IND Overview

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Investigational New Drug

- Used in clinical investigations
- Must be covered by an Investigational New Drug Application (IND)
  - Synonymous with a “Notice of Claimed Investigational Exemption for a New Drug”

Regulation

- The regulations in 21 CFR 312 cover procedures and requirements for Investigational New Drug Applications (INDs)
- These regulations define the roles and responsibilities of FDA reviewers, IND sponsors, and clinical investigators

The IND

- No User Fee for INDs. www.fda.gov/oc/pdufa/default.htm
- 21 CFR 601.50 *Confidentiality of data & information in an IND notice for a biological product*
  - (a) The existence of an IND notice for a biological product will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.
- Additional information is submitted to IND as amendments.
- Regulatory mechanism for new drug development

Definitions: I/C

(b) The term "interstate commerce" means

(1) commerce **between** any State or Territory and any place outside thereof, and

(2) commerce **within** the District of Columbia or within any other Territory not organized with a legislative body.

Sponsor

Definition

21 CFR 312.3(b)

- an individual, company, institution, or organization that takes responsibility for and initiates a clinical study

Sponsor

General Responsibilities

21 CFR 312.50

- Selecting qualified investigators
- Ensuring study monitoring
- Maintaining an effective IND, and
- Ensuring AE risk information is provided to the FDA and investigators

Investigator

Definition

21 CFR 312.3(b)

- an individual under whose immediate direction the study drug is administered or dispensed. If a team is involved, the leader is the investigator; other team members are sub-investigators

Investigator

General Responsibilities

21 CFR 312.60

- Ensuring the study is conducted according to the plan
- Protecting the rights, safety and welfare of subjects, and
- Control of drug under investigation

Sponsor-Investigator

Definition

21 CFR 312.3(b)

- an individual who both initiates and conducts a study and under whose immediate direction the study drug is administered or dispensed.
- must follow the requirements for both a sponsor and investigator

Sponsor-Investigator

General Responsibilities

- For sponsors…21 CFR 312.50
  - **AND**
- For investigators…21 CFR 312.60

A General Principle

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects…

21 CFR 312.22

Clinical Investigation
21 CFR 312.3

- Any experiment in which a drug is …
  - administered to,
  - dispensed to,
  - or used involving…

  one or more human subjects.

Clinical Investigation 21 CFR 312.3 (cont.)

…an experiment is defined as any use of a drug except for the use of a marketed drug in the course of medical practice.

Even FDA-licensed products are subject to IND regulations,

- if used in a clinical investigation and
- one or more of the exceptions under 21 CFR 312.2(b) doesn't apply.

IND Content Requirements 21 CFR 312.23

- Format pertains to all sponsors and sponsor-investigators and fosters efficient review
  - Cover Sheet (and Form FDA 1571)
  - Table of Contents
  - Introductory Statement and General Investigational Plan
  - Investigator's Brochure
  - Clinical Protocol
  - Chemistry, Manufacturing and Control (CMC) Information
  - Pharmacology and Toxicology Information
  - Previous Human Experience
  - Additional Information
  - *ICH-Common Technical Document Format*

Introductory Content Elements 21 CFR 312.23(a)(1-3)

- Cover Sheet (Form FDA 1571)
- Table of Contents
- Introductory Statement (description of product, formulation, route, broad study objectives, relevant previous use, foreign experience)
- General Investigational Plan (rationale, indication, general approach, anticipated studies including number of subjects and possible risks)

Investigator's Brochure (IB)

- **Contents [21 CFR 312.23(a)(5)] :**
  - Brief product description
  - Pharm/tox summaries
  - Previous human experience
  - Description of anticipated risk and any special monitoring needs
  - Updates as appropriate

- **Distribution [21 CFR 312.55(a)]:**
  - Before study begins, sponsor shall provide to each clinical investigator. (Not required for sponsor-investigators).

Updating Investigators with New Information about Study Vaccine

- Sponsors are required to update all investigators with new information about the study vaccine. **[21 CFR 312.55(b)]**
- Particularly, adverse events and safe use
- May be done by
  - distributing updated IB
  - reprints or published studies
  - reports or letters to investigators
- In accordance with IND safety reporting requirements **(21 CFR 312.32).**

IND Amendments
21 CFR 312.30-33

- Protocol amendments
- Information amendments
- IND safety reports
- Annual reports

IND Protocol Amendments 21 CFR 312.30

- A new protocol
- Safety or design-related changes to an existing protocol
- New investigator (notification is required within 30 days of being added)
- Must submit to FDA before implementation
- IRB approval is needed prior to implementation

IND Information Amendments 21 CFR 312.31

Information amendments advise the FDA of:

- New toxicology, CMC or other technical information
- Notice of discontinuance of a clinical study
- Other, not within scope of protocol amendments, safety report or annual report.

IND Safety Reports
21 CFR 312.32

- ***Sponsor is required to promptly review all information relevant to the safety of the drug that is received from any source, foreign or domestic.***

- **15-day (calendar) report**
  - Notify FDA & all investigators in writing
  - Any serious and unexpected AE, associated w/ use of drug (including information from non-IND studies); or,
  - any finding in laboratory animals that suggests a significant risk for human subjects.

- **7-day (calendar) report**
  - Notify FDA via phone or fax
  - Any fatal or life-threatening AE associated w/ use of drug

IND Safety Reports
21 CFR 312.32 (cont.)

- **Reporting Format or Frequency:**
  - FDA may request different from required.
  - Sponsor may propose different from required & adopt such, if FDA agrees in advance.

- **Sponsor Follow-up of AEs:**
  - Shall promptly investigate all safety information received.
  - Shall submit AE follow-up information as soon as available.
  - Shall submit a report w/in 15 days for any adverse drug experience not initially determined to be reportable, but is so reportable as a result of sponsor's investigation.
  - Shall submit results of investigation of other safety information in information amendment or annual report.

Annual Reports
21 CFR 312.33

- Submit within 60 days of the anniversary of “in effect” date
- Include enrollment, demographic and conduct status information for each study
- Adverse event summaries (safety reports, deaths, dropouts)
- Drug action information
- Preclinical study status information

IND Review Process

- FDA does not approve INDs
- IND is “in effect” after 30 days, unless placed on clinical hold by FDA
- Clinical holds may occur at any point in the life of the IND & may affect a single study or entire IND
- FDA communication may occur at any time during the course of the IND and is advisory unless accompanied by a clinical hold order under 21 CFR 312.42

Grounds for Clinical Hold 312.42(b)
(Most commonly seen with vaccine INDs)

- **Phase 1, 2 or 3 studies:**
  - Unreasonable risk of harm to human subjects
  - Unqualified investigators
  - Misleading, incomplete or erroneous investigator brochure
  - Insufficient information in IND
- **Phase 2 or 3 Studies only:**
  - Plan or protocol for investigation is clearly deficient in design to meet its stated objectives.

21 CFR 314.106 Foreign Data

- Acceptance of foreign data in an application generally is governed by §312.120.

- Foreign Data Submissions must include:
  - investigator's qualifications
  - description of research facilities
  - protocol summary & study results
    - case records/additional info on request
  - product information
  - to support efficacy, data must demonstrate that study is adequate & well-controlled (§314.126)
  - conformance with ethical principles

312.120 Foreign clinical studies not conducted under an IND

- FDA may accept foreign clinical studies, which meet the following criteria, in support of clinical investigations in the US and/or marketing approval:
  - well designed
  - well conducted
  - performed by qualified investigators
  - conducted in accordance with ethical principles acceptable to the world community
- Required data submissions
  - 21 CFR 120(b)

Office for Human Research Protections (OHRP)

- **Resources for International Trials**
  - **Ethical Codes**
  - **Regulatory Standards**
  - **Compilation of National Policies**
- **At** http://www.hhs.gov/ohrp/international/

Exports
312.110

- **(b) *Exports*. An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:**

- ***An IND is in effect and person who receives the drug is an IND investigator***

- ***Drug complies with the laws of the country to which it is being exported***

Requests for export

- **FDA authorizes shipment of the drug for use in a clinical investigation.**
  - **Person exporting the drug sends a written certification to:**
  - **The Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857**
  - **Request must provide adequate information:**
  - ***Not in conflict with the importing country's laws***
  - ***cGMP***

Exportation may not proceed until FDA has authorized exportation of the investigational new drug.

CBER's Bioresearch Monitoring Program

- **Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS)**
  - Ensures quality & integrity of data submitted to CBER
  - Ensures rights & welfare of human research subjects are protected
- **Inspections**
  - Random surveillance of ongoing studies
  - Investigates complaints/referrals from staff
  - Clinical investigators, Sponsor/Monitor/CROs, IRBs, GLP/Nonclinical Labs

Administrative Actions

- Warning Letter
- Determine if the data are reliable
  - Complete and accurate?
- Clinical hold
- Initiate termination of IND
- Initiate disqualification of investigator
- Refer to Office of Criminal Investigations
- ***Standards are the same regardless of where IND is being conducted.***

Acceptance of Foreign Data

- *Guidance for Industry: Acceptance of Foreign Clinical Studies,*
- *Guidance for Industry: ICH (E5) Ethnic Factors in the Acceptability of Foreign Data*
- *Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trails,*
- *Guidance for Industry: ICH (E6) Good Clinical Practice, Consolidated Guidance*

US Code of Federal Regulations

- 21 CFR 50 - Protection of Human Subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 58 - Good Laboratory Practices
- 21 CFR 210, 211 - Good Manufacturing Practices
- 21 CFR 312 – INDs
- 21 CFR 312.110 Export
- 21 CFR 312.120 Foreign Data
- 21 CFR 314.106 Foreign Data
- 21 CFR 314.126 - Adequate and Well-Controlled Studies

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