CLINICAL INVESTIGATOR

How do I put together an IND 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, and in certain cases, for clinical treatment

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 of 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

- Certain research involving marketed drug products
  - 21CFR 312 (b)
- Bioavailability or Bioequivalence studies in humans
  - 21 CFR 320.21(b) (c) and (d)
- Radioactive drugs for certain research studies
  - 21 CFR 361.1

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 320.21(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

- Guidance for Clinical Investigators, Sponsors and IRBs-Investigational New Drug Applications (INDs)-Determining whether Human Research Studies Can Be Conducted Without an IND.

- 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 (RDRC): 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

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
- Usually reserved when an official response is not needed

How do I apply for an IND exemption [21 CFR 312.2]

Other Divisions require submission of an IND or PIND (no FDA Form 1571)

- Review done by Clinical/MO reviewer
- Short turn around time
- Letter sent granting/denying the exemption

Regulatory and Administrative Components

- Cover Letter
- Regulatory Forms
- Table of Contents
- Introductory Statement and General Investigational Plan
- Investigator Brochure
- Clinical Components
  - Protocol
  - Previous Human Experience
- Non Clinical Components
  - Animal Pharmacology and Toxicology (PT)
  - Chemistry, Manufacturing and Controls (CMC)
- Other information as necessary

Cover Letter

- Cover letter
  - Typically 1 page
  - Submission identifier-”Initial Investigational New Drug Application
  - Brief explanation of the intended investigation (type and title of the study)
  - Investigational New Drug Product’s name and proposed formulation
  - Disease or condition under investigation
  - IND manufacturer’s name and contact information
  - Reference to an existing IND application (if applicable)
  - Addressed to the Division Director

Regulatory Forms

- FDA Form 1571
- Instructions:
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.http
- FDA Form 1572-Statement of Investigator
- FDA Form 3674-Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank

Table of Contents

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

Introductory Statement and General Investigational Plan (2-3 pages)

- 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

Investigator 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

Clinical Components

- Clinical Protocol
- Previous Human Experience with the Investigational Drug

Protocol

- For each planned clinical study or trial
  - Include protocol number and/or title
- Protocols for subsequent studies are submitted as Protocol Amendments
  - Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Previous Human Experience

- If investigational drug has been investigated or marketed, provide summary of previous experience, including published materials relevant the safety and efficacy
- If marketed outside US, provide information on all countries where the product has been marketed or withdrawn (and why)
- Letter of authorization, with right of reference if product is the subject of an another existing IND application
- State if no previous human experience exists

Chemistry, Manufacturing, and Controls (CMC)

- Submit information on
  - Drug Substance
  - Drug Product
  - 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

Animal Pharmacology and Toxicology Information (*Pharm/Tox, PT*)

- Adequate information about the drug's pharmacology and toxicology (in vitro or animal studies) to support their use in humans
  - Kind, duration and scope of the animal and other studies required will depend on the duration and nature of the proposed clinical investigation
  - 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
  - Guidance for Industry-M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization of Pharmaceuticals

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

Tips

- 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 and must be submitted in triplicate (1 original and two copies)

Tips

- 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
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

More Tips

- Proofread your submission
- Provide a Table of Contents
- Divide your submission with tabs, not with colored paper
- Initial IND submission with 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
- Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf
- 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 SecureEmail@fda.hhs.gov
- Pre-assigned application number:
  - Send one email per application number request to cderappnumrequest@fda.hhs.gov.

Additional Resource

- Investigator-Initiated Investigational New Drug (IND) application
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm