U.S. FOOD & DRUG ADMINISTRATION

REdI Conference – Spring 2018

Introduction to Investigational New Drug Applications

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Learning Objectives

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

A Quick Poll

By a show of hands:

1. Who in the audience works on the development of new drugs?
2. Who in the audience works on the development of new biologics?
3. Who in the audience has conducted a clinical investigation or human research study with a drug or biologic?
4. Finally, who here in the audience has submitted an IND?

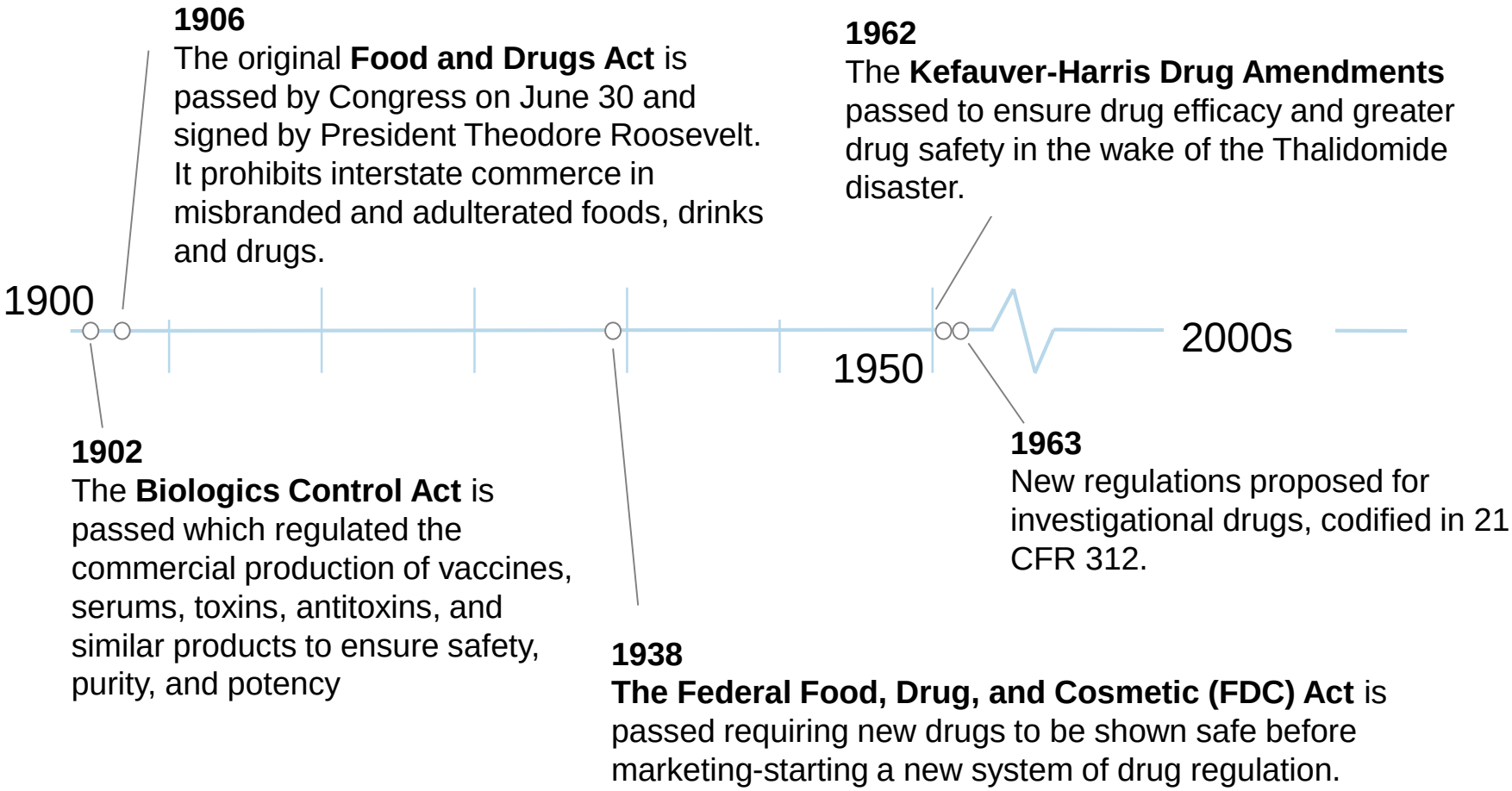
Investigational New Drug Application:

- Exemption from Food and Drug Cosmetic Act requirements to have an approved new drug application
- A means to obtain FDA permission to ship an investigational drug or biologic across state lines
- Primary location for regulatory requirements implementing this exemption are found in:

21 CFR 312

Title — Code of Federal Regulations — Section

Lega 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.

1962
The **Kefauver-Harris Drug Amendments** passed to ensure drug efficacy and greater drug safety in the wake of the Thalidomide disaster.

1902
The **Biologics Control Act** is passed which regulated the commercial production of vaccines, serums, toxins, antitoxins, and similar products to ensure safety, purity, and potency

1963
New regulations proposed for investigational drugs, codified in 21 CFR 312.

1938
The Federal Food, Drug, and Cosmetic (FDC) Act is passed requiring new drugs to be shown safe before marketing-starting a new system of drug regulation.

IND 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 Purpose continued

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.

Specifically, 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?

201(g)(1) of the FD&C Act

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…”.

In 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 a *biological* a drug?

262(i) of the Public Health Service Act

A *biological product* subject to licensure under section 351 of the Public Health Service Act may also be considered drugs within the meaning of the FD&C Act.

A *biological product* is:

> . . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable

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 a 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:

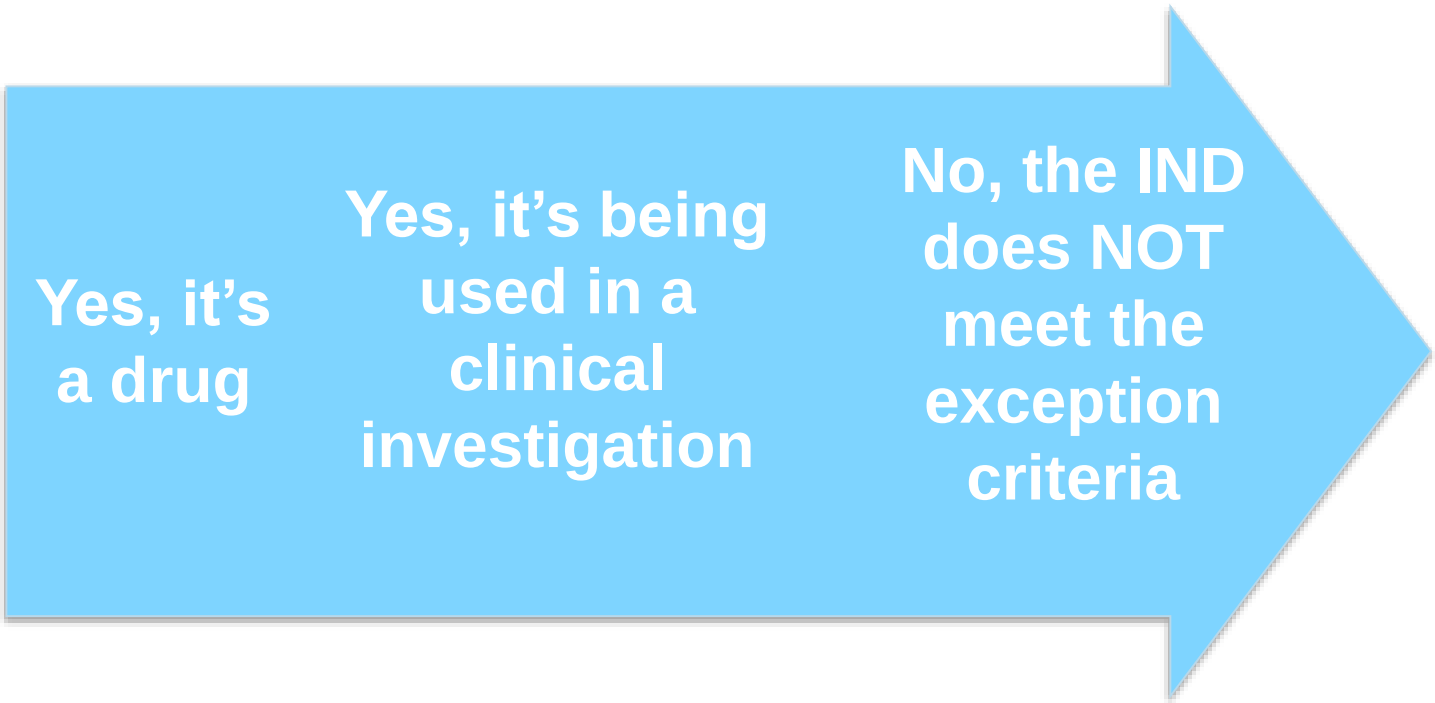
- Not for a new indication or significant labeling change
- Not to support significant change in advertising
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk
- Complies with 21 CFR 56 (IRB) and 21 CFR 50 (informed consent)
- Conducted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

Does it meet the IND exemption criteria?

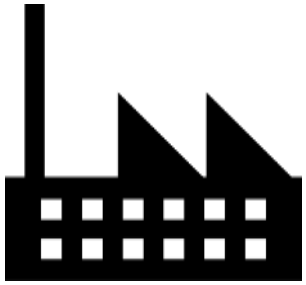
Finally, there are a few examples of specific studies that can be conducted without an IND and situations where IND exemptions apply:

- 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 [if shipped per 312.7]
- Certain bioavailability studies [21 CFR 320.31]
- Radioactive drugs for certain research uses [21 CFR 361.1]

When is an IND needed?



IND Categories



Commercial INDs: An IND for which the sponsor is either a corporate entity (i.e., a pharmaceutical company or a biopharmaceutical company).

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

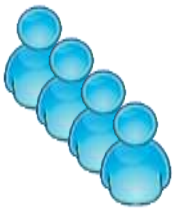
- **Product Development (Clinical Investigation) INDs** are submitted by a corporate entity or a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

- **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.

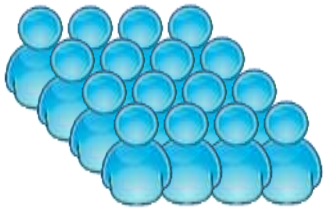
  - It applies to use of investigational new drugs when the primary purpose ***is*** to diagnose, monitor, or treat patient's disease or condition.

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.*** *Precedent* is also a big factor in determining jurisdiction.
  - 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)?

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.

- For more information on the review divisions, visit the Office of New Drugs website at:
  https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm184426.htm

Bundling:
Is one or more INDs needed?

- Bundling may be possible if one of more of the following are true:
  - There is a lack of indication/dosage clarity in an early stage of the investigation

    AND/OR
  - One indication (or closely related indications) within a single review division

    AND/OR
  - Multiple, closely-related routes of administration using same dosage formulation

    AND/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 are true:
  - The sponsor is developing an investigational new drug in two or more unrelated conditions or indications

    AND/OR

  - Multiple dosage forms of the investigational new drug are being extensively investigated

    AND/OR

  - Multiple routes of administration of the investigational new drug are being extensively investigated

Next Steps

You have determined you need to file an IND

You know which Division will review your IND

You know if it is one or more INDs

What's 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 planning to submit an IND 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. More information on additional best practices for communicating with the FDA are later in this session!

Questions?

Contact Information:
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www.fda.gov

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