Content and Format of an Initial IND Submission 21 CFR 312.23

Maureen Dillon-Parker

Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
maureen.dillonparker@fda.hhs.gov
#301-796-1400

Disclaimer

The comments expressed today are those of the presenter only and the presentation is intended only to provide a summary and general overview. It is not intended to be comprehensive nor does it constitute legal advice.

Poll Question

How many commercial and research INDs* do you think CDER received in the 2016 calendar year?

- ○ **552**
- ○ **960**
- ○ **1,669**
- ○ **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.**

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

How many INDs?

FDA

Commercial	+ Research	= Total
777	+ 892	= 1669

21 CFR 312 - INDs

Subpart A: General Provisions

- **§312.1: Scope**
- **§312.2: Applicability**
- **§312.3: Definitions and interpretations**
- **§312.6: Labeling of investigational new drug**

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 [not required]
- 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)

IND Content and Format

- **Cover Letter** [not required]
- Regulatory Forms –
  - FDA 1571 (cover sheet)
  - FDA 1572 (statement of investigator)
  - FDA 3674 (clinical trials certification)
- Table of Contents
- Introductory Statement

Cover Letter

- Typically 1-2 pages
- Addressed to the Division Director
- Submission identifier-Initial Investigational New Drug Application
- Brief explanation of the intended investigation (type/title of the study)
- Investigational product name and proposed formulation
- Disease or condition to be studied
- IND manufacturer's name and contact information
- Reference to an existing IND application (if applicable)

IND Content and Format

- Cover Letter [not required]
- **Regulatory Forms**
  - FDA 1571 (cover sheet)
  - FDA 1572 (statement of investigator)
  - FDA 3674 (clinical trials certification)
- Table of Contents
- Introductory Statement

Regulatory Forms

- Form FDA 1571 – Administrative information

  Instructions:

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

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

  Instructions:

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1572

- Form FDA 3674-Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank

Form FDA 1571

- Format - Mostly fill-in-the-blanks/check boxes
- Administrative 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	

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

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 drug, biologics and devices
- Register by date

IND Content and Format

- Cover Letter [not required]
- Regulatory Forms –
  - Form 1571 (cover sheet)
  - Form 1572 (statement of investigator)
  - Form 3674 (clinical trials certification)
- **Table of Contents**
- Introductory Statement

Table of Contents

§312.23(a)(2)

- Detailed enough to permit FDA reviewers to locate items quickly and easily
- Helpful if location of information provided by volume and page number
- Tabbed breaks between sections or electronic format

IND Content and Format

- Cover Letter [not required]
- Regulatory Forms –
  - Form 1571 (cover sheet)
  - Form 1572 (statement of investigator)
  - Form 3674 (clinical trials certification)
- Table of Contents
- **Introductory Statement**

Introductory Statement
§312.23(a)(3)

- Usually 2-3 pages
- Name of the drug, all active ingredients, drug pharmacologic class, structural formula, dosage form, route of administration, and clinical trial objectives and planned investigations
- Summary of human experience to date
- Previous foreign marketing experience (if any)

IND Content and Format

- **General Investigational plan**
- Investigator's brochure
- Protocol(s) – Clinical
- Chemistry, manufacturing, and control information

General 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)

IND Content and Format

- General Investigational plan
- **Investigator's brochure**
- Protocol(s) - Clinical
- Chemistry, manufacturing, and control information

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

IND Content and Format

- General Investigational plan
- Investigator's brochure
- **Protocol(s) - Clinical**
- Chemistry, manufacturing, and control Information

Protocol(s) - Clinical

- 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
  - Commitment to obtain Informed Consent

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

IND Content and Format

- General Investigational plan
- Investigator's brochure
- Protocol(s)
- **Chemistry, manufacturing, and control information**

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

- Drug Substance
- Drug Product
- Certificates of Analysis (COA)
- Placebo Formulation, if applicable
- Labeling information of the investigational drug
- Environmental analysis or request for categorical exclusion

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

IND Content and Format

- **Pharmacology/Toxicology Information (nonclinical)**
- Previous Human Experience
- Additional Information (drug dependence, abuse potential, radioactive, pediatric studies)
- Relevant information (foreign, previously submitted)

Pharmacology and Toxicology Information (*Non-Clinical)* §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
- Toxicology
  - Summary of toxicological effects in animals & in vitro
  - Results of acute/subacute /chronic toxicity tests
  - Reproduction / fetal effects
  - Special toxicity tests due to mode of administration

IND Content and Format

- Pharmacology/Toxicology Information
- **Previous Human Experience**
- Additional Information (drug dependence, abuse potential, radioactive, pediatric studies)
- Relevant information (foreign, previously submitted)

Previous Human Experience
§312.23(a)(9)

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

IND Content and Format

- Pharmacology/Toxicology Information (nonclinical)
- Previous Human Experience
- **Additional Information (drug dependence, abuse potential, radioactive, pediatric studies)**
- Relevant information (foreign, previously submitted)

Additional Information

§312.23(a)(10)

- 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

IND Content and Format

- Pharmacology/Toxicology Information (nonclinical)
- Previous Human Experience
- **Additional Information (drug dependence, abuse potential, radioactive, pediatric studies)**
- **Relevant information (foreign, previously submitted)**

Relevant Information

§312.23(a)(11)

- Information Previously submitted
  - Incorporate by reference or include authorization
- Material in a foreign language
  - Original and translated versions
- Number of copies
- Numbering of submissions
- Identification of exception from informed consent
  - If exception under 50.24, identify on cover sheet

IND Application-Format

- **Paper**
  - Common Technical Document (CTD) format
  - Regulatory Format (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
- Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

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

Additional 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.

Please complete the session survey:

surveymonkey.com/r/DRG-D1S03

Contact Information:
Maureen Dillon-Parker
maureen.dillonparker@fda.hhs.gov
#301-796-1400

FDA U.S. FOOD & DRUG ADMINISTRATION