FDA's Clinical Investigator Course

Preparing an IND Application

CBER Breakout Session

Clinical Considerations for Cell and Gene Therapy Products

Rachel Witten, M.D.
FDA/CBER/OCTGT/DCEPT
November 14, 2013

Cosponsored by

FDA's CDER, Office of Medical Policy
and
The Duke University School of Medicine

U.S. Department of Health and Human Services
Food and Drug Administration

Overview

- What is an IND?
- Who can apply for an IND?
- What should an IND contain?
- How does FDA review an IND?
- What resources are available?

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 (21CFR312) outline requirements for

- Use of Investigational drug
- Submission of application to FDA
- Review by FDA

Are there different types of INDs?

- **21 CFR 312 Subpart I - Expanded Access to Investigational drugs for Treatment Use**
  - § 312.310 Individual patients, including for emergency use
  - § 312.315 Intermediate-size patient populations
  - § 312.320 Treatment IND or treatment protocol

- §**312.305 Requirements for all expanded access uses**
  - Serious or immediately life-threatening with no alternative
  - Favorable risk-benefit
  - Use of the investigational drug will not interfere with investigations to support a marketing application
  - Appropriate IRB approval

Who can apply for an IND?

- **IND applicant is call 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**

  An individual who both initiates and conducts the clinical trial

Obligations of Sponsors and Investigators Conducting Clinical Trials

Sponsor's obligations (21 CFR § 312.50-312.59)

- Select qualified investigators
- Providing Investigators with needed information
- Ensure investigation is promptly monitored
- Report adverse events and new risks
- Maintain adequate records

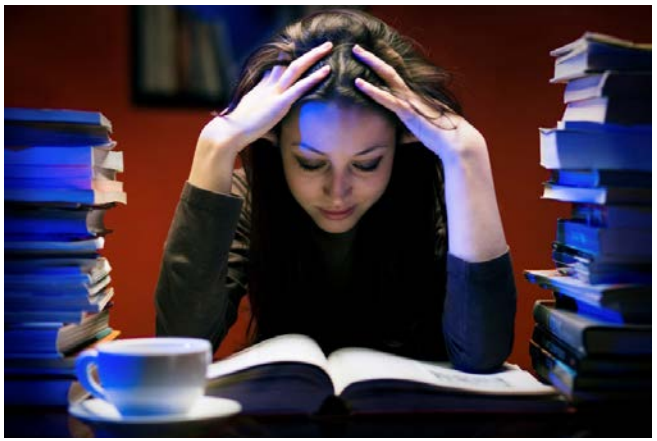
Investigator's obligations (21CFR §312.60-312.69)

- Ensure safety and welfare of subjects under care
- Adherence to the protocol
- Adverse event reporting
- Obtain IRB approval for investigations
- Maintain adequate records

Preparing For Your First IND Submission

Begin at the Beginning

- The time required to prepare an IND will depend on available information on product characterization, pre-clinical data, and available clinical data.
- Study the relevant FDA instructions and forms.
- Determine how your organization can best meet those requirements.



When is an IND required?

An IND application is required for:

- Clinical investigation of a new drug or biologic

- Change to an existing approved drug or biologic, including a new:
  - Indication or significant labeling or advertising change
  - Dosage form and schedule
  - Route of administration
  - Patient population (e.g., pediatric, gender)

When is an IND not required?

Exemption 21 CFR §312. 2 (b)

When ALL the following criteria are met:

- Drug or biologic product is lawfully marketed in the United States
- No intent to support new use or labeling change
- No intent to support change in advertising
- No new factor such as route of administration, dosage, or study population that significantly increases risk
- No promotion or representation of product as safe or effective treatment for condition under study

The IND process: Application

- Form 1571 (21 CFR. §312.23(a)(1))
- Table of Contents (21 CFR. §312.23(a)(2))
- Introductory Statement (21 CFR. §312.23(a)(3))
- General Investigational Plan
- Investigator's Brochure (21 CFR. §312.23(a)(5))
- **Clinical Protocol 21 CFR. §312.23(a)(6))**
- Form 1572 (21 CFR. §312.23(a)(6))
- Chemistry, Manufacturing & Control (21 CFR. § 312.23(a)(7))
- Pharmacology & Toxicology (21 CFR. §312.23(a)(8))
- Previous Human Experience (21 CFR. §312.23(a)(9))
- Additional Information

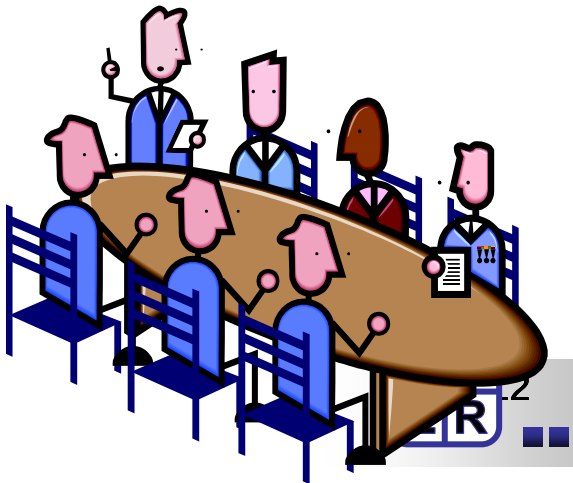
The IND process: Submission

- **Step 1:Pre-IND meeting with FDA**
  - Highly recommended for new product
- **Step 2: Submission of complete IND package**
  - All forms, all sections, 3 copies or electronic
- **Step 3: FDA will notify 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

Pre-IND meeting

- Highly recommended for new products
- May discuss product, pre-clinical, clinical, and regulatory issues
- This meeting is usually scheduled three to nine months before the planned IND submission



Pre-IND meeting: Clinical Issues

- Objectives of the proposed study
- Background, general investigational plan, rationale, previous pre-clinical and clinical experience, selection of dose and route of administration
- Study design
- Protocol outline: Sample size, inclusion and exclusion criteria, concomitant medications, study schedule, safety monitoring, stopping rules
- Outcome measures and brief description of data analysis plan
- Overall clinical development plan; consider Target Product Profile
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf

OCTGT Review Team

- Regulatory project manager
- CMC product reviewer
- Preclinical pharm/tox reviewer
- Clinical reviewer
- Biostatistician

Clinical trial design

- Objectives
- Choosing a Study Population
- Control Group and Blinding
- Dose Selection
- Treatment Plan
- Monitoring and Follow-up
- Safety reporting requirements

Cellular and gene therapy products
Phase 1 Studies

- Focus primarily on assessing the safety, tolerability, and feasibility of a product
- Optimal dose and administration:
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Usually small studies
- Usually enroll patients with the disease being studied
- Safety monitoring plans
- Safety reporting requirements

Phase 2 Studies

- Play a critical role in selection of primary and secondary endpoints, dosing regimen(s) and study population(s)
- Provide information on product bioactivity and durability of response
- Expand safety database
- Primary focus is collection of preliminary data to help determine:
  - Whether the drug or biologic product has effect in a defined patient population
  - The relationship between dose and efficacy
- Are typically well controlled, closely monitored
- Phase 2 studies are important for planning subsequent Phase 3 confirmatory trials

End of phase 2 (EOP2) meeting

- Discuss/justify dose and regimen for Phase 3
- Present and discuss safety data
- Present clinical activity data
- Specify target population
- Specify characteristics of control arm
- Discuss statistical plan
- Discuss initial Pediatric Study Plan
- Consider Special Protocol Assessment
  - Agreement regarding study design
  - Statistical Analysis Plan (important!)

18

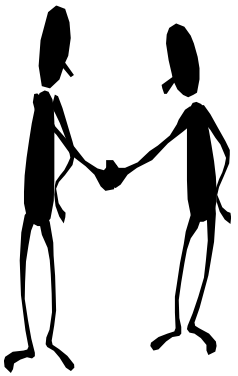
Pediatric Study Plan (PSP)

- The sponsor must submit an initial PSP within 60 calendar days after the day of the EOP2 meeting
- The initial PSP must include an outline of the pediatric study or studies, including:
  - Study objectives
  - Design
  - Age groups
  - Relevant endpoints
  - Statistical approach
- The sponsor may submit a request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation (21 USC 355c(e)(2)(B))

Special Protocol Assessment (SPA)

- Is an agreement between FDA and a sponsor on design and analysis of a Phase 3 trial
- FDA has 45 days to review proposed protocol, statistical analysis plan, case report forms, and questions posed by the sponsor
- Significant protocol amendments must be agreed to in writing
- Guidance for Industry: Special Protocol Assessment

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm080571.pdf



Phase 3 studies

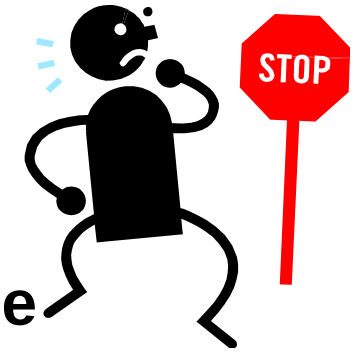
- Designed to provide evidence of effectiveness of drug or biologic product. Must be adequate and well-controlled. Two trials usually required
- Phase 3 studies may also include controlled and uncontrolled trials (e.g., long-term, open-label extensions of controlled trials)
- Performed after obtaining preliminary evidence suggesting efficacy of specific doses of the drug or biologic product
- Intended to gather sufficient information about efficacy and safety needed:
  - To evaluate the overall benefit-risk relationship of the drug or biologic product
  - To provide an adequate basis for labeling

Clinical trial: Safety Monitoring

- For early-phase: Based on pre-clinical study data and also on theoretical concerns
- For later-phase trials: Based on above plus accumulating human safety data
- Monitoring and Follow-up
  - General considerations
    - Safety
    - Bioactivity – may be slow or delayed
  - Special considerations for CGT products
    - Immunogenicity
    - Persistence
    - Migration
    - Shedding
    - Growth and development
- Stopping rules should be considered for all studies under IND

Clinical Hold

(21 CFR §312.42)



A clinical hold is an order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation

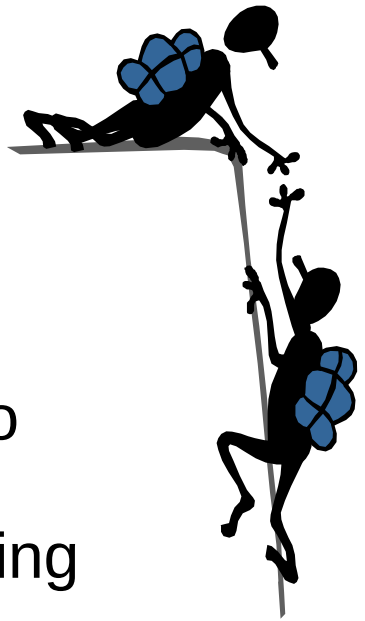
Partial

- A delay or suspension of only part of the clinical work requested under the IND

Complete

- A delay or suspension of all clinical work requested under an IND
- Can occur at any stage of clinical drug or biologics development

Deficiencies leading to Clinical Hold



- Subjects are or would be exposed to unreasonable and significant risk
- Lack of staggering between the subjects
- Unclear or inadequate eligibility criteria
- Insufficient information has been submitted to assess the risk to subjects
- Insufficient data to support the intended starting dose
- Inadequately described product preparation or formulation
- The Investigator Brochure is misleading, erroneous, or incomplete

Deficiencies leading to Clinical Hold
.....continued

Safety monitoring

- Anticipated toxicities inadequately monitored
- Lack of appropriate Toxicity Scale
- Individual Subject Treatment Discontinuation Criteria absent or unreasonable
- Study Stopping Rules absent or unreasonable
- Withdrawn subjects not adequately followed
- Long-term follow-up insufficient or inadequately described

Grounds for Clinical Hold: Phase 2 or 3 studies

A Phase 2-3 study may be placed on clinical hold for the reasons mention before in addition to:

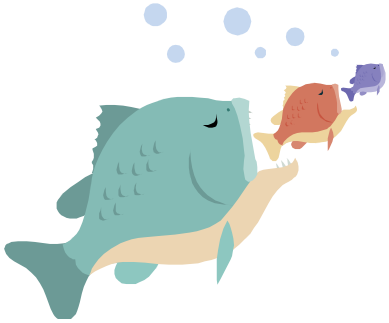
The plan or protocol for the clinical investigation is clearly deficient in design to meet its stated objectives

21 CFR 312.42(b)

Cell and Gene Therapies: Unique Issues

- Product manufacturing and characterization
- Phase 1 studies of cell and gene therapies are almost never carried out in normal volunteers and usually enroll patients with the targeted disease
  - Metabolic fate of product may not follow standard drug pharmacokinetics
  - Distinct product mechanism of action requires appropriate trial design which may differ from that for drugs
  - Dose selection
    - Cellular product may be a mixture of cell types
    - Gene transduction rates can be highly variable
  - Consideration of unique toxicity profiles and monitoring
  - Long-term follow-up

Life cycle of an IND



- IND becomes a “Living Document”
- Updated by sponsor over time to include study data, new protocols, protocol amendments, safety reports, new technical information, new efficacy data, and other relevant information

How do you make changes to an IND?

Send an amendment

- Protocol Amendment (21 CFR §312.30)
- Informational Amendment (21 CFR §312.31)
- Safety report (21 CFR §312.32)
- Annual Report (21 CFR §312.33)
- Response to FDA request for information

How to avoid problems?

- **Don’t ignore Pre-IND Input from FDA!**
- Create reviewer-friendly submission
- Include copy of the protocol, including details of safety monitoring plan
- Background information
- Scientific rationale
- Previous human experience (letter of cross reference to other INDs)
- Rationale for dose selection
- Endpoints (primary and secondary)
- Stopping rules
- Informed Consent and assent forms
- **Be available for any discussion during the first 30 days!**

Resources for Sponsors

- Interact with **FDA:**
  - Early interactions with **FDA** are critical
  - Call us, meet face-to-face; formal or informal dialogue is encouraged
  - Know the **FDA** guidance documents
  - Advisory Committee meetings
  - Workshops
  - Webinars

Quiz

Question 1

In developing a clinical protocol, the following should be considered:

I. Objectives and purposes of the study
II. Inclusion and exclusion criteria
III. Design of the study including the dose, the schedule and route of administration
IV. Plans for evaluation and monitoring of the trial subjects

A. I, II, III
B. I, III
C. III
D. I, IV
E. All of the above

Quiz

Question 2

Which of the following constitutes a reason that FDA may use to put a study on clinical Hold

A. The sponsor did not have a pre-IND meeting with FDA prior to IND submission

B. One of the associate investigators is not a dentist

C. The Investigator Brochure is misleading, erroneous, or incomplete

D. The sponsor complains that the 30-day IND review is too slow

Guidance for industry

- Gene therapy clinical trials-observing subjects for delayed Adverse Events
  http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719.pdf

- Draft guidance: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2013).
  http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm359073.pdf

- Pediatric Study Plans: Content of a and Process for Submitting Initial pediatric Study Plans and Amended Pediatric Study Plans
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf

Contact Information for CBER/OCTGT

- **Speaker:** Rachel Witten M.D.
  rachel.witten@fda.hhs.gov

- **Regulatory Questions:**
  Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov
  or by calling (301) 827-6536

- **OCTGT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Public Access to CBER

- **CBER website**

http://www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 301-827-1800

- **Consumer Affairs Branch (CAB)**

Email: ocod@fda.hhs.gov
Phone: 301-827-3821

- **Manufacturers Assistance and Technical Training Branch (MATTB)**

Email: industry.biologics@fda.gov
Phone: 301-827-4081

- **Follow us on Twitter**

https://www.twitter.com/fdacber

Thank you!