IND Basics

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Highlight

- What is an IND?
- When is an IND required?
- Who should apply for IND?
- What should an IND application contain?
- What are the different types of IND?
- How do I navigate the FDA offices for guidance?

Terminologies

- Investigational New Drug (IND): new drug or biologic used in a clinical investigation
- IND application: request to FDA to authorize administration of a new drug or biologic to humans (i.e. a "Notice of Claimed Investigational Exemption for a New Drug")
- Investigator: individual under whose direction a drug is administered
- Sponsor : an individual, company, institution, or any organization that takes responsibility for and initiates a clinical investigation
- Sponsor-Investigator: strictly an individual who both initiates and conducts an investigation.

What is an IND?

- The IND is a request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not an approved drug or biologic
- IND regulations 21 CFR 312
  - procedures and requirements for IND application
  - defines the roles and responsibilities of FDA reviewers, IND sponsors, and investigators

21 CFR 312 ~ FDA objectives

- To assure the safety and rights of subjects in all phases of the investigation
- In Phase 2 and 3 to help assure the scientific quality for evaluation of drug's safety and effectiveness

When is an IND Required?

Motivating questions: True/False

1. A chemist discovered that a novel derivative of catechins has potent protease inhibition in vitro and minimal toxicity in human cell lines and in animal studies……[True or False]

2. A scientist formulated an inhalational form of aspirin and wants to see if this would have more profound effect on migraine……..[True or False]

3. Two years later this same scientist wants to see if inhalational aspirin can stop inflammation in the brain……..[True or False]

4. A physician working with a manufacturer of an antibiotic approved 7 years ago by the FDA plans to show that this medication will have broader spectrum coverage if administered at twice the recommended dosage……[True or False]

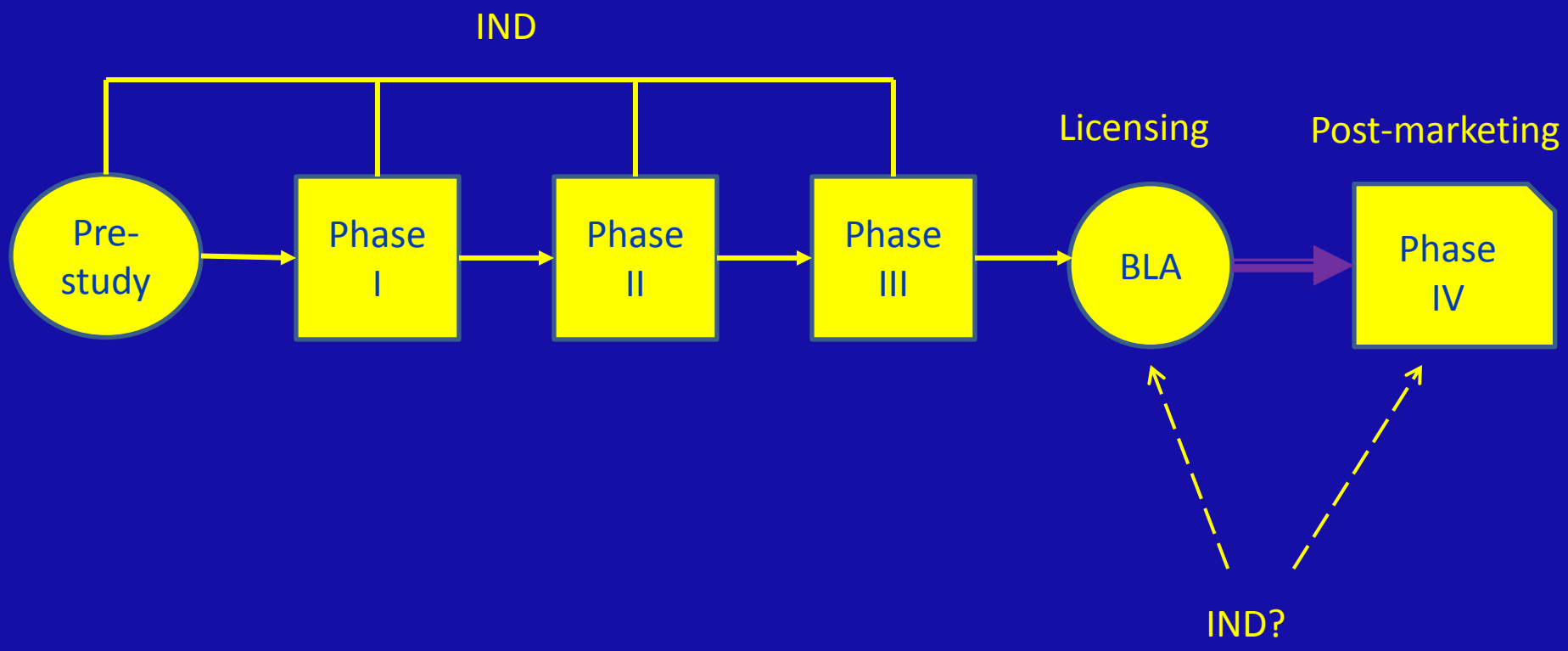
Motivating questions: True/False

5. A midwife found success in use of orange oil, aromatherapy oil in her labor patients, and plans to establish its efficacy in a large study of women during delivery……[True or False]

6. A neuroscientist has developed a new reagent for detecting Alzheimer's disease pathology in blood cells ……[True or False]

7. Forms of sugar are used as placebo in clinical studies, but not available in skin patches: a scientist developed a skin patch of sucrose to be used as placebo in efficacy studies of drugs delivered transdermally [True or False]

General Flow of Events



IND is Needed for .....

- Novel biologics, compounds, medicines
- Change in the approved route of administration of an existing drug
- Change in the approved dosage level of an existing drug
- Change in the approved patient population of an existing drug
- Substantial change in the promotion of an approved drug

IND Exempt

- Natural compounds “generally regarded as safe” (GRAS)
  - Aromatherapy oils
  - Active ingredients of dietary agents

Other IND Exempt Criteria

- The study is not designed to support approval of a new indication or a change in label
- Study is not intended to support a significant change in the advertising for the product
- Study does not involve a route of administration, dosage level or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug
- The study is conducted in compliance with the IRB and informed consent regulations
- The study is conducted in compliance with regulations regarding promotion and charging for investigational drug
- Study does not intend to invoke 21 CFR 50.24 (Exception from Informed Consent requirements for emergency research)

Again, IND is not needed for ……

- Drugs legally marketed for indicated use
- Study not intended to support new indication or significant labeling change
- Study not intended to support significant change in advertising
- Study doesn't involve change in route of admin, dosage, or use that significantly increases patient risks
- IVD biological for confirmatory diagnostic procedure
- Intended for tests of in vitro or lab research animals
- Placebo products

Who should apply for IND?

- A sponsor (e.g. drug or biological company)
- A sponsor-investigator
- Any entity that wants to conduct clinical research with an investigational product (e.g. Private Foundations, Government agencies)

IND Application: Content

- Cover Sheet (and Form FDA 1571)*
- Table of Contents
- Introductory Statement and General Investigational Plan
- Investigator Investigator's Brochure (or Plan)
- Clinical Protocol
- Chemistry, Manufacturing and Control (CMC) Information
- Pharmacology and Toxicology Information
- Previous Human Experience
- Additional Information

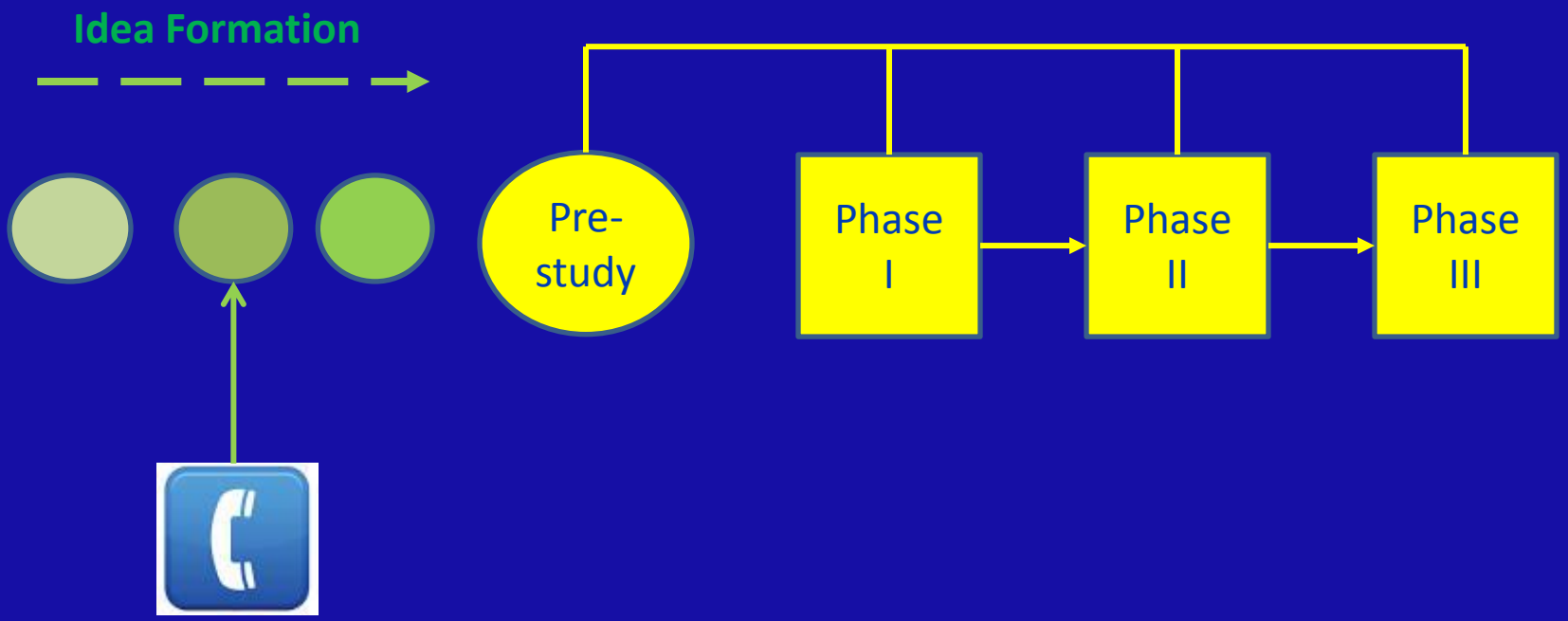
* http://www.fda.gov/opacom/morechoices/fdaforms/1571es.pdf

If you are a Sponsor-Investigator

- Obtain a signed 1572* from each investigator (§ 312.53(c)) and
- Submission of the name and qualifications of each investigator to the IND is required (§ 312.23(a)(iii)(b)
- However, submission of Form 1572 is not required
- But for ease of submission, many Sponsors choose to submit the 1572

* http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

When to initiate IND?

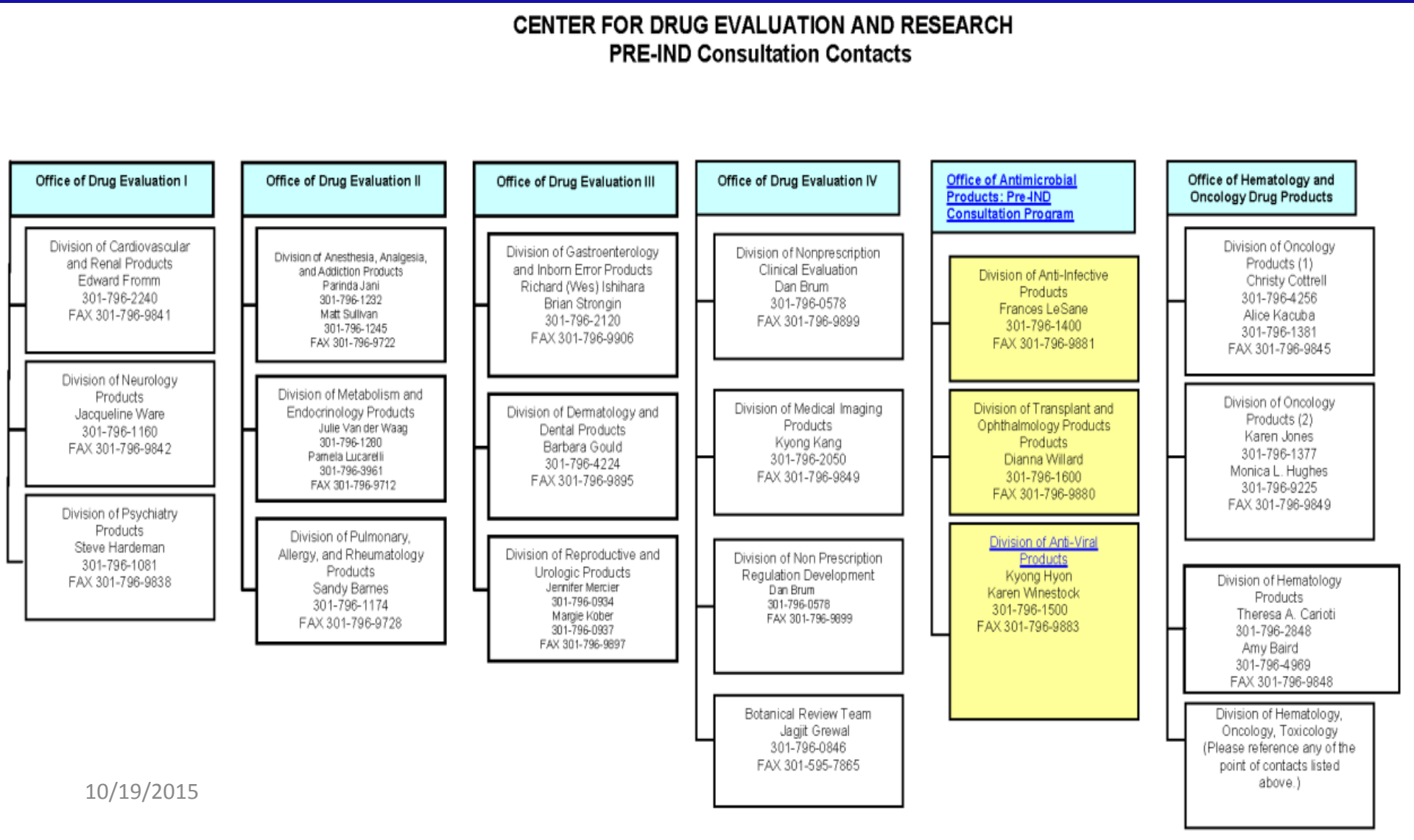


Seek Pre-IND Meeting*

- Questions concerning clinical monitoring for an anticipated end organ toxicity
- Discuss the adequacy of preclinical toxicology studies
- PK issues, e.g. related to dosing schedules, known/unidentified metabolites
- If novel dose-escalation scheme is proposed
- Problems with drug substance, drug product, or formulation intended for human use

* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/UCM166356.pdf

FDA Pre-IND Contact



Types of IND

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND
  - It is also used for patients who do not meet the criteria of an existing study protocol
  - if an approved study protocol does not exist
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place

IND Categories

- Research
  - Primarily research-driven, not marketing approval
  - IND can be a single volume If preclinical and manufacturing information can be cross-referenced to a prior IND
  - *e.g. IND submission by HU Physician*
- Commercial
  - Ultimate goal is to obtain marketing approval
  - *e.g. Submission by a Pharmaceutical Company*

IND Application Tenets: Product Labeling Requirements

- Immediate package must be labeled:
  - "Caution: New Drug – Limited by Federal (or United States) law to investigational use"
- No false or misleading statements
- No representation that drug is safe or effective for indicated use

IND Application Tenets: Promotion & Charging for Investigational Drugs

- No representation that drug is safe or effective for indicated use
- No commercial distribution or test marketing
- No prolongation of study
- Prior written approval from FDA required to "charge" for drug, unless being used under "treatment" IND

IND Application Tenets: Clinical Study Phases

- Phase 1 – first time in human
  - Small number of healthy volunteers
  - Closely monitored – focus on safety, with very stringent stoppage rules
- Phase 2 – controlled studies to evaluate effectiveness
  - Small number of subjects with condition to be treated
  - Closely monitored – focus on efficacy & safety (stringent stoppage rules)
- Phase 3 – expanded controlled & uncontrolled studies
  - Large number of subjects with condition to be treated
  - Focus on efficacy (& safety) (stoppage rules still needed)

IND Filing Process & Determination

- The FDA IND Review Process Includes: Safety, Medical/clinical Chemistry, Pharmacology/ Toxicology and Statistical
- FDA is required by regulation to respond within 30 days of the filing of an initial IND
- IND is considered to be in effect if no issues are identified
- FDA can place the study on clinical hold if issues cannot be resolved within this 30 day period
- Partial Hold – A delay or suspension of part of the clinical work under an IND
  - e.g. IND with 2 protocols where 1 can proceed and 1 is on clinical hold

Reasons for Clinical Hold

- Phase I clinical holds
  - Subject safety concerns
- Phase II & III clinical holds
  - Concerns about safety or efficacy
- Treatment IND clinical holds
  - Alternative treatment drug now commercially available
  - Sponsor not diligently pursuing marketing approval
  - Administrative oversights by Sponsor

Other Reasons for Clinical Hold

- Subjects would be exposed to an unreasonable and significant risk
- Insufficient information to assess risk to subjects
- Clinical investigators are not qualified
- The plan or protocol is clearly deficient in design to meet its stated objectives
- Investigator's Brochure is misleading, erroneous, or materially incomplete
- More reasons can be found in 21 CFR 312.42

Responsibilities of Sponsors (21 CFR 312.50-59)

- Select qualified investigators
- Providing Investigators with needed information
- Ensure study conducted in accordance with Investigational Plan
- Ensure investigation is properly monitored
- Promptly report adverse events and new risks to FDA and all investigators
- Maintain adequate records
- Updates over time to include protocol amendments, study data, safety reports, manufacturing changes, preclinical reports, annual reports

Responsibilities of Investigators (21 CFR 312.60-68)

- Perform investigation consistent with protocols
- Ensure safety and welfare of subjects under care
- Obtain IRB approval for investigations
- Promptly report any adverse events to Sponsor
- Maintain adequate records

IND Amendments

- INDs are updated via amendments:
  - Protocol amendments (21 CFR 312.30)
  - Information amendments (21 CFR 312.31)
  - Safety reports (21 CFR 312.32)
  - Annual reports (21 CFR 312.33)
  - Response to FDA request for information

Protocol Amendments

- A new protocol
- Modifications to an existing protocol
  - Protocol amendments must be submitted to FDA prior to implementation
  - IRB approval is required prior to implementation
- New investigator or updated 1572 form

Other Amendments

- Clinical data (not protocol related)
- Pharmacology or toxicology data
- Chemistry Manufacturing and Control (CMC) information
- Notice of discontinuance of a clinical study

Annual Reports

- Must be submitted within 60 days of the anniversary date that the IND went into effect.
  - Information that should be provided includes:
  - Brief summary of each study in progress under the IND
  - Summary of information obtained during previous year (most frequent AE's by body system, IND safety reports, deaths, dropouts, list of preclinical studies, CMC or microbiological changes)
  - Updated general investigational plan for coming year

IRB Responsibilities 21 CFR 50, 56

- Sec. 56.108 IRB functions and operations
- Sec. 56.109 IRB review of research
- Sec. 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
- Sec. 56.111 Criteria for IRB approval of research
- Sec. 56.112 Review by institution
- Sec. 56.113 Suspension or termination of IRB approval of research

IRB must realize that the FDA is staffed by humans and can make mistakes

Motivating questions: True/False

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Revisiting Motivating Questions: True/False

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Summary: what we learnt

- A basic understanding of the form and content of an IND submission
- An introduction to the regulatory basis of the requirements of an IND
- Information on the required forms: 1571, 1572
- The basics of different types of INDs including single patient and emergency submissions
- Responsibilities of sponsors, investigators and IRB in the IND process

Further Resources

FDA/CBER

Attn: Office of Cellular, Tissue, and Gene Therapies
Document Control Center/HFM-99/Suite 200N
1401 Rockville Pike
Rockville, MD 20852

Fax: 301-827-9796

Phone: 301-827-5102

Email: CBEROCTGTRMS@fda.hhs.gov

Further Resources

- Information about the general processes of OCTGT:

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm.

- Website regarding CBER IND/IDE process:

  http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm