



U.S. Food and Drug Administration

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# FDA's Clinical Investigator Course

## *Preparing an IND Application: CBER Breakout Session*

# Clinical Considerations for Cell and Gene Therapy Products

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**FDA/CBER/OCTGT/DCEPT**  
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U.S. Department of Health and Human Services  
**Food and Drug Administration**



# ■ ■ ■ What is FDA looking for (in an IND)

- IND process
- Clinical protocol and review process
- Informed consent and assent
- Possible clinical hold issues



## ■ ■ ■ 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, disease state)



## When is an IND not required?

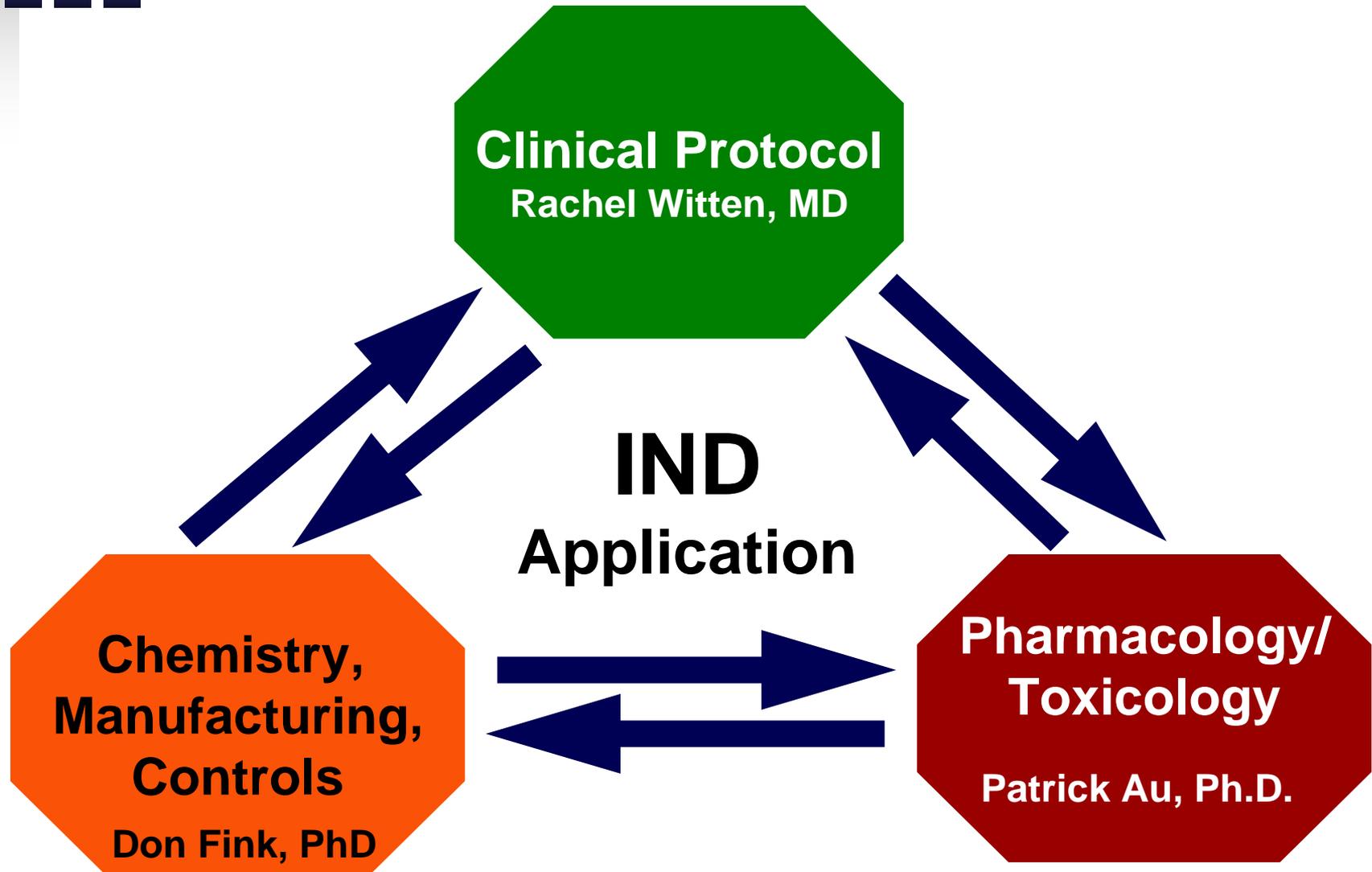
### Exemption 21 CFR§312. 2 (b)

#### When ALL criteria are met:

- Drug 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 at significantly increased risk
- No promotion or representation of product as safe or effective treatment for condition under study

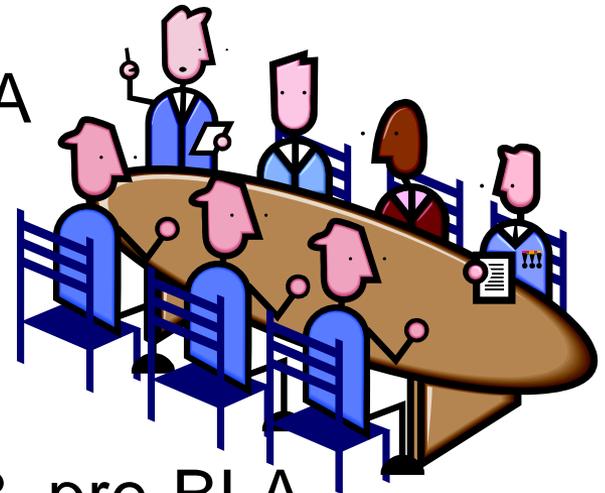
# ■■■ The IND process application Components

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



# Interactions with FDA

- FDA maintains confidentiality of all information throughout the entire process
- Informal interactions
  - Non-binding on sponsor or FDA
- Pre-pre-IND Teleconference
- Pre-IND Meeting
- IND milestone meetings
  - End of Phase 1, Pre-Phase 3, pre-BLA (or NDA)
  - Others as needed



## Pre-IND meeting with FDA

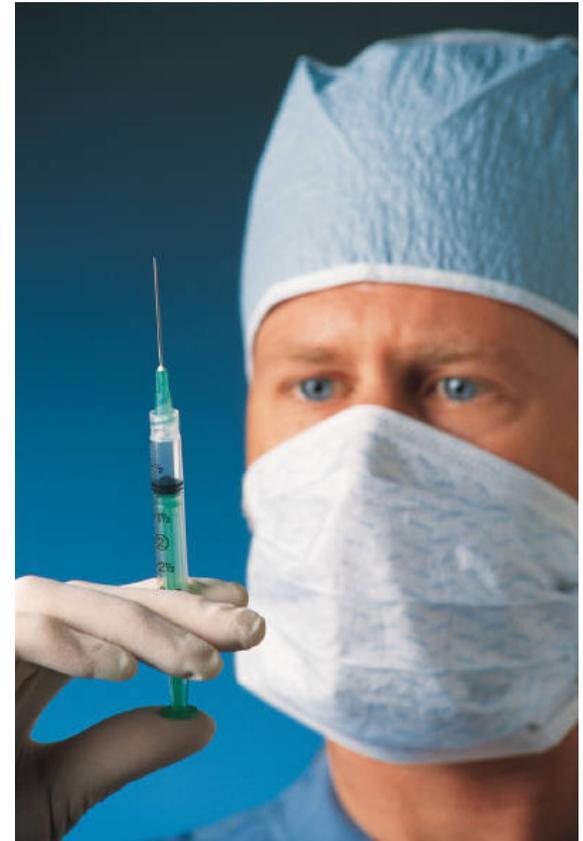
- ✓ Highly recommended for new products
- ✓ Discuss product (CMC), pre-clinical, and clinical issues

### Clinical issues to discuss at pre-IND stage

- 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

# What is a Clinical protocol

- Written plan for how the drug or biologic is to be studied and the procedure to be followed by each investigator
- Specific content of the clinical protocol depends on the phase of the study





## Contents of a Clinical Protocol (21 C.F.R. § 312.23 (a) (6))

- ❑ A statement of the objectives and purpose of the study.
- ❑ The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
- ❑ A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
- ❑ The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.



## Contents of a Clinical Protocol (21 C.F.R. § 312.23 (a) (6)) *continued*

- ❑ A description of the observations and measurements to be made to fulfill the objectives of the study.
- ❑ A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.
- ❑ The name and address and a statement of the qualifications of investigators (Form 1572); the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

# ■ ■ ■ Studies Conducted under IND: Phase 1

- Include the initial introduction of an investigational new drug or biologic into humans.
- Typically, closely monitored and may be conducted in patients or normal volunteer subjects.
- Designed to determine:
  - The metabolism and pharmacologic actions of the drug in humans. (Note: the PK/PD considerations may differ among drugs, cell therapies, and gene therapies.)
  - The side effects associated with increasing doses, and, if possible, to gain early evidence of biologic activity and perhaps efficacy.
- Focus is on obtaining information about the drug's safety profile. Dose-finding, PK/PD information is obtained in order to help design subsequent Phase 2 studies.
- The total number of subjects is generally in the range of 20 to 80.

## ■■■ Studies Conducted under IND: Phase 2

- Include controlled clinical studies conducted to evaluate:
  - Preliminary evidence of efficacy of the drug for a particular indication or indications in patients with the disease or condition under study.
    - The evidence may rely on biomarkers, surrogates, or clinical outcomes
  - The common short-term side effects and risks associated with the drug
- Phase 2 drug studies are typically well controlled, closely monitored, and usually conducted in no more than a few hundred subjects.
  - For cell and gene therapies, the size of Phase 2 studies is often limited by practical concerns, but Phase 2 is important for planning subsequent Phase 3 confirmatory trials.

## ■ ■ ■ Special Protocol Assessment

- Requested by IND sponsor, generally after an end-of-phase 2 meeting.
- Goal is to reach formal agreement on Phase 3 protocol design.
- 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 by FDA and IND sponsor.
- Guidance for Industry



# Studies Conducted under IND: Phase 3

- Expanded controlled and uncontrolled trials (e.g., long-term open-label extensions of controlled trials)
  - Performed after obtaining preliminary evidence suggesting effectiveness of specific doses of the drug
  - Intended to gather sufficient information about efficacy and safety needed:
    - To evaluate the overall benefit-risk relationship of the drug, and
    - To provide an adequate basis for labeling.
  - Phase 3 studies usually enroll from several hundred to several thousand subjects

# Clinical Trial Safety Monitoring

- Take into account product characteristics (e.g., cell persistence, vector biodistribution and potential for insertional mutagenesis; transgene's potential for promotion of cancer) when determining duration of long-term monitoring
- Base on pre-clinical study data and also on theoretical concerns
- Present as a table of scheduled assessments
- Types of assessments and time points for data collection should be sufficient to capture expected and unexpected adverse events.
- Stopping rules should be considered for all studies under IND, and may be required for higher risk studies.



## Common Deficiencies Leading to Clinical Hold

- Unreasonable and significant risk, with need to change the eligibility criteria, safety monitoring plan, or stopping rules
- Insufficient information to assess the risk to subjects
- Insufficient data to support the intended starting dose
- Inadequately described product preparation or formulation



## Common Deficiencies Leading to Clinical Hold *cont.*

Dose regimen:

- Mode of administration of product risky or inadequately described
- Proposed dose increases too aggressive
- Failure to stagger enrollment of new product with unknown risks
- Dose modification plan unclear
- Repeat treatment plan unclear or not supported



## Common Deficiencies Leading to Clinical Hold *cont.*

### Safety monitoring:

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

# Unique Issues Pertaining to Cell and Gene Therapies

- Product manufacturing and characterization, especially autologous products
- Unique aspects of early-phase studies
  - Metabolic fate of product may not follow standard drug pharmacokinetics. Pharmacodynamic properties may also differ from those of drugs.
  - Distinct product mechanism of action requires appropriate trial design, which may differ from that for drugs.
    - Defining optimal biologic dose (OBD) rather than maximum tolerated dose (MTD)
    - Consideration of unique toxicity profiles and monitoring
    - Long-term follow-up issues

# Components of Informed Consent

## 21 C.F.R .Part 50

- ❑ Ensure voluntary participation
- ❑ For research participants 18 years of age or older, informed consent must include the following information:
  - Why research is being done
  - What researcher wants to accomplish
  - What will be done and for how long
  - Risks and benefits of the trial
  - Other available treatments
  - Notification that participant can withdraw from the trial at will
  - Whether there is compensation for unexpected injuries

# ■■■ Informed Assent

U.S government policy states that children 7 years of age and older must assent (agree) to participate in clinical trial

- Child's active agreement to participate
- Age of assent determined by IRB or local requirements
- Ability to assent determined by Investigator





## Subpart D requirements for studies in children.

### **45 CFR §46.404, 21CFR50.51: Minimal risk**

Risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests

**45 CFR §46.405, 21CFR50.52: Greater than minimal risk** and prospect of direct benefit

**45 CFR §46.406, 21CFR50.53: Minor increment over minimal risk** and **no** prospect of direct benefit

Experiences to subjects commensurate with actual or expected medical situations, and likely to yield generalizable knowledge of vital importance about subject's disorder

Assent of child and permission of parents required

**45 CFR §46.407, 21CFR50.54: Significant risk** and special opportunity



## Obligations of Sponsors and Investigators Conducting Clinical Trials

- Sponsor's obligations (21 C.F.R. § 312.50)
  - Management of **IND**
  - Safety reports
  - Transportation/shipment of drug
  - Collection of unused drug
  - Records: maintenance and retention
- Investigator's obligations (21 C.F.R. § 312.60)
  - Assure IRB review and informed consent
  - Adherence to protocol
  - Adverse event reporting
  - Trial supervision
  - Records: maintenance and retention



# How do you make changes to an IND?

## Send an amendment

- Protocol Amendment (21 CFR 312.30)
- Informational Amendment (21 CF 312.31)
- Safety report (21 CFR 312.32)
- Annual Report (21 CFR 312.33)
- An amendment can be made at any time during the life of an IND



## How to avoid a problem ?

- Follow regulations
- Follow GCP
- Interact with **FDA**:
  - Early interactions with **FDA** are critical
  - Know the **FDA** guidance documents
  - Call us, meet face to face; formal or informal dialogue is encouraged



## 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

# 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, schedule and the 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





# True or False

- Question 2. Safety evaluation remains top priority in all phases of clinical studies.



## Contact Information

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**Regulatory Questions: Contact the  
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**[Patrick.Riggins@fda.hhs.gov](mailto:Patrick.Riggins@fda.hhs.gov)**

**or by calling (301) 827-6536**





*Thank you*

