meeting or they can be Written Response Only (WRO); some divisions only provide Pre-IND comments as WRO
- Should I submit the IND in paper or electronic format?
  - Commercial IND submissions must be submitted in eCTD format Non-commercial are accepted in paper but electronic is encouraged.

Frequently Asked Questions

- Will IND number be same as corresponding pre-IND?
  - Yes; the Pre (P) will be removed [and status updated]
- When will I be assigned an IND number?
  - A pre-assigned eCTD IND application number can be requested in advance at: http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm163184.htm.
  - However, an IND number will be assigned after the IND application is received by FDA if there is no pre-assigned number.
- When can I start clinical trials?
  - Unless you are contacted, you may begin 30-days after FDA receives your IND application. However, it is advisable that you contact the division for assurance there are no issues.

Frequently Asked Questions

- Can my IND cross-reference another IND?
  - Yes, an IND can cross-reference another commercial or non-commercial IND provided a **letter of authorization** is submitted to allow for the reference.
  - If it is your own IND, it would be helpful to provide direct links/identify location in submission to referenced material.

- Do I need to submit an IND if the indication is different than the indications of the FDA approved drug product/legally marketed drug product in USA.
  - Yes, an IND is needed if an approved product is for a new indication or in a new patient population

Frequently Asked Questions

- Can another indication be added under same IND?
  - Protocols to study additional indications can be submitted under the same IND provided the indications are reviewed by the same review division and there is no change to the product and dosage form.

- Can different dosage forms be investigated under same IND?
  - Separate INDs should be established
  - Exception may be an early in development proof-of-concept study investigating different dosage forms of the same product; IND continues with selected dosage form.

Frequently Asked Questions

- I have a combination product-Which is the lead Center?
  - Primary Mode of Action (PMOA)
  - Request for Designation (RFD)
  - https://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm#assignment
  - combination@fda.gov.

Frequently Asked Questions

- I am submitting an IND for a drug-device combination product to CDER. What information do I need to include?
  - All information on the entire combination product; All the details on the drug and device that typically would be submitted in an IND and IDE

Where do I send my IND?

only if research IND

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

IND Application-resources

- 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
- Pre-assigned application number:
  - Send one email per application number request to cderappnumrequest@fda.hhs.gov

Questions?

Please evaluate this session:

surveymonkey.com/r/DRG-D1S03

FDA U.S. FOOD & DRUG ADMINISTRATION