History of IND Regulations

- 1906: Pure Food & Drugs Act – regulated adulterated/misbranded food & drugs
- 1938: Food, Drugs, & Cosmetics Acts – required premarket review for safety
- 1962: FDCA Amendments – the birth of IND regulations, required premarket review for efficacy
  - substantial evidence of effectiveness for the product's intended use.
  - evidence had to consist of adequate and well-controlled studies
  - establish rules for investigations of new drugs, including a requirement for informed consent
21 CFR 312
- Subpart A – general provisions
- Subpart B – IND Application
- Subpart C – Administrative Actions
- Subpart D – Responsibilities of Sponsors and Investigators
- Subpart E – Drugs Intended to Treat Life-threatening and Severely-Debilitating Illnesses
- Subpart I – Expanded Access to Investigational Drugs for Treatment Use
IND Regulations

- Apply to all clinical investigations of products that are subject to 505 of the FDCA except as provided in 21 CFR 312.2
  - No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application is effective with respect to such drug.

- Apply to drugs and biological products
When is an IND required?

- All research that does not meet the exceptions outlined in 21 CFR 312.2

- Research using drug(s) that are not FDA approved
- Research using FDA approved drug(s) being used outside the FDA approved labeling – exceptions
- Research using an FDA approved drug where the research is intended to be submitted to the FDA to revise labeling, new indication, new study population, etc.
When is an IND not required?

- 21 CFR 312.2:
  - Lawfully marketed drug
    - Not intended to be used to support a new indication or significant change in labeling
    - Not intended to support a significant change in advertising
    - The route of administration, dosage level, use in a patient population or other factor do not significantly increase risks (or decrease the acceptability of the risks) associated with its use
    - Conducted in compliance with 21 CFR 56 (IRBs) and 21 CFR 50 (Informed Consent)
    - Conducted in compliance with 21 CFR 312.7 (Promotion)
Other exemptions

- A clinical investigation involving an in vitro diagnostic biological product (blood grouping serum, reagent red blood cells, and anti-human globulin) when they are intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and it is shipped in compliance with 312.160.

- A drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 312.160.

- Clinical investigation involving a placebo if the investigation does not otherwise require an IND
Submitting an IND to the FDA

- 21 CFR 312 Subpart B: Investigational New Drug Application
  - Provides the requirements for a submission of an IND to the FDA
  - Provides the regulatory authority for IND research
Where will your IND Submission go?
Documents to include in an IND Submission

- 21 CFR 312.23 – content of an IND submission

- 1571
  - Cover Sheet for the submission – required – provides a summary of the submission, helps with routing the submission when it is processed by the review division

- Table of Contents
Introductory Statement
- brief summary of the product
- research objectives
- proposed duration of research

General Investigational Plan
- overview of the research plan
- summary of the previous human use with the product
Investigator’s Brochure – required under 21 CFR 312.55
- Chemistry of the product
- Pharmacology data
- Toxicology data
- Summary of any human experience with the product
- Possible risks and side effects
- 21 CFR 312.55 requires sponsors provide an IB to each investigator
Protocol(s)
- 21 CFR 312.23 (a)(6) provides guidance on protocol content
  - Phase I
  - Phase II & III

Chemistry, Manufacturing, & Control (CMC) data
- Product composition, manufacturing, stability, control data

Pharmacology data
- Product mechanism of action, absorption, distribution, metabolism, excretion data
IND Submission Documents cont.

- Toxicology data
  - Data from completed animal studies, reproductive studies, data specific to mode of administration, NOEL (no observable effect level)

- Previous human experience data

- Additional Information
  - Drug dependence & abuse potential, radioactive drug information, pediatric studies

- Relevant information – any information requested by the FDA to aid in the review
IND submission can reference data the FDA already has on file

- Often used for investigator-initiated studies of pharmaceutical products.

- Cross reference letter from product sponsor (pharmaceutical company).

- Letter is submitted to the FDA by the owner of the IND that is being cross referenced. The letter authorizes the FDA to reference the data during the review of the new IND submission.
Submitting the IND

- Submit an original application and 2 copies (paper submissions)
  - May be called later and asked to submit additional review copies

- Mail submission to:
  Food & Drug Administration
  Center for Drug Evaluation and Research
  Central Document Room
  5901-B Ammendale Road
  Beltsville, MD  20705

- Electronic submission – eCTD – specific requirements
FDA review of the IND

- The IND is assigned an IND number when it is received by the Document Room at the FDA

- FDA has 30 days to review the IND and make a determination
  - The clock starts when the submission is received in the door – not when the review division receives it
The regulations allow for an investigation to begin 30 days after the FDA receives an IND Application.

Shipping Investigational product – 21 CFR 312.40
- 30 days after FDA receives IND
- Earlier if FDA authorizes – CDER Acknowledgement letters

Investigator will receive a letter acknowledging the receipt of the IND submission and providing the 30 day safety date.
FDA review of the IND

- 30 day safety review
  - The IND will be assigned to a review team

- The team will consist of members representing each of the scientific review divisions: Chemistry, Clinical Pharmacology, Pharmacology/Toxicology, Microbiology, Clinical

- Team can contain additional specialist as needed

- Each member will perform a review of the content of the submission related to his/her specialty
FDA review of the IND

- Animal Pharmacology and Toxicology Studies – Does the preclinical data suggest the product is reasonably safe for initial testing in humans? Is there data on its use in humans (foreign use)?

- Manufacturing Information - Can the company adequately produce and supply consistent batches of the drug for the trial(s)?

- Clinical Protocols - Will the initial-phase trials expose subjects to unnecessary risks?

- Investigator Information – Are the proposed investigator’s qualified to fulfill their clinical trial duties? Are they committed to obtaining informed consent, IRB approval, and to adherence to the IND regulations?
FDA Review - 30 day safety meeting

- All members of the review team present their analysis of the submission

- Each member provides an opinion on whether the IND is
  - Safe-to-proceed
  - Partial Hold
  - Full Hold

- Division leadership (Director, Associate Director) as final authority

- After the meeting the PI will be contacted with the outcome
Typically the 30 day safety review will result in recommendations for changes to the study
- FDA has 30 days to finalize the safe-to-proceed letter

Technically study can begin once the 30 day waiting period has passed but many times the recommendations will impact the conduct of the trial – recommend waiting to receive the comments
Clinical Hold regulations – 21 CFR 312.42
- Partial hold/Full hold
- Hold decisions are telephoned to the sponsor prior to the 30 day safety date

Hold letter will provide reason for hold and additional comments/recommendations from the review

Sponsor – submit full response to FDA addressing all hold issues – Complete Response

FDA review of Complete Response – 30 day review
IND Management

- Sponsor responsibilities – 21 CFR 312.50
- Investigator responsibilities – 21 CFR 312.60
- Sponsor-Investigator’s – responsible for requirements of both roles
IND Maintenance

- Protocol Amendment
  - New protocol – 21 CFR 312.30(a)
  - Changes to protocol – 21 CFR 312.30(b)
    - safety/scope/scientific quality
  - New Investigator(s) – 21 CFR 312.30(c)
    - within 30 days

- Annual Report – 21 CFR 312.33
  - Within 60 days of anniversary date of safe to proceed determination
Safety Reports

- IND Safety Reports – 21 CFR 312.32
  - 15-day written reports
    - Serious/unexpected/associated
    - Animal finding that suggests Significant Risk to humans
  - 7-day fax/telephone reports
    - Unexpected/associated/fatal or life threatening
  - 15-day follow-up reports
    - As soon as information available
Closing the IND

- **Withdrawal** – 21 CFR 312.38
  - Sponsor request
  - Submit request to FDA in writing

- **Termination** – 21 CFR 312.45
  - FDA initiated
  - Reason

- **Inactivation** – 21 CFR 312.44
  - Sponsor or FDA initiated
  - Annual reports not required
  - Protocol Amendment required to reactivate IND – 30 day review
Questions?
Stacy Newalu  
QI/QA Program Manager  
Division of Research Integrity & Compliance  
University of South Florida  

813-974-3885  
snewalu@research.usf.edu