



What is an IND?

ASGCT Clinical Trials Training Course
May 17, 2010

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Disclosure

- No financial relationships to disclose.

Overview

- Regulatory Framework
- What is an IND?
- Who can apply for IND?
 - What are the applicant's responsibilities?
- What should an IND contain?
- How does FDA review an IND?
- What resources are available?



FDA Mission Statement

The FDA is responsible for **protecting the public health** by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

The FDA is also responsible for **advancing the public health** by helping to *speed innovations* that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.



Regulatory Framework

- Federal regulatory authority is a 3-tiered system
- Statutes (Laws)
 - passed by Congress and signed by the President
 - Food, Drug & Cosmetic Act, Public Health Service Act
- Regulations
 - details of the law
 - written by the Agency and approved by the Executive Branch
 - IND regulations 21 CFR Part 312
 - IRB and informed consent regulations 21 CFR Parts 50 & 56
- Guidance Documents
 - the Agency's interpretation of the Regulations
 - written and approved within the Agency



FDA Regulation of Clinical Research

- FDA regulates clinical research in the US that involves drugs, biological products, and medical devices regardless of funding source
- Clinical investigations with an investigational new drug are to be conducted under an IND

What is an IND?

Investigational New Drug Application-

- A formal document with defined structure and content
- Purpose is to request exemption from premarketing requirements and to allow lawful shipment of drug for clinical investigation.
- Regulations (21 CFR 312) outline requirements for:
 - Use of investigational drug
 - Submission of application to FDA
 - Review by FDA

Who can apply for an IND?

- IND applicant is called a “sponsor”
 - Person who takes responsibility for and initiates a clinical investigation
- IND sponsor may be a company, institution, or an individual
- IND sponsor-investigator
 - The individual who both initiates and conducts the clinical trial

Responsibilities of IND Sponsors

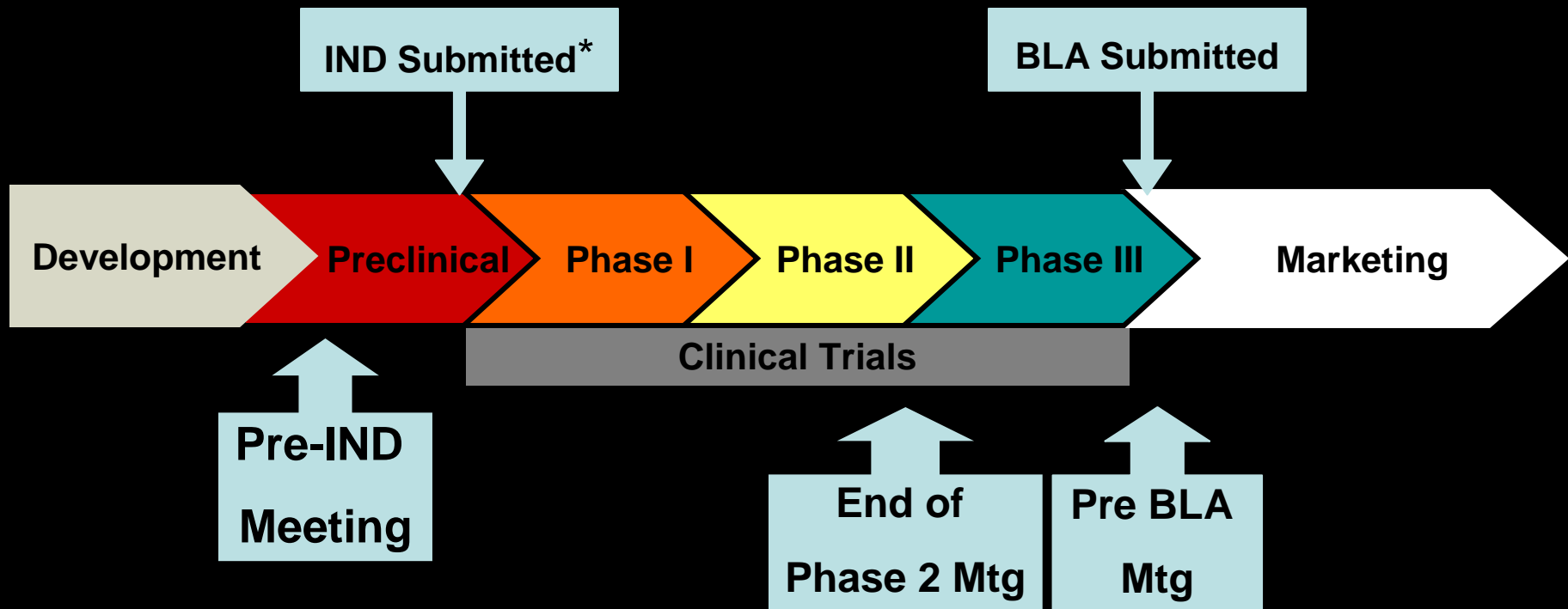
- Select qualified investigators
- Conduct study in accordance with protocol
- Personally supervise the investigators
- Informed consent of study participants
- Report adverse events and new risks
- Communicate with IRB
- Maintain adequate records

Life Cycle of an IND

- IND becomes a “living document”
- Updated by sponsor over time to include study data, protocol amendments, safety reports, new technical information, etc.
- Product development under an IND



Regulatory Timeline



*FDA checks for OBA submission for GT



Phases of Investigation (21 CFR 312.21)

- Phase I Investigational Studies
 - Designed to evaluate safety and side effects
- Phase II Investigational Studies
 - Designed to evaluate efficacy and dose ranging
- Phase III Investigational Studies
 - Expanded study, additional information on efficacy and safety

Early Phase Regulatory Roadmap

Discovery Phase

Basic Research
Proof-of-
Concept

Pre-pre-IND
Informal discus-
sions with FDA

Pre-IND
Discussion
with FDA

Original IND
Submission

Proceed to
Phase 1 Safety
Study

*What are your
plans? Pre-
submission advice*

Phase I Safety Study

- Evaluation by FDA - 30 days
- Prove ability to manufacture “safe” biologic (sterile, free of adventitious agents and contaminants)
- Adequate product characterization
- Sufficient preclinical toxicological studies
- Adequate clinical trial design



Elements of an IND application

<input type="checkbox"/> Form FDA 1571	21 CFR 312.23(a)(1)
<input type="checkbox"/> Table of Contents	21 CFR 312.23(a)(2)
<input type="checkbox"/> Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
<input type="checkbox"/> Investigator's brochure	21 CFR 312.23(a)(5)
<input type="checkbox"/> Protocols	21 CFR 312.23(a)(6)
<input type="checkbox"/> Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
<input type="checkbox"/> Pharmacology and toxicology data	21 CFR 312.23(a)(8)
<input type="checkbox"/> Previous human experience	21 CFR 312.23(a)(9)
<input type="checkbox"/> Additional information	21 CFR 312.23(a)(10)



Chemistry, Manufacturing, & Controls

- CMC= Product manufacturing and testing
- How do you make the product?
 - Processing and manufacturing
- What do you use to make the product?
 - Cell or tissue source
 - Vector or genetically modified cell if gene therapy
 - Reagents and components
 - Equipment
- Product Safety and Quality testing
- Product Stability
- Other controls- product container labels, tracking
- Product comparability (when applicable)



Pre-Clinical

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
 - Identify, characterize, quantify the potential local and systemic toxicities



Clinical:

Early Phase Considerations

- Optimal dose and administration
 - Starting dose level/dose escalation scheme
 - Route of administration
 - Dose schedule
- Define appropriate patient population
- Staggering of dose escalation
- Safety Monitoring plans
- Safety Reporting requirements

IND Submission Process

- Step 1: Pre-IND meeting with FDA
 - Highly recommended for new products
- Step 2: Submission of complete IND package
 - all forms, all sections, 3 copies or electronic
- Step 3: FDA will notify IND Sponsor within 30 days* whether study may proceed or whether the IND has been placed on clinical hold

*Studies may not begin until either 30 day review period is complete, or you receive FDA notification that you may proceed

IND Status (definitions)

- Pending: IND is in initial 30-day review period.
- In Effect: Study may proceed
- Hold: An order issued by FDA to delay a proposed clinical investigation or to suspend an ongoing clinical investigation (21 CFR 312.42).
- Partial Hold: A delay or suspension of part of the clinical work under an IND
 - e.g., IND has 2 protocols, one may proceed and one may not.

Grounds for Clinical Hold – Phase 1 Study

- Subjects are or would be exposed to a significant & unreasonable risk.
- Insufficient information has been submitted to allow FDA to assess the risks to the subjects in the proposed clinical investigation. Grounds used most frequently

Grounds for Clinical Hold – Phase 1 Study

- Clinical investigators named in the IND are not qualified by reason of their scientific training & experience to conduct the investigation.
- The investigators brochure is misleading, erroneous, or materially incomplete.

Grounds for Clinical Hold – Phase 2/3 Study

- A Phase 2/3 study may be placed on hold for the reasons above in addition to:
 - The plan or protocol for the clinical investigation is clearly deficient in design to meet its stated objectives.

See 21 CFR 312.42(b) for these and additional grounds for clinical hold



Objective of FDA Review

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

and, in Phase 2 and 3, 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.

[21 CFR 312.22(a)]



IND Review Process

- A Team Approach to IND Review:
 - Regulatory Project Manager
 - Product reviewer
 - Pharmacology/Toxicology reviewer
 - Clinical reviewer
 - Statistics
 - Consults as needed
- Within 30 days (in effect or hold)
 - Outstanding hold and non-hold issues conveyed by phone and detailed letter is issued.
 - Must satisfactorily address hold issues prior to proceeding

IND Review Process (cont.)

- Emphasis of review is on data to support:
 - Product safety and characterization
 - Manufacturing and quality control issues
 - Scientific rationale
- Sound scientific principles
 - Pre-clinical studies
 - Product development
 - Clinical protocol



FDA Review (cont.)

- Review is based on the best available science
- Input from FDA advisory committees and collaboration with scientific community is valued
- Regulation uses existing development and marketing paradigms
- Agency encourages early interactions with sponsors as necessary in order to facilitate an efficient and effective product review process



How do I make changes to an IND?

- Send an amendment
- Amendment = Any document, from the sponsor, in support of their IND
- An amendment can be made at any time during the life of the IND

Types of Amendments

- Protocol Amendments
 - New protocol, Protocol changes, New investigator
- Safety reports
 - Serious and unexpected clinical adverse event or laboratory finding affecting safety
 - SAE within 15 days, life-threatening within 7 days
- Annual reports
 - A summary report on progress, findings, changes and future plans
 - Must be submitted within 60 days of anniversary
- Information Amendments
 - Everything else



Resources for Sponsors

- Interactions with FDA
- FDA Guidance documents
- Advisory Committee Meetings
- Workshops
- Other outreach by FDA

Interactions with the FDA

- Informal interactions
 - Non-binding on sponsor or FDA
 - All discussions about specific products remain confidential
- Pre-Pre IND
- Pre-IND
- IND milestone meetings
 - End of Phase 1, Pre-Phase 3, pre-BLA
 - Others as needed

FDA Guidances- CMC

- Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) 2008
- Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) 2008



FDA Guidances

- Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events, 2006
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 2007
- Pre-marketing Risk Assessment, 2005
- Development and Use of Risk Minimization Action Plans, 2005

Website for OCTGT Info

- <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>
- How to request a meeting
- IND process
- Other requirements and policies
- Guidance documents
- Advisory committees

Tips for IND Sponsors

- Use available resources to educate yourself about IND process
 - How to submit and maintain an IND
 - Your responsibilities as a Sponsor
- Communicate with the FDA
- Create reviewer-friendly submissions
- Start solving the problems early: plan ahead



Challenge to Review of INDs



Summary- Risk Assessment for OCTGT Clinical Trials

- Product safety and characterization
- Preclinical toxicology studies
 - Define expected toxicities
 - Appropriate starting dose
- Pre-marketing clinical studies
 - Early phase (safety, dose optimization)
 - Late phase (efficacy)
- Post-marketing safety
 - Pharmacovigilance

Contact Information

- **OCTGT Regulatory Issues**
 - **Dr. Patrick Riggins (Branch Chief RPM)**
patrick.riggins@fda.hhs.gov 301-827-5366
- **General information for OCTGT and related regulatory references**
 - <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>