



U.S. Food and Drug Administration

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CLINICAL INVESTIGATOR

How to put together an application?

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Class outline

- Definitions
- When do I need to submit and IND
 - Exemptions
- Content and Format IND
- Processes
 - What should I expect after I submit an IND
- Tips

IND- legal definition

(21 CFR 312.1)

- “An Investigational New Drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug”

Definitions

21 CFR 312.3

- IND
 - Investigational New Drug Application
 - Notice of Claimed Investigational Exemption for a New Drug

- Investigational New Drug
 - New drug or biologic that is used in clinical investigation

More definitions

- Clinical Investigation
 - Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects
- Subject
 - A human who participates in an investigation either as a recipient of the investigational drug or as a control. A subject may be a healthy human or a patient with a disease

One more definition

- Investigator
 - Individual who actually conducts a clinical investigation
- Sponsor
 - A person who takes responsibility for, and initiates a clinical investigation
- Sponsor-Investigator
 - An individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed

An IND is needed when...

- Research involves a drug
- Research is a clinical investigation
- Clinical Investigation is not *exempt* from IND regulations

Is it a drug?

- “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease...” [21 USC 321 (g)(1)(B)]
- “articles (other than food) intended to affect the structure or any function of the body...” [21 USC 321 (g)(1)(C)]
- a drug is defined by intended use, not the nature of the substance (e.g. cranberry juice)

Is it a clinical investigation?

- A “clinical investigation” is “any experiment in which a drug is administered or dispensed to, or used involving one or more subjects.”
- An “experiment” is “any use of a drug except for the use of a marketed drug in the course of medical practice”
- Not limited to commercial development

IND Exemptions

[21 CFR 312 (b), 320.31, and 361.1]

- Certain research involving marketed drug products
- Bioavailability or Bioequivalence studies in humans
- Radioactive drugs for certain research studies

IND Exemptions for marketed products [21 CFR 312.2(b)]

- The drug product is lawfully marketed in the US AND
- Study is not intended to be reported as a well-controlled study for a new indication or significant labeling change AND
- Study is not intended to support a significant change in advertising AND
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk (or decreases the acceptability of risk) AND
- The investigation is conducted in compliance with requirements for review of an IRB and informed consent AND
- The investigation is not intended to promote or commercialize the product

IND Exemptions for BA or BE studies

[21 CFR 320.31(b) (c) and (d)]

- The drug product does not contain a new chemical entity, is not radioactive labeled and is not cytotoxic
- The dose (single dose or total daily dose) does not exceed the dose specified in the approved labeling
- The investigation is conducted in compliance with IRB and IC regulations
- The sponsor meets the requirements for retention of test article samples

IND Exemption for Radioactive Drugs

[21 CFR 361.1]

- Clinical Investigations using Cold Isotopes
 - Research is intended to obtain basic information regarding metabolism, human physiology, pathophysiology, or biochemistry
 - Research is not intended for immediate therapeutic, diagnostic, or preventive benefit
 - Administered dose is known not to cause any clinically detectable pharmacologic effect
 - Quality of cold isotope meets relevant quality standards

Guidances

- Draft Guidance for Industry-Investigational New Drug Applications (INDs)-Determining Whether Human Research Studies Can be Conducted Without an IND-Draft Guidance-October 2010
- Guidance for Industry-IND Exemptions for Studies of Lawfully Marketed Drugs or Biologic Products for the Treatment of Cancer
- Draft Guidance for Industry and Researchers-The Radioactive Drug Research Committee: Human Research Without and Investigational New Drug Application

How do I apply for an IND exemption

[21 CFR 312.2]

- Must meet all criteria describe above
- Most cases can be determined by the sponsor-investigator
- Study endpoints will determine which Division will review your request
- Contact the Chief Project Manager
 - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM206032.pdf>
- Office of the Ombudsman
 - <http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/ucm197508.htm>

How do I apply for an IND exemption

[21 CFR 312.2]

- Some Divisions allow an informal route (e-mail) but request need to include:
 - Name, address, phone #, fax #, e-mail address and affiliation
 - Brief summary of study, including title, purpose hypothesis, condition or disease, pt demographics, drug, dose, route and duration of therapy, and endpoints
- Other Divisions require submission of IND
 - Review done by Clinical/MO reviewer
 - Short turn around time
 - Letter sent granting the exemption

Content and Format of an IND

[21CFR 312.22 and 312.23]

- A. Cover sheet (FDA Form 1571)
- B. Table of contents
- C. Introductory statement and general investigational plan
- D. Investigator's brochure
- E. Protocols
- F. Chemistry, manufacturing and controls
- G. Pharmacology and Toxicology information
- H. Previous human experience with the investigational drug
- I. Additional information

A. Cover sheet

- FDA Form 1571
- Form 1572, and Form 3674
 - <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>
- Filling out the Forms
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm>

B. Table of Contents

- Tabbed breaks between sections

C. Introductory statement and general investigational plan

- Brief introductory statement
 - Name of the drug, and all active ingredients, drug's pharmacologic class, structural formula, formulation of dosage form, route of administration, and broad objectives and planned investigations
- Brief summary of previous human experience
- Brief description of the overall plan for investigation of the drug in the next year

D. Investigator's brochure

- Only necessary if study is conducted in multiple sites
- Using a product under development?
 - Obtain IB from commercial sponsor

D. Investigator's brochure

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

E. Protocol-Phase 1

- An estimate of the number of subjects involved
- A description of inclusion criteria and safety exclusions
- A description of the dosing plan, including the duration, dose, dose escalation, schedule and a method for dose determination
- Details on Safety monitoring

E. Protocol-Phase 2 and 3

- Statement of the objective(s) of the study
- Name, address, and statement of qualification of each investigator and sub-investigator
- Inclusion and exclusion criteria, and estimated number of subjects
- Description of trial design

E. Protocol-Phase 2 and 3

- Description of clinical procedures, laboratory tests and other measures to monitor the effect of the drugs and minimize risk
 - Table (time-and-events table) that reflects which activities will take place-Safety
- Method for determining the doses to be administered, planned maximum dosage, and duration of individual subject exposure to drug
 - Stopping rules
- Description of observations and measurements

E. Protocol-Tips

- Include copy of the protocol
- Protocol title
- Hypothesis/Research question
- Background and rationale
- Rationale for dose selection
- Endpoints (primary, secondary)
- Stopping rules
- Reviewed by IRB before 1st subject is enrolled

F. Chemistry, Manufacturing, and Controls (CMC)

- Sufficient CMC information to ensure the proper identity, strength, quality, and purity of the investigational drug
 - DMF (Drug Master File)
 - COA (Certificate of Analysis)
 - Package Insert
 - Dietary Supplement
 - Compounded product
 - Placebo

CMC-Drugs not marketed in the US

- Investigated under a cross-referenced IND
 - Letter of Cross-Reference
 - Letter of Authorization
- Approved and marketed ex US
 - Components and Composition of the drug
 - Name of manufacturer or supplier of the drug
 - English version of the labeling
 - Certificate of analysis (COA)

CMC-additional information

- Description of plan for disposal of any unused portion of the drug
- Label for the immediate packaging of the drug with the statement “Caution: New Drug-Limited by Federal Law to investigational use”
- Environmental assessment or a statement requesting categorical exclusion

CMC-special cases

- Botanicals
 - Guidance for Industry-Botanical Drug Products
- Using a Device?
 - Information on manufacturer, model, and conditions of use (e.g., carrier gas, flow rate, temperature)
 - FDA cleared for its intended use?
 - If not, contact the Division for further input

G. Animal Pharmacology and Toxicology Information (*Pharm/Tox*)

- Adequate information about the drug's pharmacology and toxicology (in vitro or animal studies) to support their use in humans
 - Guidance for Industry-Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products

Pharm/Tox

- FDA approved drug
 - Copy of the current labeling
 - Statement that the drug will be used in the same dose, duration, route of administration as described in the labeling
- Not FDA approved but being studied under cross-reference
 - Letter of Cross Reference or LOA
- Only approved in foreign markets

Pharm/Tox- Safety basics

- LOTS of Pharm/Tox information
 - Know toxicology profile and NOAELs
 - Check starting dose and duration of exposure (safety margin)
 - Check dose escalation
 - Check stopping criteria, safety monitoring
 - Submit study reports

Safety basics-Phase 2 and 3 Studies

- Target population (eligibility criteria)
- Dose and duration of treatment
- Drug-Drug interaction
- Safety monitoring (general, cardiac eye)

H. Previous Human Experience

- Letter of Cross Reference
- Include a rationale for use of the drug outside the current labeled dose, duration or in combination with other drugs
- Copies of Published Materials

I. Other important information

- Drug Dependence and abuse potential
- Radioactive drugs
- Pediatric Trials

Regulatory information

- FDA Form 1571-Investigational New Drug Application
- FDA Form 1572-Statement of Investigator
- FDA Form 3674-Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank
- FDA Form 3500-MedWatch Form
 - <http://inside.fda.gov:9003/Administrative/Forms/FDA/>
 - <http://inside.fda.gov:9003/Administrative/Forms/FDA/CDER/default.htm>

Where do I send the 3 copies of my IND?

- **For a Drug:**
 - Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266
- **For a Therapeutic Biological Product:**
 - Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

IND submission: the first 30 days

- IND arrives to the Central Document Room
 - If electronic: loaded in the Electronic Document Room (EDR)
 - If paper: Sent to the White Oak Document Room
 - Data entered into DARRTS (Document Archiving, Reporting, and Regulatory Tracking System)
 - IND assigned to Division by indication (endpoints)

IND submission: the first 30 days

- IND forwarded to CPMS (Chief, Project Management Staff)
- PM (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
 - Clinical Pharmacology
 - Biostatistics
 - Microbiology (Antimicrobial and antiviral drugs)
 - 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” or will be placed in clinical hold
- Some Divisions issue a “safe to proceed letter”; Otherwise, “no news is good news”
- INDs are not approved

FDA's objective in reviewing the IND

- To assure the safety and rights of subjects
- To help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety (Phase 2 and Phase 3)
 - Clinical subjects are protected in conjunction with IRBs and Informed Consent

Tips

- Although not required, a cover letter is extremely useful
 - Contact phone #
 - E-mail address
- The initial IND submission (and each subsequent submission to the IND) should be accompanied by a Form FDA 1571 and must be submitted in triplicate (1 original and two copies)
- Submission should be in red/orange/green binders
 - U.S. Government Printing Office (GPO)
Washington DC 20404-0001
202-512-1800
Forms 2675, 2675a and b

More Tips

- Proofread your submission
- Provide a Table of Contents
- Divide your submission with tabs, not with colored paper
- One protocol
- Be available for any discussion during the first 30 days
- If you do not get funding, withdraw the IND

IND application-Format

- Paper
 - Common Technical Document (CTD) format
 - Regulatory Format (21 CFR 312.23)
- Electronic
 - Must use CTD format
 - Physical media
 - Electronic Submission Gateway (ESG)

IND 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>
- Small Business Assistance
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069898.htm>

IND Application-more resources

- Electronic Submissions Gateway:
 - <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>
 - Preparation/Registration/Policy Questions: esgprep@fda.hhs.gov
 - Technical Issues: esgreg@gnsi.com
- Secure e-mail account:
 - Contact Wendy Lee at: wendy.lee@fda.hhs.gov
- Pre-assigned application number:
 - Send one email per application number request to cderappnumrequest@fda.hhs.gov.

Guidances

The screenshot shows a Windows Internet Explorer browser window displaying the FDA's 'Guidances' page. The browser's address bar shows the URL: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. The page content includes the U.S. Department of Health & Human Services logo and navigation links for various FDA categories. A sidebar on the left lists different types of guidance documents, such as 'General and Cross-Cutting Topics' and 'Advisory Committee Guidance Documents'. The main content area features a search box for 'Search FDA Guidances', a sign-up option for email updates, and a detailed paragraph explaining that guidance documents are advisory and do not create legal rights. A bolded notice is present regarding employee compliance with good guidance practices. Contact information for the FDA Office of the Ombudsman is provided at the bottom of the main content area.