

How Do You Know When an IND is Required?

**Application Submission Steps for
Investigators and Research Staff**

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Agenda

- How to Determine if/when an IND is needed?
- What are the essential items for an IND Application?
- FDA Submission Guidelines and Timelines
- Understand How the FDA Submission Guidelines Work
- UHCMC IRB Policy Relating to an IND

Learning Objectives

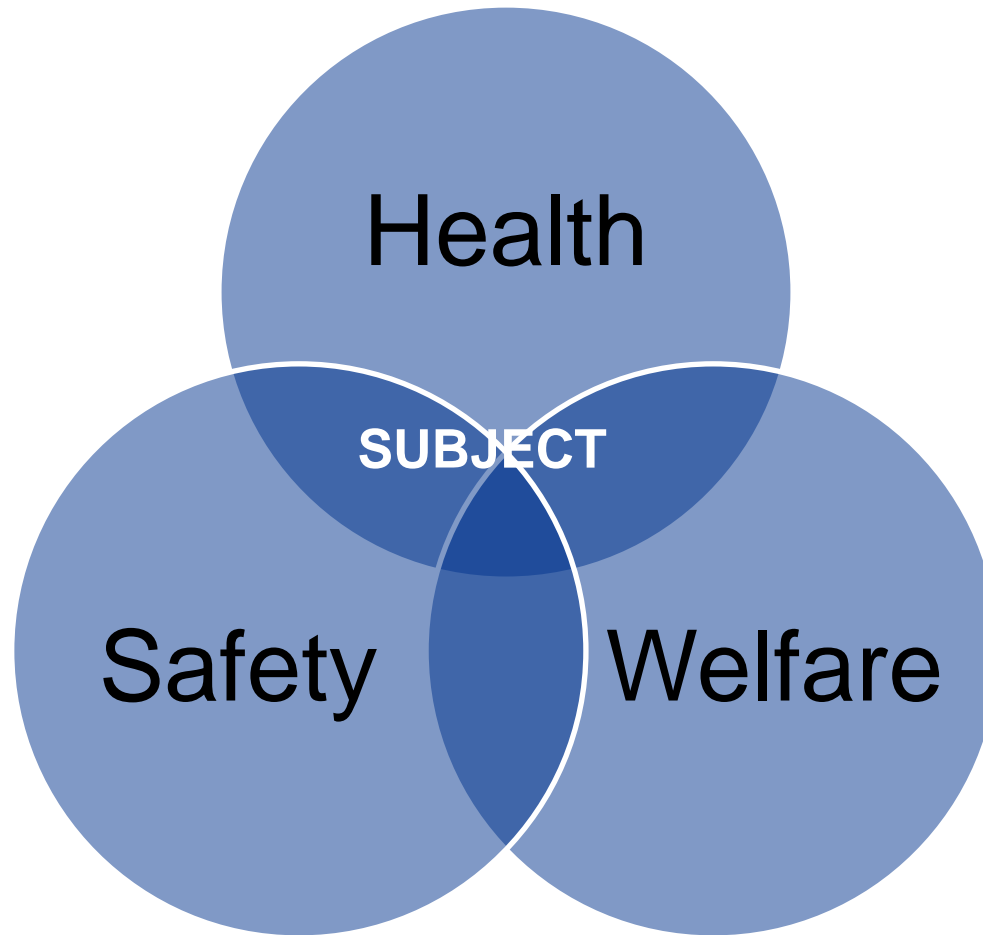
- Acknowledge the appropriate situation when an IND is required
- Understand FDA expectations for a complete IND Application
- Discuss standard FDA submission timelines and application guidelines
- Similarities/differences with UHCMC IRB Policies

The Challenge

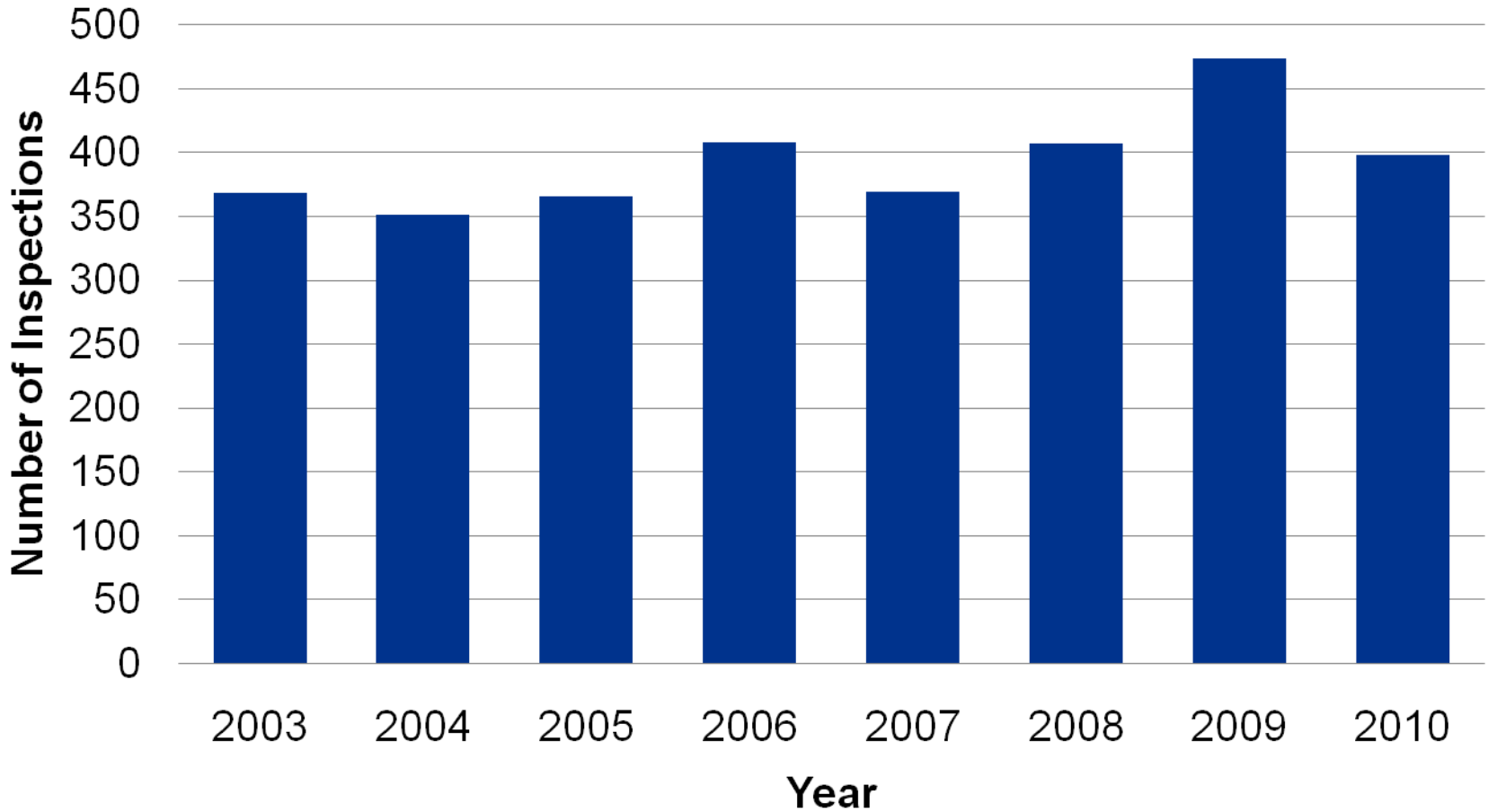
David Lepam, the FDA's Senior Advisor on Clinical Science states that, "Where problems have come in recent years, the majority have come in studies where the investigator was also the sponsor." Because the investigator now maintains also the responsibility of the sponsor, there is a lost level of oversight that comes from separate sponsors and investigators.

Guide to Good Clinical Practice, January 2005

What is most important in human clinical research?

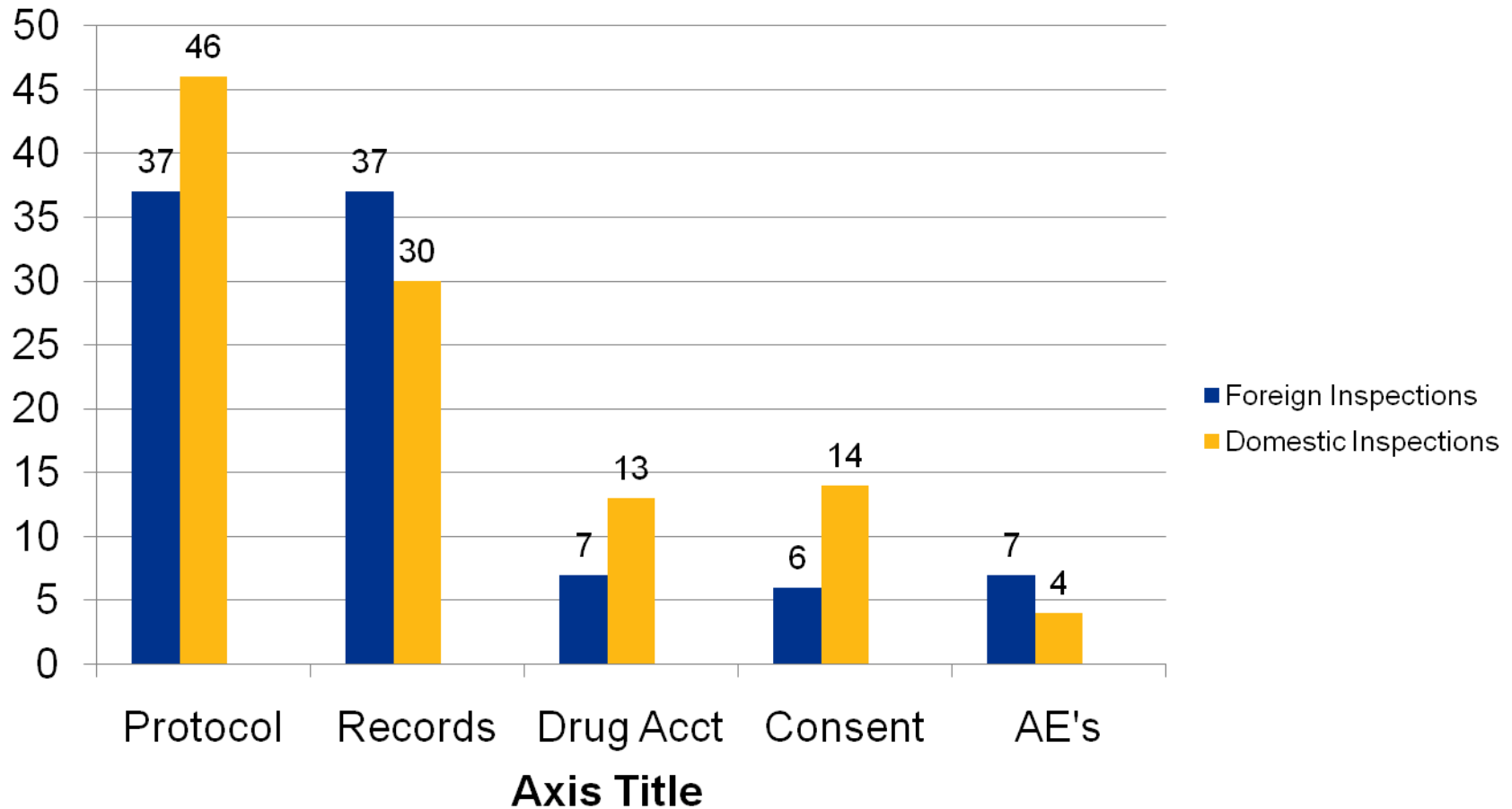


Clinical Investigator Inspections* (CDER, FY 2003-2010)



*Based on inspection start date [4/01/2011]
Leslie Ball, MD, FDA DSI

Clinical Investigator Inspections Frequency of Deficiencies* (CDER, FY 2010)



*Based on letter issue date; Inspections may have multiple deficiencies, [4/01/2011]

Leslie Ball, MD, FDA DSI

FDA PI Inspections

- 2006-2010: FDA Warning Letters Investigators
 - **PI Involvement**
 - **PI Engagement**
 - **PI Control of the Study: Clinical Trial Plan**
 - **PI Oversight: Site, Staff, Satellite Staff**
 - **PI Delegation: To Medically Qualified Staff**
 - **PI and Staff Training**

Understanding the Basics

Building a Foundation

- Regulated under 21 CFR part 312, a **drug** is defined as:
 - Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease. In addition, articles (other than food) intended to affect the structure or any function of the body of man or other animals.

It is important to note that the drug definition is not limited to compounds intended only for a therapeutic purpose.

Understanding the Basics

Building a Foundation

- Regulated under 21 CFR part 312, a ***Clinical Investigation*** is defined as:
 - An experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.
- In contrast, the use of a lawfully marketed drug in the course of medical practice involves the use in an individual patient where the primary intent is to treat the patient but not to study the safety or effectiveness of a drug in any systematic way.

The IND Exemption Process

Determining When a Full IND
Application is Not Always Necessary

The IND Exemption Process

*****Always Remember*****

The determination of the need for an IND does **not** depend on whether the intent of the clinical investigation is commercial or non-commercial. Also, it does **not** depend on the number of subjects to be enrolled or the clinical condition of the subjects. However, unless the clinical investigation meets **ALL** of the following exemptions, it is subject to IND Regulations:

IND Exemption Criteria

21 CFR 312.2

- The drug product is lawfully marketed in the United States
- No intent to report the investigation to the FDA as a well-controlled study in support of a **new** indication
- No intent to use clinical information to support any significant **change** in the labeling of the drug.
- Investigation is conducted in compliance with IRB review requirements
- Investigation is **not** intended to promote or commercialize the product
- The investigation does **not** involve:
 - New Route of Administration
 - New Dose
 - New Patient Population
 - Or other factor that would **significantly increase the risk** associated with the use of the drug

IND Exemption Criteria: Taking a Closer Look

Helping to Decipher One of the Most Difficult Issues in Determining the Need for an IND

IND Exemption Criteria: Taking a Closer Look

Investigators need to carefully consider the risk implications of any disease/condition of use in the study that could deviation from the conditions of use described in the drugs labeling, paying particular attention to the following:

IND Exemption Criteria: Taking a Closer Look

- **Dose:** Increases in dose, frequency, or duration of administration, compared to the already approved labeling dose regimens, can be significant increase in the risk.
- **Route of Administration:** The conversion of an oral route of administration to an injectable route could present significant changes.
- **Patient Population:** The known and unknown possibilities can vary considerably across different treatment populations.

When an Exemption Does Not Apply

Provisions for the “Unsure” Investigator

Pre-IND Meeting Request

FDA's Help in the Determination of an IND

Any sponsor planning to conduct an IND can request an Pre-IND Meeting to discuss with the FDA any questions that need to be resolved before the IND submission.

- *The meeting is not required, but recommended by the FDA to expedite the approval process.*
- *The timing/scheduling of the meeting is dependant upon the complexity of issues up for discussion*

Pre-IND Meeting Request

FDA's Help in the Determination of an IND

The pre-IND meeting request letter should contain the following items:

- Product Name
- Chemical name and structure
- Statement Requesting a Review meeting
- Brief statement of the purpose of the meeting
- Specific objectives expected from the meeting
- A proposed Agenda, including estimated time for each item and designated speakers
- Draft list of specific questions (grouped by clinical and non-clinical)
- List of individuals who will attend the meeting from the sponsors institution
- List of FDA disciplines requested to be present
- List of suggested dates and times that work for the sponsor

Pre-IND Meeting Request

FDA's Help in the Determination of an IND

****Always Remember****

The sponsor should include a Request for Type B Meeting on the Top of the letter to the FDA.

A Type B meeting signifies to the FDA that:

- Pre-investigational new drug application
- Certain end-of-Phase 1 meeting
- End of phase 2 or 3 phase meeting

Pre-IND Meeting Request

FDA's Help in the Determination of an IND

The FDA will respond to a request for a Pre-IND meeting within 14 days of receipt of the meeting request letter. *However*, the FDA will generally schedule the meeting within 60-90 days from the receipt of written request.



Pre-IND Meeting Package

Providing the FDA with Sufficient Information

- Once a Pre-IND meeting has been scheduled, a *Meeting Package* will need to be submitted to the agency on behalf of the sponsor.
- The Pre-IND meeting package provides the FDA with additional background information for the scheduled meeting.
- The Pre-IND meeting package should be submitted roughly **4 weeks prior** to the scheduled meeting date.
- The Meeting will generally be a **1 hour telephone** discussion

Pre-IND Meeting Package

Providing the FDA with Sufficient Information

Pre-IND Meeting Packages should contain the following:

- *Product name and application number*
- *Chemical name and structure*
- *Proposed indication*
- *Dosage, route of administration, and dosing regimen*
 - *Frequency and duration*
- *Updated list of sponsor or applicant attendees, affiliations and titles*
- *Background section that includes the following*
 - *History of the development program and events that lead to the meeting*
 - *Status of product development (target indication for use)*

Pre-IND Meeting Package

Providing the FDA with Sufficient Information

Pre-IND Meeting Packages should contain the following:

- *Brief statement summarizing the purpose of the meeting*
- *Proposed Agenda*
- *Listing of all final questions to be discussed during the meeting*
 - *Must be grouped by discipline*

The sponsor should organize the material according to the agenda to expedite the review of materials by the agency.

The IND Application for the Sponsor- Investigator

Compiling the Pieces for an Approval

Types of IND's

Understanding the Differences

- **Investigator Initiated IND**
 - Submitted by a physician who both initiates and conducts the investigation, and under whose immediate direction the investigational drug is administered or dispensed.
 - This type of application would be submitted for a protocol using an unapproved drug or an approved product for a new indication or in a new patient population.
- **Emergency Use IND**
 - Allows the FDA to authorize the use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with the 21 CFR 312 regulations
- **Treatment IND**
 - Submitted for experimental drugs showing promise in clinical testing for immediate life threatening conditions, while the final clinical work is conducted and the FDA review takes place.

Phases of a Clinical IND Investigation

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a drug that was previously untested is divided into three phases.

Although the phases are generally conducted in sequence, they could also overlap

Phases of a Clinical IND Investigation

Phase 1: First in Humans

Phase 1: Phase 1 includes the initial introduction of an investigational new drug in humans

- Phase 1 studies are typically monitored very closely and can be conducted in patients or normal volunteer subjects.
- Phase 1 studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with the drug, and the evidence on effectiveness.

The total number of patients/subjects can vary, however is generally in the range of 20-80.

Phases of a Clinical IND Investigation

Phase 2: Controlled Clinical Trial

Phase 2: Phase 2 studies include well controlled clinical trials conducted to evaluate the effectiveness of the drug for a given indication.

- Phase 2 studies look to determine the common short term side effects and risks associated with the investigational drug.
- Phase 2 studies are generally well controlled, closely monitored, and conducted in a relatively small number of patients/subjects.

The number of enrolled patients/subjects generally does not exceed several hundred.

Phases of a Clinical IND Investigation

Phase 3: Expanded Clinical Trial

Phase 3: Expanded controlled and uncontrolled trials.

- Phase 3 studies are performed after preliminary evidence suggesting effectiveness of the drug has been obtained.
- Phase 3 trials are intended to collect the remaining information regarding effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug
- Phase 3 trials are designed to provide sufficient basis for labeling.

Phase 3 studies generally include from several hundred to several thousand patients/subjects.

Principles of an IND Submission

Evaluation Standards of the FDA

Before an investigator begins writing their IND application, it is important to note that the FDA's primary objectives in reviewing an applications (all phases) will be to assure the rights and safety of the subjects.

- **Specifically in Phases 2 and 3**, the FDA will also help assure that the scientific evaluation of the drug is adequate to support the drug investigation
- **Phase 2 and 3 clinical** trials will need to yield a high likelihood that the investigations are capable of meeting standards for marketing approval.

IND Application

IND Content and Format

The following items are listed by the FDA to be included, as numbered below:

**** Cover Letter: Not required but strongly recommended.*

- A) Cover Sheet : FDA Form 1571
- B) Table of Contents
- C) Introductory Statement and General Investigational Plan
- D) Investigator Brochure
 - A) Not required if protocol is a single site

IND Application

IND Content and Format

- E) Protocols
- F) Chemistry, Manufacturing, and Control Information
- G) Pharmacology and Toxicology Information
- H) Previous Human Experience with the Investigational Drug/Product
- References

IND Application Content and Format Breakdown

Cover Sheet : FDA Form 1571

Please see handout for Discussion and questions

IND Application

Content and Format Breakdown

Introductory Statement and General Investigational Plan

- This section should be brief; no more than 2-3 pages
- Section intended to place the investigational plan for the drug into perspective for the FDA and helps the FDA to anticipate the sponsor needs.
- Statement of the drug has been withdrawn from marketing or investigation
- Brief overview of the previous human experience with the drug
 - (also OK to reference other IND's)
- Ensure this section is clear and concise; it will be the reviewers first glance at the outlined intentions of your protocol

IND Application

Content and Format Breakdown

Protocol

- In general, FDA allows for Phase 1 protocols to be much less detailed than Phase 2 or 3
- Protocols should be directed primarily at providing an outline of the investigation
 - Estimate of the number of patients to be enrolled
 - Description of safety exclusions
 - Description of dosing plan
 - Include duration, dose, method to be used in determining dose

IND Application

Content and Format Breakdown

FDA Regulations State the Following MUST be Included in the Protocol Section:

- 1) Statement of objective and purpose of the study
- 2) Names and address and statement of qualification of the sponsor
 - 1) Should also include qualifications of investigators to be working under the direction of the sponsor
- 3) Criteria for patient selection
- 4) Design description
 - 1) Control group
 - 2) Method to minimize bias

IND Application

Content and Format Breakdown

FDA Regulations State the Following MUST be Included in the Protocol Section:

- 5) Method for determining dose to be administered
- 6) Description of observations and measurements to be made to evaluate endpoints/objectives of the study
- 7) Description of all clinical procedures and lab tests used to monitor the subject

IND Application

Content and Format Breakdown

Chemistry, Manufacturing and Control Information

- ** It should be noted that the amount of information to be submitted depends on the scope of the proposed clinical trial.
- ** Sufficient information should be submitted to assure proper identification of the product, quality, purity, and strength of the investigational drug.

IND Application

Content and Format Breakdown

FDA Regulations State the Following MUST be Included in the Chemistry, Manufacturing and Control Section:

- Information/description of the drug substance (including its physical, chemical, and biological components)
 - Include the name and address of drug manufacturer
 - Method of drug preparation
 - Any applicable test methods for the product
 - A copy of all labeling of the product

IND Application

Content and Format Breakdown

Pharmacology and Toxicology Information

- Information should be submitted regarding studies involving animals or in vitro work. This is the work that the sponsor concluded that it is reasonable and safe to conduct the proposed clinical trial investigation.
- The kind, duration, and scope of animal and other tests may differ depending on the clinical trial, however, as the drug development progresses, the sponsor is required to submit informational amendments
 - Updates regarding safety

IND Application Content and Format Breakdown

Pharmacology and Toxicology Information

- A summary of the toxicological effects of the drug in animals and in vitro is also required.
- Summary should include results of acute and chronic toxicity tests, tests on reproduction or effects of a fetus

IND Application

Content and Format Breakdown

Previous Human Experience with the Investigational Drug

- Information on if the drug has been investigated or marketed previously, either in the United States or in other countries
- Information if the drug has been used in other trials
- Information on if the drug is a combination of drugs previous investigated or marketed
- Information on if the drug has been marketed outside of the United States

Additional Application Elements

The following Documents will need to be submitted with the IND application for review by the FDA:

- CV's for all individuals listed on the protocol
- FDA form 1572
- FDA form 3455
- FDA form 3674

Understanding Responsibilities Not Just Another Form

When an investigator signs a 1572, what are they committing to?

- To conduct the study in accordance with the protocol
- To personally supervise or conduct the investigation
- To inform the subjects of the investigational status of the test article
- To report adverse events to the sponsor
- To read and understand the procedures
- To inform all support personnel of the investigational requirements

Understanding Responsibilities Not Just Another Form

When an investigator signs a 1572, what are they committing to?

- To maintain adequate records and make them available for inspection
- To assume responsibility for initial and continuing review by the local IRB
- To promptly report study changes and unanticipated risks to the IRB
- Not to make changes in the research without IRB/FDA approval
- To comply with the requirements regarding the obligations of the clinical investigation.

Final Steps

Compiling the Application

- IND Applications must be submitted in Triplicate Form
- Label, Label, Label!!!!!! Remember to label each section of the application and its elements very clearly for the agencies review
- 2 Hard Copies, 1 Electronic Copy
 - One original/one copy
 - Electronic copy must be exact replica of hard copy

Final Steps

Where to Direct the Application?

Drugs

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

Therapeutic Biologics

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705

FDA Receipt of the IND

The FDA Time Clock Begins

- Upon receiving the IND application, an IND number will be assigned
 - This number will be used until the completion of the trial as a reference number with the agency
- Once the application has been routed to the proper reviewing division, the sponsor investigator will be sent an acknowledgement letter

FDA Review Process

Typical FDA IND Review Team

- Regulatory Reviewer
- Clinical Medical Officer
- Product Reviewer (s)
- Statistician
- Pharmacology/Toxicology Reviewer

Generally, a single review team will follow a drug from its initial IND application through the New drug application approval decision and into post-marketing phase.

FDA Receipt of the IND

When Can an Investigator Begin Their Trial?

****Important To Note****

- The FDA has 30 days to respond to an application based on the official date of receipt.
- Officially, the study may proceed 30 days after the FDA receives the application
 - Unless the sponsor is otherwise notified by the FDA

IND's are technically not issued an approval letter; unless there is ongoing correspondence with the FDA regarding stipulations or changes.

FDA Receipt of the IND

Clinical Hold and How to Proceed?

If the IND Application is unable to be approved within 30 days, the application will be placed on **Clinical Hold** by the FDA.

- A sponsor investigator can continue their pursuit of an approval with the agency even though a clinical hold has been placed
 - Timeline formality by the Agency
- The sponsor can/will continue to stay in communication with the FDA and respond to their inquiries until an approval is reached.
- Once approval is reached, a formal communication will be given to the sponsor
 - Hard copy letter

Problem Area's for Investigators

How to Avoid the Pitfalls

Some of the Most Common Problems with IND Applications:

- Data lacking to support proposed dose
- Inadequate report of prior investigation
- Questionable scientific soundness
- Poorly defined stopping rules
- Undefined statistical analysis
- Undefined endpoints
- Inconsistencies
- Lack of specific references

Addressing the Changes Items that Require an IND Modification

Once the IND is in affect, the sponsor may need to amend the application:

- *New Protocol*
- *Addition of new test of procedure*
- *Addition of new investigators*
- *Changes in Protocol*
 - *Drug dose*
 - *Drug duration*
 - *Significant changes to the drug affecting the safety and risks to the subject*

Addressing the Changes Numbering of IND Submissions

****Important Notation****

Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number.

The Initial IND is required to be numbered 000, and each subsequent submission (i.e., amendments, report, correspondence) is required to be numbered chronologically in sequence.

Policies

UHCMC Policies Relating to FDA Sponsor-Investigator Research

- Per UHCMC Policy: Investigational Drugs Used in Research, all drugs with an Investigational Drug Exemption number require full Board approval.
- In accordance with FDA Regulations 21 CFR 312, the following requirements are applicable to all UHCMC sponsor-investigators holding an IND:
 - *Maintaining the IND*
 - *Obtaining Qualified Investigators and Monitors*
 - *Providing necessary training and education for investigators*
 - *Monitoring the Investigation*
 - *Controlling the investigational drug*
 - *Reporting SAE's to FDA and Investigators*
 - *Maintaining accurate records*
 - *Implementing SOP's*

Policies

UHCMC Policies Relating to FDA Sponsor-Investigator

When a UHCMC investigator is the sponsor of an IND, the UHCMC IRB requires the investigator to meet with a representative of the Office of Research Compliance and Education to review their FDA responsibilities as a sponsor investigator.

Research Staff Education and Training is mandatory per FDA; if you're aware of an investigator beginning an IND or an IND that is already in progress, please contact the Office of Research Compliance to ensure proper training.

Thank you for Attending Today's Lecture

Questions??????