Demystifying the IND

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Disclosure slide

- Kerry Jo Lee, MD: Nothing to disclose
- Kevin Bugin, MS: Nothing to disclose
- The views expressed in this presentation are our own and not necessarily those of the FDA

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Talk Overview

- Why do you need an IND?
  - When to submit one
  - Exemptions
- Types of INDs
- IND Processes (pre IND, submission, and post IND)

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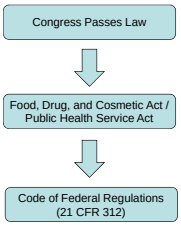
Why do you need an IND?



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When to Submit an Investigational New Drug (IND) Application?

- 21 CFR 312 contains the regulatory requirements for INDs for both drugs and biologics
- Any human research study must be conducted under an IND application if:
  - The research involves **a drug** as defined in section 201(g) of the FD&C Act (21U.S.C. 321 (g)(1))
  - The research is **a clinical investigation** as defined in the IND regulations (21CFR 312.3)
  - The clinical research is **not exempt** from the IND requirements

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Does Your Research Involve a Drug under Clinical Investigation?

- DRUG generally includes (201(g)(1) of FD&C Act)
  - An article intended for use in the **diagnosis, cure, mitigation, treatment, or prevention of disease**… AND
  - An article (other than food) intended to **affect the structure or any function** of the body…"
    - However, if an edible product that might otherwise be a conventional food is intended for a use other than providing taste, aroma, or nutritive value, such as blocking the absorption of carbohydrates in the gut, **the product becomes a drug because the primary purpose of consuming it has changed**
- CLINICAL INVESTIGATION (21 CFR 312.3(b)):
  - An experiment in which a drug is administered, or dispensed to, or used involving, **one or more human subjects**, …except for the use of a marketed drug in the course of clinical practice

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When Do Exemptions From the IND Requirements Apply to Your Research?

Your protocol would be exempt from IND requirements if your study:

- Involves a drug product that is lawfully marketed in the US

AND

- Conditions for exemption described under 21 CFR 312.2 (b) are met

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Your Research Involves a Drug Product Lawfully Marketed in the US

Criteria for exemption from the IND regulations (21 CFR 312.2(b)) :

- There is **no intent** to report the investigation to FDA as **a well-controlled study in support of a new indication** and no intent to use it to support any other significant change in the **labeling** of the product
- Your investigation is **not intended** to support a significant change in the **advertising** of the product
- The investigation does **not involve a route of administration, dose, patient population, or other factor that significantly increases the risk** (or decreases the acceptability of the risk) associated with use of the drug product
- The investigation is conducted in compliance with the requirements for review by an **IRB** (21 CFR 56) and **Informed Consent** (21 CFR 50)
- The investigation is **not intended to promote or commercialize** the drug product (21 CFR 312.7)

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How Do You Decide About the Risk Criterion?

- Are there changes in route of administration that trigger safety concerns?
  - Safety concerns regarding sterility, pyrogenicity, hypersensitivity, variation in metabolism
  - Safety concerns regarding similar bioavailability between administration routes
- Are there changes in dose, frequency, duration of administration compared to the approved dosing regimen?
  - Ex. Pediatric vs adults
- How is the intended patient population different from the patients for whom the product has been approved ?
  - Disease-specific background risks differ across populations
  - Risk acceptability may be different for treatment of life-threatening conditions vs. disease prevention or symptomatic relief

*Refer to **Guidance for Clinical Investigators, Sponsors and IRBs : Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND** for examples*

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Dietary Supplements (DS)

- Under the Dietary Supplement Health and Education Act (1994), a dietary supplement is not a drug
  - DS may include: vitamins, minerals, herbs, amino acids, concentrates, metabolites, and combinations of ingredients
  - DS may come in tablets, capsules, softgels, liquids, powders, etc
- However, if the clinical investigation is intended to evaluate the DS's effect on structure or function of the body in it's ability **to diagnose, cure, mitigate, or prevent a disease**, an IND application is required

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Pre-IND consultation

- A consultation provided to sponsors and investigators planning to submit an IND application
  - Pre-IND package may include:
    - » IND product characteristics
    - » manufacturing processes
    - » development plan
    - » design of the planned investigation in humans, AND
    - » specific questions to the Agency about any or all of the above

FDA's Guidance for Industry: Formal Meetings Between FDA and Sponsors or Applicants, May 2009

FDA's Guidance for Industry: IND meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Control, May 2001

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Examples of Types of IND Applications

- Commercial IND application
- Sponsor Investigator (research) IND application
  - Investigational product for a clinical trial conducted by investigator, for example, for a new disease
  - Approved product investigated for a new disease
- Expanded Access IND application
  - Use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options
  - Intended to improve access to investigational drugs for patients who may benefit from investigational therapies

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Expanded Access IND Applications

- A range of IND mechanisms for expanded access applications are intended to provide access to investigational drugs **outside of traditional clinical investigations**
  - INDs for treating individual patients, including emergency use (21 CFR 312. 310)
  - INDs supporting administration of the drug to more than one patient but not widespread use (Intermediate size patient population IND) (21 CFR 312.315)
  - Widespread use under a treatment IND (21 CFR 312.320)

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Patient Access to Investigational New Drugs

- Expanded Access (21 CFR 312 Subpart I)
  - "when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition…to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition"
- Examples
  - Omegaven
  - Zelnorm®
  - Domperidone

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm407311.htm

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Emergency IND Applications: Procedures 21 CFR 312.310/21 CFR 56.102

- These are intended for emergency situations "defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval"
- FDA may authorize shipment of the drug for a specified use in advance of submission of an IND
- A request for such authorization may be transmitted to FDA by telephone or other rapid communication means
- Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization

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The Treatment IND for Larger Populations

- Expanded access IND for special *populations* as opposed to the individual
- Regulatory mechanism to facilitate the availability of promising new drugs as early in the drug development process as possible and before general marketing begins
- Intended to fill gaps that may occur in between a trial and drug approval while company is pursuing drug approval with due diligence
- Must not interfere with enrollment in pivotal trials for drug approval

21CFR312.35 Submission of IND for treatment use

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Sponsor/Investigator's Responsibilities, CFR 312.50-70 Investigator's IND Application

- Assurance that an investigation is conducted according to the signed investigator's statement (Form 1572), the investigational plan, and the applicable regulations
- Protection of the rights, safety, and welfare of subjects under the investigator's care (includes obtaining of the Informed Consent and interaction with IRB)
- Responsibilities for the control of drugs under investigation

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Additional References

- 21 CFR 312
- Guidance Document: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well-Characterized, Therapeutic, Biotechnology-derived Products, Nov 1995
- Guidance Document: Investigational New Drug Applications (INDs) Determining Whether Human Research Studies Can Be Conducted Without an IND 2013
- Information for Investigators http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

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www.fda.gov

So, you submitted an IND.

Now what?

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Quick Overview of CDER

- Structures
  - Organizational
  - Review Team
  - Regulatory

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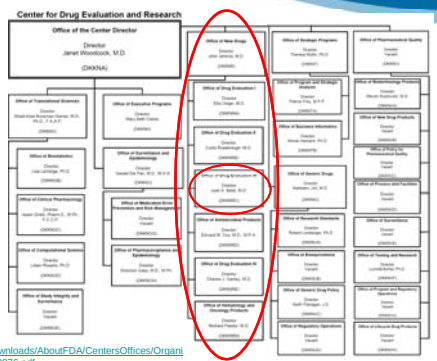
Organizational Structure



http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM439876.pdf

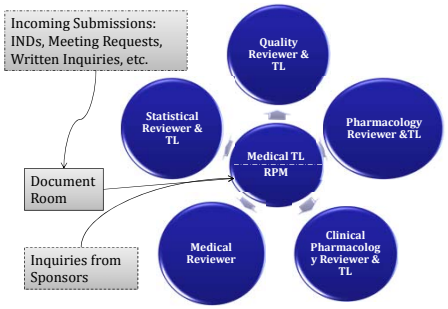
Structures: OND Divisions

Signatory	• Division Director • Deputy Director • Deputy Director for Safety
Medical Teams	• Medical Team Leader • Medical Reviewer
Nonclinical Teams	• Nonclinical Team Leader • Nonclinical Reviewer
Project Mgmt	• Chief, Project Management Staff • Regulatory Project Managers

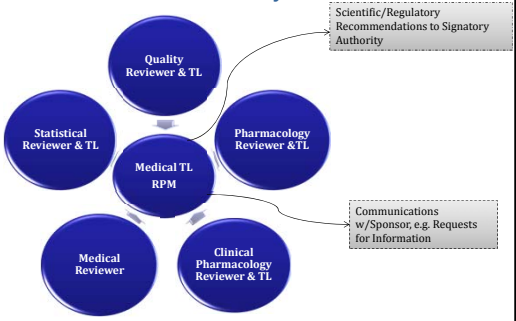
Structures: Review Teams

- Regulatory Project Manager (RPM)
- Medical Team Leader (TL)
  "Cross Discipline Team Leader"
  - Medical Reviewer
  - Nonclinical Reviewer
  - Clinical Pharmacology Reviewer
    Pharmacometrics, Pharmacogenomics
  - Biostatistics Reviewer
- Quality Reviewer
  Drug Substance, Drug Product, Micro, Immunogenicity, Others

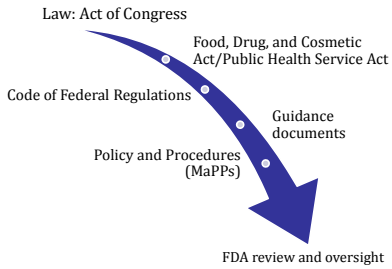
Structures: Team Dynamics



Structures: Team Dynamics



Structure: Regulatory



Process: What to expect

- **Pre-IND Submission Activities**
- IND Submission and Review
- Post-Submission Activities and Responsibilities

Process: Pre-IND Submission Activities

- Pre-IND Meeting
  - Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants
    - Search: "Formal Meetings" @ www.FDA.gov
- Tracked Timeframe: Type B
  - Meeting date: ~60 days from date of request
  - Formal meeting request required
  - Background package: due to FDA 4 weeks prior to meeting date
- Pre-IND file created

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Process: Pre-IND Submission Activities

- Other Formal Meetings to Plan For:
  - Certain End-of-Phase 1 Meetings (Type B)
  - End-of-Phase 2 Meetings (Type B)
  - Pre-NDA/Pre-BLA Meetings (Type B)
  - Others (Type C)
- Other Correspondence

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Process: IND Submission/Review

- IND Content and Format (21 CFR 312.23)
  - Notify FDA
  - Submit one original and two copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

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Process: IND Submission/Review

- 30-day safety review "clock"
  - Acknowledgment Letter generally issued within 7 days
  - RPM will communicate the "30- day safety review date"
- Reviewers are assigned upon receipt
  - Document Room processing time
- Internal Safety Review and Internal Meetings
- Studies cannot be begin until 30 days after the date of the IND submission, unless notified sooner by the FDA. If your study is placed on clinical hold, you may not begin studies.

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Process: IND Submission/Review

- Frequency and timing of communications between sponsor and FDA can vary
- Clinical Holds
  - Defined by 21 CFR 312.42
  - Teleconferences: ***be available*** *to discuss potential hold issues*
  - "Complete Response to Clinical Hold"

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Process: IND Submission/Review

- Clinical Holds
  - What are grounds for a clinical hold?

1. Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
2. Clinical investigators are not qualified
3. Investigator Brochure is misleading
4. IND does not contain sufficient information to assess risks to subjects
5. The IND is for a study of a drug intended to treat a disease or condition that affects both genders but one gender is being excluded.

For Phase 2/3 studies:

6. The plan or protocol is clearly deficient in design

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Process: IND Submission/Review

- Clinical Holds, criteria continued:

  Expanded Access INDs

  8. Criteria for expanded access do not satisfy the requirements for expanded access or for an ongoing protocol if the criteria are no longer satisfied

  9. Any investigation can be placed on hold if that study is not designed to be adequate and well-controlled.

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Process: Post-Submission and Responsibilities

Sponsors of IND applications are responsible for sending periodic updates and reports related to their applications to FDA. All submissions with IND application amendments or reports should include Form 1571 (PDF) sent along with the respective amendment or report.

Safety Reporting	Annual Reports	IND Withdrawal	Other Responsibilities
• 21 CFR 312.32	• 21 CFR 312.33	• 21 CFR 312.38	• 21 CFR 312.50 through 312.70

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IND Applications: Process and Procedures

For More Information, see FDA website, Investigator-Initiated Investigational New Drug (IND) Applications

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients

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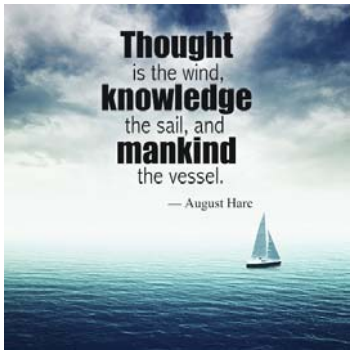

Thank you!

Questions?

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