FDA Investigational New Drug Applications for Sponsor-Investigators

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Overview

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- Objectives
- What is an IND?
- Key roles in IND-regulated research
- The Pre-IND
- The IND
- Logistics and ongoing IND management
- Advice

Objectives

Focusing on sponsor-investigator research with an investigational product, the objectives of this workshop are:

- Define and discuss the sponsor-investigator role
- Summarize an overview of the IND development, submission and management process
- Identify and locate resources to support the IND process
- Explain some of the common challenges in sponsor-investigator INDs

NOTE: All references to the Code of Federal Regulations are taken from the eCFR (ecfr.gov, Title 21)

What is an IND?

Investigational New Drug Application (IND)

A request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product (IP) to humans. An approved IND also serves as an FDA exemption allowing shipment of IP across state lines prior to an approved Marketing Application.

LMIV, NIAID

An IND concerns…

- Clinical investigation
  - Any experiment in which a drug is administered, dispensed to or used, involving one or more human subjects, except the use of a marketed drug in the course of medical practice.
- Investigational new drug
  - A new drug or biological product (IP) not yet approved by the FDA, or an FDA-approved IP not yet approved for a new use, in the process of being tested for safety and effectiveness.
- "Off Label Use" for treatment purposes?
  - No. This does not require an IND, unless research focused.

What is a drug?

- A drug is a substance:
  - Recognized by an official pharmacopoeia or formulary
  - Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  - Intended to affect the structure or any function of the body (other than food)
  - Intended for use as a component of a medicine (but not a device)

- Biological products are generally covered by the same laws and regulations, but differ in their manufacturing processes: chemical versus biological process.

What is a biological product?

- A biological product (biologic) is a medical product that is:
  - (Usually) made from natural sources (humans, animals or microorganisms)
  - Intended to diagnose, treat or prevent diseases and medical conditions
  - Examples include:
    - Vaccines
    - Blood and blood products
    - Allergenic extracts, (i.e. allergy shots)
    - Human cells and tissues used for transplantation
    - Gene therapies
    - Cellular therapies
    - Tests to screen potential blood donors for infectious agents, such as HIV

Three types of research INDs

1. Investigator-initiated/Sponsor-investigator IND
2. Emergency Use IND
   - Allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
3. Treatment IND
   - Submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Exemptions from IND requirement

- Investigation(s) of a drug product ***lawfully marketed*** in the United States is exempt from filing an IND if ALL the following apply:
  - Does not support a new indication or significant change in the labeling;
  - Does not support a significant change in product advertising;
  - Does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks);
  - The investigation is conducted in compliance with the requirements for institutional review (21 CFR 56) and informed consent (21 CFR 50);
- Other exemptions:
  - In vitro diagnostic biological product, blood grouping serum, reagent red blood cells, anti-human globulin, drug(s) solely for tests in vitro or in lab research animals, use of a placebo if IND not otherwise required.

Exercise: Does this require an IND?

1. In regular medical practice, a clinician has observed a reduction in migraine headaches among patients taking a specific prescription anti-coagulant medication. The clinician recommends the drug to a few other patients who have not responded to migraine treatment.

   No

2. A clinical investigation of the effects of an unregulated, commonly-available, over-the-counter Magnesium supplement on depression.

   Yes

3. A clinical psychologist wants to conduct an unmasked study of the “placebo effect” by randomizing a group of people to receive either a sugar pill (placebo) or nothing for 6 weeks.

   No

4. A clinical research group wants to test an investigational vaccine adjuvant with an established, licensed vaccine. The adjuvant has been tested with several other vaccines previously.

   Yes

Key roles in IND-regulated research

- Sponsor
  - A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation.
- Investigator
  - An individual who actually conducts a clinical investigation (*i.e.*, under whose immediate direction the drug is administered or dispensed to a subject).
- Sponsor-investigator
  - An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual.

Sponsor-investigator: dual responsibilities

Sponsor

- Select qualified investigators and provide the information needed to conduct an investigation properly
- Ensure proper monitoring
- Ensure investigation is conducted in accordance with the IND's investigational plan and protocols
- Ensure that FDA and all participating investigators are promptly informed of significant new adverse effects or risks
- Maintain and retain study records
- Maintain reporting to FDA

Investigator

- Ensure investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations
- Protect the rights, safety, and welfare of subjects
- Control investigational drugs
- Obtain the informed consent of each human subject
- Maintain and retain study records
- Submit safety and progress reports to sponsor
- Ensure proper IRB review and reporting

What is the FDA's role in reviewing INDs?

- HUMAN SUBJECTS PROTECTION
  - Assuring the safety and rights of subjects
- Phase I
  - Focus on safety
- Phase II and III
  - Safety
  - Is the scientific quality adequate to evaluate the drug's effectiveness and safety?
  - Is the investigation likely to yield data adequate to support marketing approval?
- FDA team-based reviews:
  - All team members focus on safety
  - Pre-clinical experts (DVM, PhD) to evaluate sufficiency of pre-clinical data
  - Clinical experts (MD, PhD) to evaluate clinical development plans, endpoints
  - Statisticians to evaluate trial design, size, sequence, endpoints

Exercise: Whose responsibility is this?

A. Sponsor
B. Investigator
C. Sponsor-Investigator
D. FDA

A	C	Identify and contract study monitor
A	B	Protect the safety, health and welfare of subjects
C	D	
B	C	Conduct clinical investigation
D		Assess scientific quality of proposed clinical investigation
A	C	Develop core study documents: protocol, Investigator's Brochure

The Pre-IND Meeting

- Not required, but very helpful to:
  - Identify and avoid unnecessary studies
  - Ensure studies are designed to provide useful information
  - Gain FDA support for proposed strategy
  - Minimize potential for clinical hold
  - Obtain regulatory insight
  - Minimize costs
  - Clearly define endpoints and goals
  - Allow early interactions with FDA
- Type B Meeting Request

- Timeline:
  - Submit formal Pre-IND Meeting Request in required format
  - FDA responds within 21 days of receipt: meeting granted or denied
  - If granted, meeting scheduled to occur within 60 days of request receipt
  - Pre-IND Meeting Package must be received by FDA no later than 30 days before scheduled Pre-IND meeting
  - FDA will send preliminary responses no later than 2 days prior to meeting. Cancel or proceed.

IND content: Forms, Section A

- 1571 Investigational New Drug Application
- 1572 Statement of Investigator
- 3674 Certification of Compliance
- May be required for Phase II or higher trials (or sponsored trials):
  - 3454 Certification: Financial Interests and Arrangements of Clinical Investigators
  - 3455 Disclosure: Financial Interest and Arrangements of Clinical Investigators

Link to FDA Forms – https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-forms-and-instructions

IND content: application

- Excellent guidance document
- IND sections:
  B. Table of Contents
  C. Introductory Statement and General Investigational Plan
  D. Investigator's Brochure (body in appendix)
  E. Protocols (body in appendix)
    - Phase I outline allowed. ***Suggest at least fully developed synopsis.***
    - Phase II and higher require complete protocol(s)
  F. Chemistry, Manufacturing, and Control Information
  G. Pharmacology and Toxicology Information
  H. Previous Human Experience With the Investigational Drug
  I. Other Important Information (drug dependence/abuse potential, radioactive)
  J. Relevant Information (if IP to be used with a device)

IND content: appendices

- Package inserts for approved drugs
- Letters of Cross Reference (a.k.a. Letter of Authorization)
  - Drug Master File(s)
  - Existing IND(s)
- Full study documents: IB, protocol, consent form(s)
- Pre-IND responses
- Complete pharmacology and/or toxicology reports
- Other items as requested by FDA (i.e. clinical dilution procedure)

Exercise: In which IND section would you include…?

A. Forms
B. Table of Contents
C. Introductory Statement and General Investigational Plan
D. Investigator's Brochure
E. Protocols
F. Chemistry, Manufacturing, and Control Information
G. Pharmacology and Toxicology Information
H. Previous Human Experience With the Investigational Drug
I. Appendix

__C__ Rationale supporting the proposed clinical trial

__D__ Statement of which appendix has complete Investigator's Brochure

__I__ Full body of clinical protocol

__F__ Copy of label for investigational drug

__H__ Summary of findings from previous studies with the IP in humans

__A__ Form 3674

__G__ Discussion of the effects of IP in experimental mouse models

__B__ The page number on which you can find Appendix A

__F__ Reference to Letter of Authorization from IP manufacturer for information on the IP's components and composition

How much time should I budget for IND prep?

Task	Approx Time
Study concept development	Team dependent (1-2 months)
Sourcing IP	Situation dependent (1-2 months)
Pre-IND process	Minimum 2 months
Study document development (protocol, IB, consent)	Team dependent (1-2 months)
Letters of Cross Reference	Dependent on others (try giving deadline of 2 weeks)
CMC and/or toxicology data, reports (if required)	Dependent on product/manufacturer (months)
Writing IND content	Team dependent (1-2 months)
TOTAL	**6 months, "Good Case Scenario"**

Where do I send the application?

Center for Drug Evaluation and Research (CDER)

- Prescription drugs
- Generic drugs
- Over-the-counter-drugs
- Monoclonal antibodies for in vivo use
- Proteins intended for therapeutic use
- Immunomodulators
- Agents intended to alter the production of cells in vivo

Center for Biologics Evaluation and Research (CBER)

- Allergenics
- Blood and blood components
- Antitoxins, antivenins and venoms
- Devices
- Gene therapy
- Human tissue and cellular products
- Vaccines
- Xenotransplantation products

To submit an IND to either Center, send hard copies or a flash drive to the relevant Central Document Room.

What happens after I submit the IND?

- If 30 days pass after FDA receives the IND with no communication from FDA, the IND is in effect and the trial may proceed.
- What is Clinical Hold?
  - An order issued by FDA to delay proposed clinical investigation or suspend an ongoing investigation.
  - During Clinical Hold:
    - Subjects may not be given the investigational drug
    - No new subjects may be recruited
    - Subjects already in the study should be taken off the investigational drug unless specifically permitted by FDA
- Why might an IND be placed on Clinical Hold by FDA?
  - Phase I
    - Unreasonable and significant risk of illness or injury
    - Clinical investigators not qualified
    - The investigator brochure is misleading, erroneous, or materially incomplete
    - IND insufficient
    - Reproductive toxicity
  - Phase II and III
    - All of the above, and study design deficient to meet stated objectives

Coming off Clinical Hold

- FDA notifies sponsor of Clinical Hold order by “rapid communication” with follow-up written explanation within 30 days.
- Resumption of trial activities only after deficiencies are corrected:
  - Sponsor submits response to FDA determination
  - FDA has 30 days from receipt of sponsor’s response to decide whether to lift or maintain Clinical Hold.

National Cancer Institute

IND amendments

Changes requiring an amendment to the IND include:

- Protocol amendments
  - New protocol
  - Amended protocol
    - Revisions that significantly affect subject safety, scope of the investigation or scientific quality.
    - Once submitted, the amendment may be implemented without waiting for FDA approval/30 days. IRB approval IS required prior to implementation.
- New investigator
  - Notify FDA within 30 days of adding a new investigator with a new 1572 and CV
- New information
  - New toxicology, chemistry or technical info; discontinuance; and serious, related, unexpected, significant adverse events, or fatal, life-threatening events (not covered under IND Safety Reports)

IND Reports

- IND Safety Reports (see FDA guidance on Safety Reporting Requirements for INDs)
  - The sponsor must report in an IND safety report any suspected adverse reaction(s) to study treatment that is both serious and unexpected. The sponsor should ensure that the event meets all three of the definitions: Suspected adverse reaction; serious; unexpected.
  - IND Safety Report must be submitted to FDA and all participating investigators as soon as possible and no later than 7 days (for life-threatening event) or 15 days of learning of the event.
- IND Annual Report
  - Submit within 60 days *after* the anniversary date of when the IND went into effect
  - FDA guidance for Annual Report content:
    - Individual study information
    - Summary information
      - Safety
      - Drop outs
      - Changes (new pre-clinical studies, manufacturing, microbiological, documents)
      - Plan for upcoming year

IND Advice

- FDA staff are helpful. Engage them.
- Web searches yield good results; lots of guidance available.
- Keep the IND neat and organized with consistent headers, levels, formatting. The format and content are prescribed. Follow the instructions.
- Don't recreate the wheel. IND templates are available (as well as Pre-IND):
  - Duke
  - Mt. Sinai
  - ReGARDD
- Things NOT to worry about **(these may change)**:
  - The Common Technical Document (CTD) format
  - Setting up a WebTrader account on the FDA's electronic gateway
- Monitoring can be done be an entity internal to the institution/organization

Exercise: Put items in chronologic order (number)

- 2 Submit Pre-IND Meeting Package
- 6 IND compiled and complete
- 10 IRB approval
- 4 Solicit Letters of Cross Reference
- 7 Submit protocol and supporting materials to your IRB
- 1 Submit Pre-IND Meeting Request
- 8 Submit IND to FDA
- 5 IND content written, including protocol, Investigator's Brochure and consent form
- 11 Start recruiting for your study
- 3 Pre-IND Meeting
- 12 First IND Annual Report submitted
- 9 30 day window expires with no Clinical Hold

Questions?

Thank you and have fun!