

REdI Conference – Spring 2017

Introduction to Investigational New Drug (IND) Applications

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Learning Objectives

- Introduce the IND Process and Clinical Trial Regulation
- Discuss how to determine if an IND is needed
- Summarize the types of INDs
- Share information on the Pre-IND Consultation

Poll Question: IND

What is the extent of your knowledge regarding an IND?

- IND? What is an IND?
- I have heard of an IND.
- I know what an IND is.
- I have submitted an IND.
- I have submitted an IND and I know why I did.

What is an IND?

Investigational New Drug Application:

- Exemption from Food and Drug Cosmetic Act
- A means to obtain FDA permission to ship an investigational drug or biologic across state lines
- 21 CFR 312 is the primary location of the implementing regulations for this exemption

Legal and Regulatory History

- 1906
 - The original **Food and Drugs Act** is passed by Congress on June 30 and signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks and drugs.
- 1938
 - **The Federal Food, Drug, and Cosmetic (FDC) Act** requiring new drugs to be shown safe before marketing-starting a new system of drug regulation.

Legal and Regulatory History

- 1962
 - **Thalidomide**, a new sleeping pill, is found to have caused birth defects in thousands of babies
 - **Kefauver-Harris Drug Amendments** passed to ensure drug efficacy and greater drug safety
 - Proposed that drug sponsors had to submit "reports of pre-clinical tests" before clinical testing
- 1963 IND Regulations (21 CFR 312)

IND's Purpose

- 1) Notifies Regulators of intent to begin clinical studies in US
- 2) Provides preclinical data indicating that the drug is reasonably safe to administer to humans
- 3) Provides information about manufacturing process and chemistry background
- 4) Describes the initial clinical study being proposed
- 5) Provides assurance that an Institutional Review Board will approve the study before it begins

IND's Purpose cont'd

- In addition to the IND submission itself, every investigator participating in the study must sign a form, maintained by the sponsor, indicating their qualifications, the location of the research facility where the study will be conducted, and the name of the IRB responsible for reviewing and approving the study protocol.

IND's Purpose cont'd

- Investigators must sign commitments to
 1. conduct the clinical study in accordance with the IRB approved protocol
 2. personally conduct or supervise the conduct of the investigation
 3. inform potential subjects that the drugs are being used for investigational purposes and
 4. report to the sponsor adverse events that occur in the course of the investigation.

When is an IND needed?

To answer if an IND is needed, one needs to ask these 3 questions:

Is it a drug?

Is it being used in a clinical investigation?

Does it meet the IND exemption criteria?

Is it a drug?

- **21 USC 321(g)(1)(B) and (C)**

The statute defines a drug as, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease...” and “articles (other than food) intended to affect the structure or any function of the body...”.

It general it is important to note that a drug is defined by its intended use, not the nature of the substance.

Also note that the second part of the definition does not apply to dietary supplements.

Is it being used in a clinical investigation?



- **21 CFR 312.3**

The regulations define clinical investigation as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice”.

A clinical investigation is typically conducted by a pharmaceutical company with the ultimate goal of commercially marketing the drug. However, that is not always the case. For example, a sponsor investigator from academia may conduct a clinical investigation with the ultimate goal of publishing the findings in journal.

Does it meet the IND exemption criteria?

21 CFR 312.2

This regulation provides for IND exemptions for certain clinical studies of approved drugs for unapproved uses.

Is the product lawfully marketed in the US as a drug under one of the following circumstances?

1. Marketed under an approved New Drug Application (NDA) or Biological Licensing Agreement (BLA)
2. Marketed under an Over the Counter (OTC) monograph

Is the indication an approved indication?

Does it meet the IND exemption criteria?

Additionally, to be IND exempted, a study must meet ALL of the following criteria:

- Not for a new indication or significant labeling change
- Not to support significant change in advertising
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk
- Complies with 21 CFR 56 (IRB) and 21 CFR 50 (informed consent)
- Conducted in compliance with 21 CFR 312.7 (promotion and charging)

Does it meet the IND exemption criteria?

There are other examples of specific studies that can be conducted without an IND and where IND exemptions apply:

- In vitro biological diagnostic products
- The following products are exempt:
 - Blood grouping serum
 - Reagent red blood cells
 - Anti-human globulin
- In vitro or laboratory research animals
- Certain bioavailability studies [21 CFR 320.31]
- Radioactive drugs for certain research uses [21 CFR 361.1]

Does it meet the IND exemption criteria?

**Yes, it's
a drug**

**Yes, it's being
used in a
clinical
investigation**

**No, the IND
does NOT
meet the
exception
criteria**

**You need
an IND!**

IND Categories

- **Commercial INDs:** An IND for which the sponsor is either a corporate entity (i.e., a pharmaceutical company or a biopharmaceutical company) or one of the institutes of the National Institute of Health.
- **Research (non-commercial):** An IND for which the sponsor is an individual investigator (you may also see the term individual sponsor-investigator used) or an academic institution.

IND Types

- **Product Development (Clinical Investigation) INDs** are submitted by a corporate entity or a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- **Clinical Treatment (Expanded Access) INDs** refer to the use of an investigational new drug outside of a clinical trial by patients, with serious or life-threatening conditions and no comparable or satisfactory alternative therapy exists, who do not meet the enrollment criteria for the clinical trial in progress.
 - It applies to use of investigational new drugs when the primary purpose is to diagnose, monitor, or treat patient's disease or condition.

Types of Expanded Access INDs

- Individual (single) patient non-emergency and emergency
- Intermediate Size patient population
- Treatment

Jurisdiction

- CDER assigns each IND to a review division.
- Review division portfolios are defined ***by primary endpoint***
- If the jurisdiction is not obvious based on the primary endpoint, then the ***safety*** of the drug is considered.

For example, does the drug have a serious risk that mandates assignment to a particular division (e.g., tumor promotion which might be assigned to the division that handles oncology products)?

Precedent is also a big factor in determining jurisdiction.

Jurisdiction

- The review divisions are responsible for handling jurisdiction issues and managing IND assignments.
- If you have a question about which review division to contact, start with the review division you consider most likely to have jurisdiction.



Division Contacts

Office of Drug Evaluation I (ODE I)

Division of Neurology Products (DNP)	301-796-2250
Division of Psychiatry Products (DPP)	301-796-2260
Division of Cardiovascular and Renal Products (DCRP)	301-796-2240

Office of Drug Evaluation II (ODE II)

Division of Metabolic and Endocrine Products (DMEP)	301-796-2290
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)	301-796-2300
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)	301-796-2280

Office of Drug Evaluation III (ODE III)

Division of Gastroenterology and Inborn Errors Products (DGIEP)	301-796-2120
Division of Bone, Reproductive, and Urologic Products (DBRUP)	301-796-2130
Division of Dermatology and Dental Products (DDDP)	301-796-2110



Division Contacts

Office of Drug Evaluation IV (ODE IV)

Division of Nonprescription Drug Products (DNDP)	301-796-2080
Division of Medical Imaging Products (DMIP)	301-796-2050
Division of Pediatric and Maternal Health (DPMH)	301-796-2141

Office of Antimicrobial Products (OAP)

Division of Anti-Infective Products (DAIP)	301-796-1400
Division of Anti-Viral Products (DAVP)	301-796-1500
Division of Transplant and Ophthalmology Products (DTOP)	301-796-1600



Division Contacts

Office of Hematology Oncology Products (OHOP)

Division of Oncology Products I (DOP1)

301-796-2330

Breast, Gynecologic, Genitourinary, Supportive care (non-hematologic)

Division of Oncology Products II (DOP2)

301-796-2320

*Gastrointestinal, Lung/Head & Neck, Neuro-oncology/Rare cancers/
Pediatric Solid Tumor, Melanoma/Sarcoma*

Division of Hematology Products (DHP)

301-796-7550

*Benign hematology, Hematologic malignancies, Hematology support,
Pediatric Hematology*

Division of Hematology Oncology Toxicology (DHOT)

301-796-2340

Nonclinical Review Division for Hematology/Oncology Products

Bundling:



Is one or more INDs needed?

Bundling may be possible if:

- There is a lack of indication/dosage clarity in an early stage of the investigation; OR
- One indication (or closely related indications) within a single review division; OR
- Multiple, closely-related routes of administration using same dosage formulation; OR
- Combination of two or more investigational new drugs for concomitant use

Bundling - Is one or more INDs needed?

Conversely, it may be appropriate for a sponsor to submit more than one IND, if one or more of the following hold true:

- The sponsor is developing an investigational new drug in two or more unrelated conditions or indications
- Multiple dosage forms of the investigational new drug are being extensively investigated
- Multiple routes of administration of the investigational new drug are being extensively investigated

Now what?

You've determined that your clinical investigation requires that:

- You need an IND
- You know which Division to send it to
- You know its one or more separate INDs

What next?

Pre-IND Consultation Program

- Pre-IND meetings are valuable for understanding proof of concept and initiating dialogue for drug development in its early stages.
- Pre-IND advice may be requested for:
 - issues related to data needed to support the rationale for testing a drug in humans;
 - the design of nonclinical pharmacology, toxicology, and drug activity studies, including design and potential uses of any proposed treatment studies in animal models;
 - data requirements for an Investigational New Drug (IND) application;
 - initial drug development plans, and regulatory requirements for demonstrating safety and efficacy.



Pre-IND Consultation Program

- FDA encourages sponsors to request a pre-IND meeting for the following:
 - drug not previously approved/licensed,
 - new molecular entity (NME),
 - planned 505(b)(2) marketing application,
 - drugs for which it is critical to public health to have an effective and efficient drug development plan (e.g., counter-terrorism),
 - drugs with substantial early development outside the United States,
 - a planned human factors development program,
 - and drugs with adequate and well- controlled trials to support a new indication.

However, a sponsor of any IND can request a pre-IND meeting.

In Summary...

- IND notifies FDA and meets legal obligations
- Required for many clinical investigations of drug, some exceptions
- Lots of nuance; contact review divisions for advice
- Highly encourage Sponsors to utilize pre-IND consultation program

Questions?

Please complete the session survey:

surveymonkey.com/r/DRG-D1S01

Personal Contact Information:

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www.fda.gov