INDs and IDEs: Responsibilities of Sponsor/Investigators

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Outline of Presentation

I. Roles and Responsibilities
II. IND
III. IDE
IV. Amendments
V. Sponsor/Investigator Responsibilities
VI. Operationalizing the IND/IDE
VII. The Institution’s Role
The Challenge

David Lepay, the FDA’s senior advisor on clinical science states that, “Where problems have come in recent years, the majority have come in studies where the investigator was also the sponsor.” Because the investigator now maintains also the responsibility of the sponsor, there is lost a level of oversight that comes from separate sponsors and investigators.

Guide to Good Clinical Practice Jan. 2005
Investigator means an individual who actually conducts a clinical investigation. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

21 CFR 312.3 (b)
Sponsor means 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 unless the sponsor is a sponsor-investigator.

21 CFR 312.3 (b)
Sponsor-Investigator means 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. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and sponsor.

21 CFR 312.3 (b)

NOTE: Corporations, agencies, or other institutions do not qualify as sponsor-investigators.
Roles and Responsibilities

Contract Research Organization

**Contract Research Organization (CRO)** means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA.

*21 CFR 312.3 (b)*
Warning Letters

...purpose to determine whether activities as both sponsor and investigator in clinical studies complied with FDA regulations

- Failure to obtain an investigator agreement from all implanting physicians
- Failure to ensure proper monitoring
- Failure to maintain records of shipment and disposition of device
- Failure to follow investigational plan
Warning Letter

- You failed to adequately supervise the conduct of the study
- You failed to disclose sufficient accurate financial information
- You failed to provide SOPs for the conduct of the trial
- Failure to maintain adequate records
What is an IND?

Investigational New Drug

- Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines.

- Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement.

- The IND is the means through which the sponsor technically obtains this exemption from the FDA.

21 CFR 312.1
When is an IND Required?

- Sponsor intends to conduct a clinical study with an investigational drug.

- Sponsor intends to conduct a study with an approved drug, but in a new indication, dose form, or dose range that is not covered in the current package insert (off label).

21 CFR 312.2
When is an IND Not Required?

The clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

- It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug?
- It is not intended to support a significant change in the advertising for the product

21 CFR 312.2
When is an IND Not Required?

- It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- It is conducted in compliance with the requirements for IRB review and informed consent.
- It is conducted in compliance with the requirements concerning the promotion and sale of drugs.
- And it does not intent to invoke 21 CFR 50.24.
IND Regulations - 21 CFR 312

- Contains procedures and requirements governing the use of investigational new drugs and biologics
- Applies to all clinical investigations of products that are subject to section 505 of the FD&C Act.
IND Application

Resources

Guidance Documents

- IND Application Process
- Content and Format of INDs for Phase 1 Studies of Drugs
- Information for Sponsor-Investigator Submitting INDs
- Pharmacology and Toxicology Guidelines

Forms


FDA Web Site

- [http://www.fda.gov/cder](http://www.fda.gov/cder)
References and Resources:

- 21 CFR 312.23 Defines IND content and format
- 21 CFR 312.22 Sponsor investigators may use pre-existing technical information if authorized to do so
- 21 CFR 312.33 Annual Reports
IND Application

FDA Jurisdiction of Products

**CDER Regulates:**
- Drugs
- Monoclonal antibodies for in-vivo use
- Proteins intended for therapeutic use
- Growth Factors
- Immunomodulators

**CBER Regulates:**
- Cellular Products
- Vaccines
- Allergenic extracts
- Blood and blood components
- Gene Therapy products

www.fda.gov/cber/transfer/transfer.htm
IND Application
Pre IND Consultation

FDA Consultation Prior to Application

- Pre IND submission
- Pre IND Consult with FDA
  - Occurs within 60 days of receipt of request
  - Typically, only one meeting per issue
  - Meeting package
  - One hour formal meeting by telephone unless unique situation
  - FDA issues official minutes

21 CFR 312.47 and 312.82
IND Application

IND Content and Format

Content of the IND

- **Differs for different products**
- **Depends on**
  1) the phase of the investigation
  2) the extent of human study
  3) the duration of the investigation
  4) the nature and source of the drug substance, and
  5) the dosage form of the drug product
IND Application

IND Content and Format

1. Cover letter (Not required by CFR)
2. Cover Sheet (Form FDA 1571) (Road Map)
3. Table of Contents (What’s where)
4. Introduction Statement and General Investigational Plan (Where you are headed)
5. Investigator’s Brochure (Preliminary package insert)
6. Protocols (Plan for collecting safety/efficacy data)

21 CFR 312.23 (a)
7. Chemistry, manufacturing, control data and environmental impact statement (how the product was made and the testing performed)

8. Pharmacology and toxicology data (data to conclude that it is reasonably safe to conduct the proposed study)

9. Previous Human Experience (same or similar products)

10. Additional Information (study, investigator, facilities, IRB, Form FDA 1572)

21 CFR 312.23 (a)
Information that has been previously submitted to the FDA under other INDs/Drug Master Files may be incorporated by reference.

A copy of a cross reference letter can be included in the information in place of the information required.

Sample text: We authorize the institution listed below to cross reference (company name) Biologics Master File (BB-MF-xxx) as described below in support of their IND application.

21 CFR 314.420
When a Sponsor Signs a 1571; What does it mean?

- Wait 30 days before beginning the study
- Not begin or continue the study if placed on clinical hold
- IRB will be responsible for review and approval of the study
- Conduct the study in accordance with all applicable regulatory requirements
- Transfer of Obligations
When an Investigator Signs the 1572;
What do they commit to?

- To conduct the study in accordance with the protocol
- To personally supervise or conduct the investigation
- To inform the subjects of the investigational status of the test article
- To report adverse events to the sponsor
- To read and understand the Investigational Brochure
- To inform all support personnel of the investigation requirements
When an Investigator Signs the 1572;
What do they commit to?

- To maintain adequate records and make them available for inspection
- To assure that the IRB is in compliance
- To assume responsibility for initial and continuing review by the IRB
- To promptly report study changes and unanticipated risks to the IRB
- Not make changes in the research without IRB approval
- To comply with the requirements regarding the obligations of clinical investigators
IND Application
Format

3 copies (An original and 2 copies)

- Numbering: Beginning with the initial IND, serial numbering with a 3 digit number
- At least 1 ½” left margin for binding
- 3 hole punched paper
- If > 2” thickness, separate into separate volumes and labeled
- Section dividers
- Sequentially number pages with table of content
- Outside wrapper of shipment(s) should identify the contents, IND application, Notice of IND change

FDA IND, NDA, ANDA, or Drug Master File Binders
http://www.fda.gov/cder/ddms/binders.htm
FDA Review Process

Typical Review Team

- Regulatory Reviewer
- Clinical Medical Officer
- Product Reviewer(s)
- Statistician
- Pharmacology/Toxicology Reviewer

A single review team will generally follow a drug from its IND application through the NDA approval decision and into post-marketing
FDA Review Process

CDER: MAPP CDER Manual of Policies and Procedures (MaPP)


- **6030.4** INDs: Screening INDs (Issued 5/9/2001, Posted 5/14/2001)

Clinical Hold

IND goes into effect (study may proceed) 30 days after FDA receives the IND, unless sponsor is notified otherwise by FDA

21 CFR 312.40

Order issued by FDA to sponsor to delay a proposed clinical investigation or suspend an ongoing investigation

21 CFR 312.42
Clinical Hold

Addressing a Clinical Hold

- Sponsor prepares amendment to the IND addressing specific issues
- The FDA response to the sponsor in writing within 30 days of receipt of the amendment

The Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Hold

21 CFR 312.42 Clinical Holds and Request for Modifications
IND Submissions

Common Pitfalls

- Data lacking to support dose proposed
- Inadequate report of prior investigations
- Questionable scientific soundness
- Poorly defined stopping rules
- Undefined statistical analysis
- Undefined endpoint
- Inconsistencies
- Lack of specific cross reference
What is an IDE?

- It is a new medical device
- It is a significant risk device
- Required by law \((sec \ 515 \ FD&C \ Act)\)
- Required by Regulation \((21 \ CFR \ 812)\)
When is an IDE Required?

Significant Risk Device

- An implant
- For use in supporting or sustaining human life substantially important in diagnosing, curing mitigating, or treating diseases, or in preventing impairment of human health

21 CFR 812.3
When is an IDE Not Required?

Examples of non significant risk device studies:

- Contact lens solutions
- TENS units for treatment of pain
- Daily wear contact lenses and associated cleaners and solutions
- Jaundice monitors for infants

*Guidance Document for IRB and Investigator/Medical Devices*
When is an IDE Not Required?

- A diagnostic device, if the sponsor complies with the applicable requirements in 809.10.c

- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
When is an IDE Not Required?

- A device intended solely for veterinary use
- A device shipped solely for research on or with laboratory animals
- A custom device as defined in 21 CFR 812.3.b, unless the device is being used to determine safety or effectiveness for commercial distribution
IDE Application

- **Cover letter**
- **Name and address of sponsor**
- **Report of prior investigations to include all prior clinical, animal and lab testing of device** 21 CFR 812.27
- **Investigational Plan** 21 CFR 812.25
- **Description of methods, facilities and controls used for the manufacture, processing, packing, storage and installation of the device, and signed investigator agreement** 21 CFR 812.43

21 CFR 812.20
IDE Application (cont.)

- Name and address of IRB chairperson where investigation is being conducted
- Institution(s) name and address where investigation is being conducted
- An example of the investigator agreement
- Monitoring plan
- Amount charged for device
- Labeling of device
- Informed consent 21 CFR 50

21 CFR 812.20
IDE Cover Letter

- Statement that enclosed is “original IDE submission”
- Include applicants mailing address, phone, fax and email which must be in the US 21 CFR 812.18
- Reference device name and indication for use
- Reference device manufacturer, address and contact information
- Indicate whether device is intended to be sold
Upon receipt of the application by FDA, an IND/IDE number will be assigned, and the application will be forwarded to the appropriate reviewing division. The reviewing division will send a letter to the Sponsor-Investigator providing notification of the IND/IDE number assigned, date of receipt of the original application, and address where future submissions to the IND should be sent.

Studies shall not be initiated until 30 days after the date of receipt of the application by FDA unless you receive earlier notification by FDA that studies may begin.
IND Amendments

- Protocol Amendment (21 CFR 312.30)
- Informational Amendment (21 CFR 312.31)
- Safety reports (21 CFR 312.32)
- Annual Reports (21 CFR 312.33)
IND Amendments
Protocol Amendment

- Reporting a new protocol using a protocol amendment is applicable when a sponsor would like to conduct a new clinical study under an existing IND. No 30 day wait.

- Changes to an existing clinical protocol if the change impacts safety, the scope of the investigation of the quality of the study.

- FDA review and IRB approval may not be required immediately for a revision if the changes eliminates apparent immediate hazards. 21 CFR 312.30 (b) (2) (ii) Requires FDA/IRB notification within 5 working days. 21 CFR 56.104 (c)

- Addition of a new investigator. Notification within 30 days of adding the investigator. 21 CFR 312.23 (a) (6) (iii) (b)
An informational amendment is used to submit any pertinent additional information to the FDA not reportable suing a protocol amendment, safety report or an annual report

Includes technical information or responses to FDA comments

21 CFR 312.31
IND Amendments
Safety Reports

IND Safety Report

- The sponsor shall notify FDA and all participating investigators in a written IND safety report:
  - Any adverse experience associated with the use of the drug that is both serious and unexpected; or
  - Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or cardinogenicity

21 CFR 312.32
IND Amendments

Safety Reports

IND Safety Reports

- Each notification shall be made as soon as possible and in no event later than 15 days after the sponsor’s initial receipt of the information.

- Each written notification may be submitted on FDA Form 3500 A or in a narrative format.

21 CFR 312.32
IND Amendments

Safety Reports

IND Safety Reports

- Use Form 1571 to file
- Indicate “IND Safety Report”
- Initial reports, follow up reports
- Send to reviewing division at FDA
- Indicate all previous similar reports files
- Provide follow up information, resolution of event from subsequent reports
Changes in the investigational plan that require prior approval:

- Change in indication
- Change in type of nature of study control
- Change in primary endpoint
- Change in method of statistical analysis
- Early termination of study (except for safety reasons)

21 CFR 812.35
IDE Amendment

Changes that do **NOT** require FDA approval, but require notification to the FDA within **5 working days** of change:

- **Emergency Use**
- **Certain Developmental Changes**
- **Changes to the Protocol** that do not affect
  - Validity of data
  - Scientific soundness of plan
  - The rights, safety, or welfare of subjects
IDE Amendment

Safety Reports

IDE Safety Reports

Report of Unanticipated Adverse Device Effects

- A sponsor who conducts an evaluation of an unanticipated adverse device effect shall report results to FDA and all reviewing IRBs and participating investigators within 10 working days after sponsor first receives notice of the effect.

- If sponsor determines adverse effect presents an unreasonable risk to subjects, termination is to occur as soon as possible, but no later than 5 working days after sponsor makes determination and not later than 15 working days after sponsor first receives notice of effect.
IND/IDE Reporting

Requirements Annual Reports

IND Annual Report

- Within 60 days of the anniversary date of the IND/IDE filing
- Study title, protocol, objectives, status, number of subjects planned versus enrolled, completed and discontinued, and description of results
- Summary: narrative or tabular reporting of SAEs, frequent and most serious by body system, summary of IND safety reports for the year, number of subjects expired and cause of death, revised IB, and resultant new information.

21 CFR 312.33
IND/IDE Reporting
Requirements Annual Reports

IDE Annual Report

- IDE number; device name and indication
- Summary of study progress
- Number of investigational sites
- Number of devices shipped
- Brief summary of results
- Summary of anticipated and unanticipated ADE
- Description of any deviations from plan

21 CFR 812.150
IND/IDE Reporting
Requirements Annual Reports

Non compliance with annual reporting requirements:

- Report Request Letter
- A Pre Termination Letter if the sponsor does not reply within 30 days of the issuance of the Report Request Letter, or
- A Termination Letter is issued if the sponsor does not reply within 30 days of the issuance of the Pre Termination Letter
Challenge to maintain final accountability and yet set up systems that allow for objectivity and minimize bias.
Sponsor Responsibilities

- CRO/Transfer of obligations
- Selecting qualified investigators/monitors
- Allocation of duties
- Trial management, data handling, record keeping, data management and conduct

- Quality Assurance / Control
- Investigational drug
- Informing investigators
- Safety reporting: FDA and investigators
- Monitoring/Auditing

21 CFR 312.50
Transfer of Obligations

- Sponsor may transfer any/all responsibilities set forth in part 312
- Any transfers shall be in writing
- If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the CRO. If all obligations transferred, statement that all obligations transferred is acceptable.

21 CFR 312.52/ICH 5.2.1
Transfer of Obligations

- A CRO assuming any responsibility of the sponsor shall comply with the specific applicable regulations and is subject to the same regulatory action as the sponsor for failure to comply with the obligation.

- Any regulations referring to “sponsor” shall apply to the CRO accepting one or more of the transferred obligations.

- While a CRO may assume any of the sponsor's responsibility, it should be emphasized that the transfer does not relieve the sponsor from responsibility for the quality of data.

21 CFR 312.52/ICH 5.2.1

Federal Register
### Operationalizing the IND/IDE

**Institutional/Sponsor-Investigator Considerations Prior to Implementation**

- **Resources**
  - IRB approval
  - Role of Pharmaceutical or Device Company
  - Training
  - Funding
  - Administar Approval

- **Financial Disclosures**
  - Indemnifications
  - Standard Operating Procedures
  - Trial Registry
  - Risk
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Resources:

- Data Management/Analysis
- Compliance with 21 CFR Part 11
- Data collection to meet safety reporting requirements and FDA annual and final reports
- Project Management
- Timelines
- Contingency Planning
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Resources: Monitoring

- Source verification, Investigational Product accountability, regulatory documents, overall compliance
- Independent
- Internal/Outsource
- Monitoring Plan (submit with IDE application)
- Investigator-Sponsor oversight and intervention

*FDA Guideline for the Monitoring of Clinical Investigations*
Operationalizing the IND/IDE Institutional/Sponsor-Investigator Considerations Prior to Implementation;

Training:
- Site Initiation
- Monitors
- Transitions
- Documentation
IRB approval:

- Parallel review
- Institutional Policies
- IRB approval not obtained until FDA assignment letter is received
Role of Pharmaceutical or Device Company:

- Define Role
- Wide range of roles/relationships
- Hands off
- Support
- Reporting requirements
Financial Support:

- Typically partial financial support from industry
- Realistic definition of costs based on processes to maintain compliance
- Hidden costs
The Office of the Inspector General has indicated in its Compliance Program Guidance for Pharmaceutical Manufactures that the provision of study drug free of change of funding for an investigator imitated study is not prohibited so long as the study is for a legitimate purpose and the funding is tied to legitimate study costs.

68 Fed. Reg. 23731

The legitimacy may be suspect if the marketing program is the approver of funding.
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Administar:

- Administar is the Medicare Fiscal Intermediary for Medicare coverage determination of CMS/FDA Category B investigational devices
- Must submit name of device and detailed approval letter demonstrating Category B status with number of sites and subjects
- Approval within 6 weeks of submission
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Financial Disclosure:

- Permitting an investigator to begin participation in an investigation, the IND/IDE sponsor shall obtain financial information that will allow an applicant to submit complete and accurate certification or disclosure statements required under Part 54. 21 CFR 312.53 and 21 CFR 812.43.

- Sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

- Maintain on file for all involved in trial.
Indemnification:

- **Determine if institution or funding agency will provide indemnification for clinical investigation**
- **Typically, very little indemnification if any is able to be secured**
- **Limited Indemnification: donation of study drug and agreement to indemnify the sponsor-investigator only for manufacturing defects**
Standard Operating Procedures:

FDA: Compliance Program Guidance Manual: Makes reference to sponsor SOPs in several areas, including monitoring, data collection, and QA

GCP ICH:

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs
- The sponsor should maintain SOPS for using electronic trial data handling and or remote electronic trial data systems
- Monitors should follow and be thoroughly familiar with the sponsor’s SOPs
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Trial registry:
The data bank was established, as required under section 113 of the FD & C Act, be a central resource to other members of the public and to health care providers and researchers. Clintrials.gov

Fair Access to Clinical Trials Act 2005

- The FACT Act would require
- Trials to be registered prior to IRB approval
- Objectives, eligibility, funding, timeline to be disclosed
- Results be made available
- Enforcement mechanisms-including monetary penalties of up to $10,000/day to sponsor for non compliance
Operationalizing the IND/IDE
Institutional/Sponsor-Investigator
Considerations Prior to Implementation

Risk:

- No or limited indemnification
- Investigator and Sponsor requirements
- Compliance with institutional policies, reporting requirements from funding source, state laws, and GCPs
Closing an IND

- An IND may be inactivated at the request of the sponsor (clinical hold > 2 yrs.) and may be reactivated with proper documentation.
- The FDA may terminate an IND that has been inactive for over 5 years.
- An IND can be withdrawn at the sponsor's request. The IND cannot be reactivated, but can only be resumed with a new IND.
- FDA can terminate.
At any time a sponsor may withdraw an effective IND without prejudice.

If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 21 CFR 312.59.

If an IND is withdrawn because of a safety reason, the sponsor shall promptly inform the FDA, all participating investigators, and all reviewing IRBs with the reason of the withdrawal.

21 CFR 312.40
A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND.

If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug.

21 CFR 312.44
The sponsor shall notify the FDA within thirty working days of completion or termination of investigation.

Sponsor shall notify IRB and participating investigations within 6 months after completion or termination.

21 CFR 312.33/ 21 CFR 812.150
The Institution’s Role

Know when research is going on and oversight

- Notification by physician
- Education (IND/IDE Assistance Program)
- Templates (application, protocols, annual reports)
- Oversight
- Mentoring
- Prior review of all publications
- Cross reference publications with IRB records
The Institution’s Role

Require Scientific Review and Appropriate Pre-Implementation Planning

- Well planned and coordinated
- Required Pre IND meeting with FDA
- Notification of clinical holds and audits
The Institution’s Role

- Ensure the study is monitored objectively
  - Review and approval of outside monitors
  - Inclusion of DSMB
- Implement measures to ensure adverse event reporting
Conclusion

- Sufficient potential scientific benefit should be identified and supported by both the PI and Institution prior to beginning the IND/IDE

- Additional regulatory requirements significantly increase the need for resources and compliance

- A sponsor-investigator should have full knowledge of the regulations before consideration of holding the IND/IDE