Best Practices for the Preparation, Submission, and Maintenance of Sponsor-Investigator INDs and IDEs:

The Investigational New Drug (IND) Workshop

PART 1: IND Exemption Studies and Pre-IND Meetings

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Before we get started…

- Please navigate to the following website on your phone/laptop:

pollev.com/oraq

ReGARDD

- Regulatory Guidance for Academic Research of Drugs and Devices (ReGARDD) is comprised of regulatory affairs specialists from North Carolina institutions that receive funding from the NIH Clinical and Translational Science Awards (CTSA).
  - UNC and RTI: NC TraCS
  - Wake Forest
  - Duke: ORAQ
- ReGARDD provides academic researchers with the regulatory tools and resources necessary to successfully navigate the pathway from discovery to clinical implementation of new drugs, biologics and medical devices.
- Website: www.regardd.org

ReGARDD

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Office of Regulatory Affairs and Quality

- **Website:** http://medschool.duke.edu/ORAQ
  - Includes new and updated **template documents**
  - Join our mailing list (Event Subscription)
  - Contact information for our staff
- **Contact for Questions:** ORAQ@duke.edu
- **Training Program:** ORAQ-TrainingProgram@duke.edu
- **ReGARDD.org**: Templates and other regulatory resources

ReGARDD
Regulatory Guidance for Academic Research of Drugs and Devices

Food and Drug Administration (FDA)

- The U.S. Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services that is tasked with protecting public health by ensuring that drugs, vaccines, other biological products, and medical devices intended for human use are safe and effective.
  - FDA is responsible for protecting and advancing public health.
- FDA Center for Drug Evaluation and Research (CDER) oversees clinical investigations involving drugs.
- FDA Center for Biologics Evaluation and Research (CBER) oversees clinical investigations involving biologics.
- FDA regulations: Title 21 of the Code of Federal Regulations (21 CFR)
  - IND Regulations: 21 CFR 312

Outline for Part 1: IND Exemption Studies and Pre-IND Meetings

- Definitions
- Products Not Lawfully Marketed as Drugs vs. Lawfully Marketed Drugs
- On-label vs. Off-label Use
- IND Exemptions
- FDA Review Process
- Specific Issues
- Case Scenarios
- Pre-IND Meetings

Outline for Part 1: IND Exemption Studies and Pre-IND Meetings

- Definitions
  - Drug
  - Investigational Drug
  - Clinical Investigation
  - Investigational New Drug Application (IND)

What is a Drug?

- A drug is anything that meets the definition of a drug per the FD&C Act *(201(g)(1))*. . .

  ". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . ."

  "…a substance (other than food) intended to affect the structure or any function of the body"

  Note: This definition includes "…compounds administered to blunt or provoke a physiological response or to study the mechanism of action or metabolism of a drug."

What is an Investigational Drug?

- An article that is not lawfully marketed in the US as a drug, *or*
- An article that is lawfully marketed in the US as a drug that is not used according to the approved label (including a new combination of approved drugs)

Note: The practice of medicine allows a physician to use any lawfully marketed drug without prior regulatory approval.

What is a Clinical Investigation?

- As defined by 21 CFR 312.2(b):

  ". . .[an] experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

  For the purposes [of the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice."

What is an Investigational New Drug Application (IND)?

- An **IND** is a regulatory submission to the FDA that permits the clinical investigation of a drug.
- An effective IND allows:
  - An investigational drug (or biologic) to be used in a clinical investigation.
  - A drug to be shipped lawfully for the purpose of conducting clinical investigations.
- Not all clinical investigations using investigational drugs require an IND.

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What are Lawfully Marketed Drugs?

- Articles that are commercially available and legally marketed in the US as drugs
- Typically synonymous with FDA-approved drug product
  - Important to note some drug products/active ingredients are considered legally marketed but are not formally approved by FDA.
- Note: Approval is for marketing a drug in a specific manner as defined by the drug labeling.

Let’s Practice…

Please open the following website on your phone/tablet:

pollev.com/oraq

Which of the following is not a lawfully marketed drug in the US?

Claritin OTC, Bayer Healthcare

Opdivo (Nivolumab), E.R. Squibb & Sons

Tamiflu (Oseltamivir), Genentech

Oseltamivir, Made in a PI's lab

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Which of the following is not a lawfully marketed drug in the US?

Coppertone SPF 50, Bayer HealthCare

Zofran (Ondansetron), GlaxoSmithKline

Ondansetron (Generic version), Sagent Pharmaceuticals

Vioxx (Rofecoxib), Merck

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Does My Clinical Study Require an IND?

Test Article

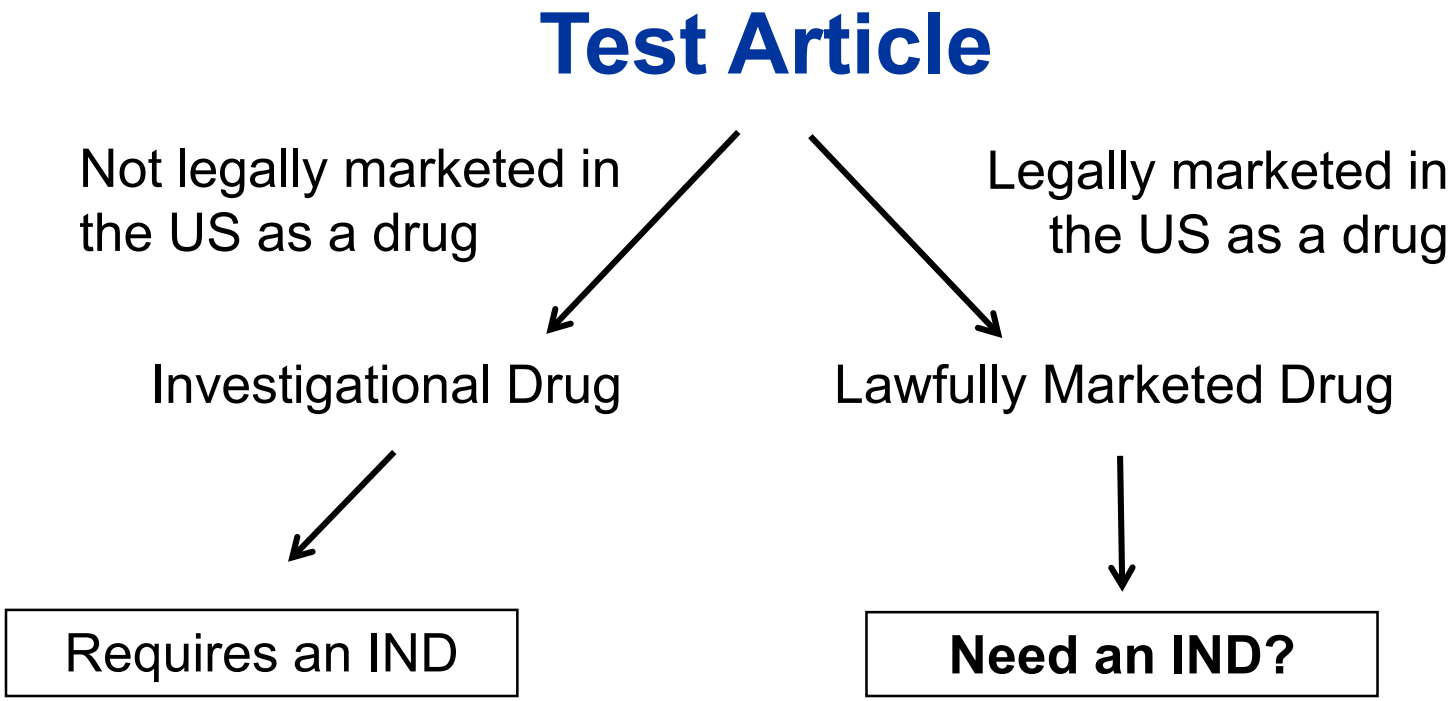
Not legally marketed in the US as a drug

Investigational Drug

Requires an IND

- Clinical investigations using a product that is not lawfully marketed in the US as a drug require an IND.

Does My Clinical Study Require an IND?



- Clinical investigations using lawfully marketed drugs may or may not require an IND.

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On-label Versus Off-label Use

- What is drug labeling?
  - Drug labeling refers to all the printed material that accompanies a drug, including the label, the wrapping, and the package insert.
  - Includes indications and usage, dosage and administration, contraindications, etc.
    - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
    - http://dailymed.nlm.nih.gov/dailymed/about.cfm

BAVENCIO- avelumab injection, solution, concentrate
EMD Serono, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BAVENCIO safely and effectively. See full prescribing information for BAVENCIO.

BAVENCIO® (avelumab) injection, for intravenous use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indication and Usage (1.2) 5/2017

INDICATIONS AND USAGE

BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of

- Adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). (1.1)
  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1, 14.1)
- Patients with locally advanced or metastatic urothelial carcinoma (UC) who:
  - Have disease progression during or following platinum-containing chemotherapy (1.2)
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (1.2)

  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.2, 14.2)

DOSAGE AND ADMINISTRATION

- Premedicate for the first 4 infusions and subsequently as needed. (2.1)
- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-mediated pneumonitis: Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening, or recurrent moderate pneumonitis. (5.1)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis. (5.2)
- Immune-mediated colitis: Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis. (5.3)
- Immune-mediated endocrinopathies: Withhold for severe or life-threatening endocrinopathies (5.4)
- Immune-mediated nephritis and renal dysfunction: Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction. (5.5)
- Infusion-related reactions: Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions. (5.7)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 20%) in patients with metastatic Merkel cell carcinoma were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema. (6.1)
Most common adverse reactions (≥ 20%) in patients with locally advanced or metastatic urothelial carcinoma were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. (6.1)

On-label Versus Off-label Use

- On-label Use
  - Same indication, same dose, same route of administration, same patient population, same drug formulation, same drug combinations
  - Studies involving the on-label use of a drug do not require an IND*

**Note: As long as data will not be used in a marketing application or to change the advertising*

On-label Versus Off-label Use

- Off-label Use
  - Any difference from what is approved in the label
  - Off-label use is common and allowed in the practice of medicine and often is the standard of care.

Let’s Practice…

An FDA approved drug HepEx is approved for intramuscular delivery in persons 18-65 years of age who have been exposed to hepatitis C. Of the following uses of the drug in a clinical trial, identify which would be considered ON-label?

Subjects age 18-65 who have been exposed to hepatitis C will receive intramuscular injections of HepEx and will also be treated with Viread, another FDA-approved drug

Subjects age 18-65 who have been exposed to hepatitis C will receive subcutaneous injections of HepEx

Subjects age 20-40 who have been exposed to hepatitis C will receive intramuscular injections of HepEx

Subjects age 18-65 who have been exposed to hepatitis E will receive intramuscular injections of HepEx

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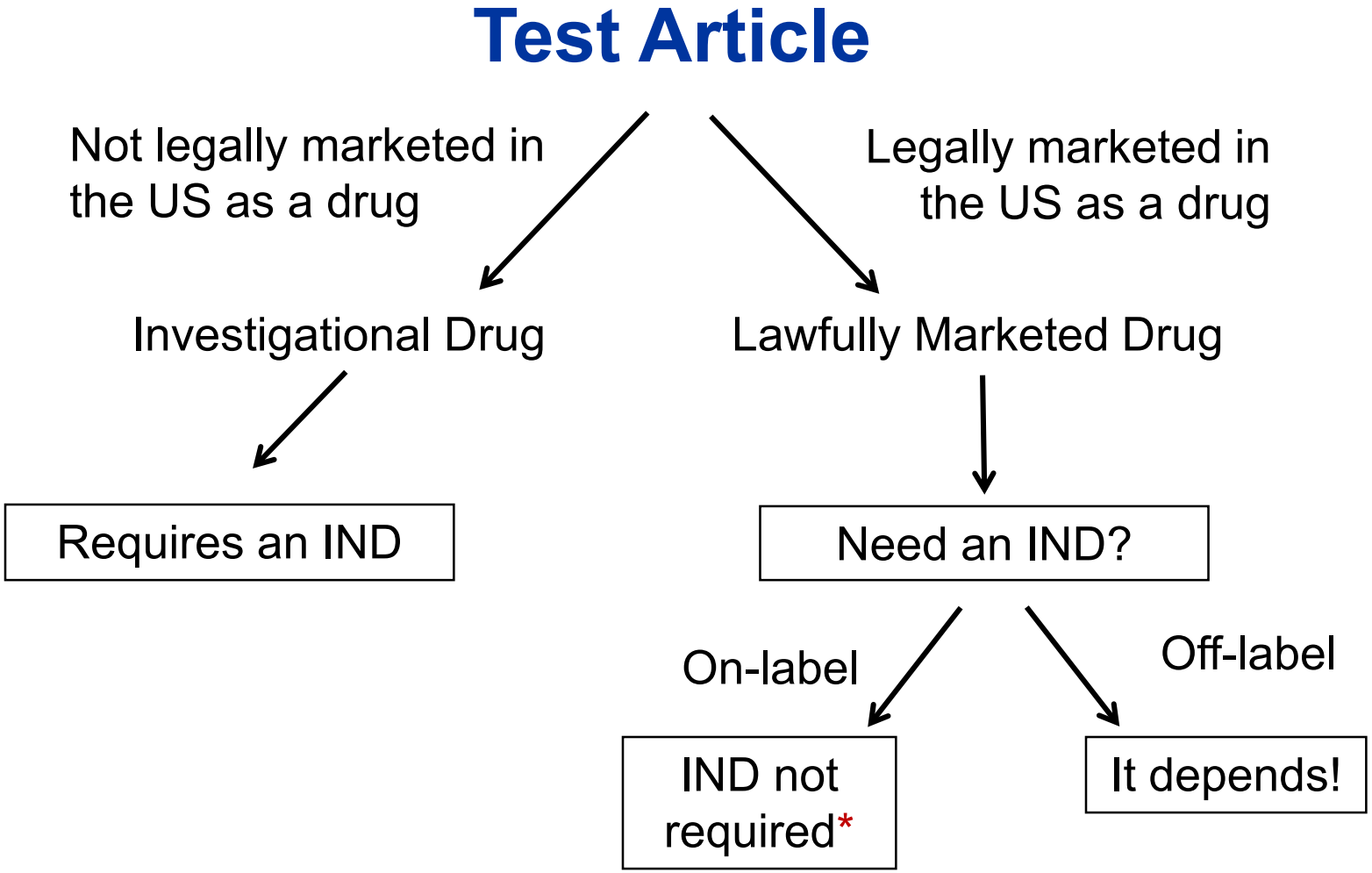
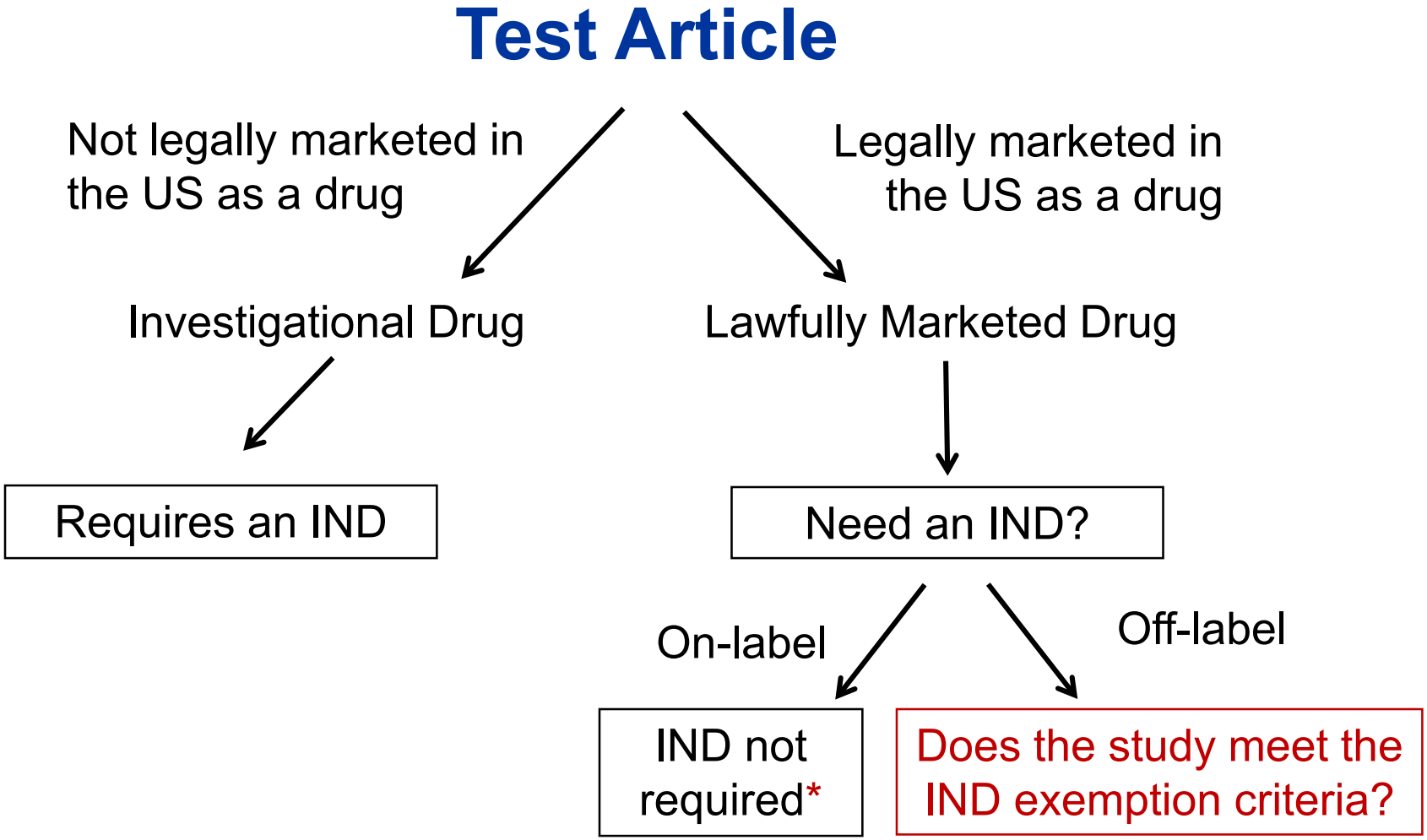
Does My Clinical Study Require an IND?



** Assuming no marketing application or change in advertising is planned*

Does My Clinical Study Require an IND?



** Assuming no marketing application or change in advertising is planned*

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Can my Study be Considered for an IND Exemption?

- First hurdle for IND exemption eligibility:

  Must be the "*investigation of a drug product that is lawfully marketed in the United States*" (21 CFR 312.2(b)(1))

IND Exemption Criteria

- A clinical investigation of a drug product that is lawfully marketed in the United States is exempt from requiring an IND if all five criteria are met:
  1. The study is not designed to support approval of a new indication or a change in label.
  2. The study is not intended to support a significant change in the advertising for the product.
  3. **The study does not involve a route of administration, dosage level, patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.**
  4. The study is conducted in compliance with the IRB and informed consent regulations.
  5. The study is conducted in compliance with regulations regarding promotion for investigational drugs.

IND Exemption Criteria #3: Risk Evaluation

- Evaluate risks of the clinical study associated with any off-label use:
  - Route of Administration
  - Dosage Level
  - Patient Population
  - Drug Combinations
  - Drug Modification

FDA Guidance on IND Exemptions

- FDA Guidance Document: "*IND Exemptions for Studies of Lawfully Marketed Drug or Biologic Products for the Treatment of Cancer*"
  - http://tinyurl.com/nqkbkd

- FDA Guidance Document: "*Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND*"
  - http://tinyurl.com/2g7z7kv

Route of Administration…

- *"There could be a significant increase in risk if a marketed drug for oral administration is converted to a dosage form that is to be administered by injection or intravenous, intrathecal, or inhalation route."*

  - FDA Guidance Document: "*Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND*"
    - http://tinyurl.com/2g7z7kv

Dosage Level…

- *"It is possible that a decrease in dose could also significantly increase risk. For example, administering a low dose of a pure polysaccharide vaccine to study subjects can induce hypo-immunologic or non-immunologic responses in the subjects and can also induce tolerance to the vaccine, thus making subjects at risk for the infectious disease the vaccine is intended to prevent"*
  - http://tinyurl.com/2g7z7kv

Patient Population…

- *"The acceptability of known and unknown risks can vary across different treatment populations... The population chosen for study could be at increased risk compared to the approved use population for a variety of reasons, such as increased age, different disease or stage of disease, concomitant illness, decreased renal or hepatic function, or concomitant therapy."*
  - http://tinyurl.com/2g7z7kv

Drug Combinations. . .

- Remember – clinical studies involving new drug combinations not supported by literature are generally not exempt.
  - *"Unless adequately described in the literature, initial studies involving new drug combinations should be performed under an IND because of the possible occurrence of synergistic toxicity."*
    - FDA Guidance Document: "*IND Exemptions for Studies of Lawfully Marketed Drug or Biologic Products for the Treatment of Cancer*"
      - http://tinyurl.com/nqkbkd

Drug Modifications. . .

- The exemption provision was not intended to require use of only the marketed product.
- Sponsor-investigators can make low-risk modifications to the lawfully marketed drug (e.g. over-encapsulation, changes to color, scoring or size for blinding purposes)
- Consult FDA and provide detailed manufacturing information such that a determination can be made.
  - http://tinyurl.com/2g7z7kv

Use of Placebo. . .

- *"A clinical investigation involving the use of a placebo is exempt. . . If the investigation does not otherwise require submission of an IND"* (21 CFR 312.2(b)(5))

Do you have to go to the FDA to get an IND Exemption?

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According to FDA. . .

- *"Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption."*
  - http://tinyurl.com/2g7z7kv
  - http://tinyurl.com/nqkbkd

IRB Submission – First Step for IND Exemption

- Investigator should submit their rationale for why the study is IND exempt directly to the IRB.
  - May use a checklist or a narrative statement.
  - Check local IRB policies.

- If IRB does not agree – then go to FDA.

Other Reasons to go to FDA for IND Exemption Determination

- Time Constraints
- Industry partner requests FDA input before they will donate drug or release funding
- The situation is unclear from the start
- Documentation required for a grant
- Your local policy requires FDA input

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If FDA Evaluates the Study

- FDA will assess risks of the study by focusing on:
  - Patient Population
  - Route of Administration
  - Dose
  - Drug Combinations
  - Drug Modifications

FDA Review Process for IND Exemptions

- Formal Process – IND submission
  - On a 30-day review clock
  - If exempt, you will receive an official letter of IND exemption.
  - If not exempt, you will have an active IND.
- Informal Process – Contact review division
  - Less work ‘up front’
  - Might get a faster response
  - FDA response may be in writing or verbal

Formal Process for Obtaining Exemption

- Study may be exempt – what should the FDA submission look like?
  - Cover Letter
  - IND
    - IND Document
    - Protocol
    - Consent
    - FDA Forms 1571, 1572, 3674
    - Letters of Authorization (if applicable)
    - Reprints from the literature (2-3 references are acceptable)

Formal Process – Cover Letter

- State in the first paragraph that you believe the study may be exempt.

- Restate the five exemption criteria and how/why you meet them.
  - Focus on safety (IND Exemption Criteria #3)

Template Documents: https://tinyurl.com/he64vq5

Informal Process for Obtaining Exemption

- Call/Email appropriate FDA review division and explain situation.
- Ask if they will consider reviewing the study.
- Send protocol synopsis and/or full protocol for review and other requested information.
- Should receive FDA determination within two weeks.

CDER Pre-IND Consultation Contacts

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301-796-2240
FAX 301-796-9841

Division of Neurology Products Jacqueline Ware
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Kyong Kang
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Division of Non Prescription Regulation Development
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Botanical Review Team
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Division of Transplant and Ophthalmology Products Products
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FAX 301-796-9880

Division of Anti-Viral Products
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Karen Winestock
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Office of Hematology and Oncology Drug Products

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Division of Oncology Products (2)
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Division of Hematology Products
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Amy Baird
301-796-4969
FAX 301-796-9848

Division of Hematology, Oncology, Toxicology

(Please reference any of the point of contacts listed above.)

http://tinyurl.com/z2kqsx7

Updated 4/12/2017

Let’s Practice…

Which of the following is NOT true?

The IRB may determine that a clinical study is IND exempt.

The FDA may determine that a clinical study is IND exempt.

If you have an active IND, you do not need IRB approval

An IRB must always approve your study

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Specific Issues

- Endogenous Compounds
- Live Organisms
- Dietary Supplements
- Radioactive or Cold Isotopes
- Research with Noncommercial Intent

Endogenous Compounds

- Endogenous compounds (those naturally found in the body)
- Often used in challenge studies to evoke physiological response, characterize a disease, or establish mechanism of action
- These studies require an IND!

Note: Although there is not intent to treat or mitigate disease, there is intent to affect the structure or function of the body.

What is a Drug?

- A drug is anything that meets the definition of a drug per the FD&C Act *(201(g)(1))*. . .

  ". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . ."

  "…a substance (other than food) intended to affect the structure or any function of the body"

  Note: This definition includes "…compounds administered to blunt or provoke a physiological response or to study the mechanism of action or metabolism of a drug."

Live Organisms

- Challenge studies with live organisms (viruses, bacteria, and fungi) administered to study pathogenesis or host response require INDs.

Note: Although there is no therapeutic purpose, there is intent to affect the structure/function of the body.

Dietary Supplements

- Dietary Supplements are defined as products taken by mouth that are intended to supplement the diet and contain a dietary ingredient.
- Examples include vitamins, minerals, herbs/botanicals, amino acids, metabolites (including extracts or combinations of these things).

Dietary Supplements

- Need for an IND is determined by intent. . .
  - Structure/Function Study = No IND Required

- Examples:
  - Studying the effect of calcium on bone mass
  - Studying the effect of fiber on bowel regularity

Dietary Supplements

- Need for an IND is determined by intent. . .
  - Therapeutic Studies require INDs (diagnose, cure, mitigate, treat, or prevent disease)

- Examples:
  - Studying the effect of calcium on osteoporosis prevention
  - Studying the effect of fiber to treat diarrhea

Radioactive Isotopes

- Can be used in clinical research without an IND:
  - Basic research only
  - Does not cause any clinically detectable pharmacological effect in humans
  - Minimize the total amount of radiation to smallest radiation dose practical to perform the study
  - Overseen by a Radioactive Drug Research Committee (RDRC)
- Cold Isotopes meeting these criteria can also be conducted without an IND.

Research with Noncommercial Intent

- The IND regulations apply to investigations regardless if the intent of the study is commercial or non-commercial.

What about cells and human tissue?

- "Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient" - 21 CFR 1271.3(d)
- HCT/Ps are not marketed as drugs, but they are used to treat patients
- What does this mean for research with HCT/Ps?

What is NOT an HCT/P?

- The following articles are not considered HCT/Ps *(In most cases no IND is required*) *-21 CFR 1271.3(d)*
  - Vascularized human organs for transplantation
  - Whole blood or blood components or blood derivative products
  - Secreted or extracted human products such as milk, collagen and cell factors
  - Minimally manipulated bone marrow for homologous use and not combined with another article,
  - Cells, tissues, and organs derived from animals other than humans
  - Blood vessels recovered with organs for use in organ transplantation

Examples of HCT/Ps

- Bone (including demineralized bone)
- Ligaments
- Tendons
- Fascia
- Cartilage
- Ocular tissue (corneas and sclera)
- Skin
- Arteries and veins
- Pericardium
- Amniotic membrane
- Dura mater
- Heart valves
- Hematopoietic stem cells derived from peripheral and cord blood
- Semen, oocytes and embryos

When do HCT/Ps need an IND? *21 CFR 1271.10*

An HCT/P is regulated solely under section 361 of the PHS Act (and does not need an IND) if it meets all of the following criteria:

1. The HCT/P is minimally manipulated
2. The HCT/P is intended for homologous use only
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent
4. Either:
   - i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
   - ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
     - a. Is for autologous use;
     - b. Is for allogeneic use in a first-degree or second-degree blood relative; or
     - c. Is for reproductive use.

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Case Scenario Questions

- Is this study eligible for an IND exemption?
- What is off label in this case?
- What kind of documentation you would provide to the IRB and/or FDA?

Scenario #1

- An investigator plans to treat lung cancer patients with three doses of checkpoint inhibitor Zyzzomab, 2 days apart at the dose indicated in the package insert, prior to tumor resection
- After tumor resection the investigator will examine changes in immune infiltrates in the tumor
- Zyzzomab is FDA approved for weekly use in patients with lung cancer after resection
- Zyzzomab will be used at the approved dose

Can this study be considered for an IND exemption?

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What is off-label in this scenario #1?

Route of Administration

Patient Population

New Drug Combination

Dosing Regimen

Drug Modification

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Scenario #1

- What kind of documentation would you provide to the IRB and/or FDA in support of an IND exemption?
  - Safety data at this dose frequency in this or other patient populations
  - Safety data using Zyzzomab before resection, if available
  - Rationale for low risk of short term Zyzzomab use before resection

Scenario #2

- An investigator plans to conduct a trial to assess the effectiveness of a commercially available probiotic to treat chronic fatigue.
- The probiotic will be used at the daily dose recommended on the packaging.

Can this study be considered for an IND exemption?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Scenario #2

- The study is not using a probiotic that is legally marketed as a drug.
  - 21 CFR 312.2(b)(1) - Must be the "investigation of a drug product that is lawfully marketed in the United States"
- In case of dietary supplements, the need for an IND is determined by intent.
  - Structure/Function Study = no IND Required.
  - Therapeutic studies require INDs (treat, diagnose, cure, mitigate disease)

Scenario #3

- An investigator plans a study in which patients with Type 2 diabetes will receive either Drug A, Drug B, or a combination of both.
- Drug A and Drug B are FDA approved for treatment of Type 2 diabetes.
- Both drugs will be used according to their approved dose and route of administration
- Neither drug mentions the other drug in their respective package inserts

Can this study be considered for an IND exemption?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

What is off-label in this scenario #3?

Route of Administration

Patient Population

New Drug Combination

Dose

Drug Modification

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Scenario #3

- What kind of documentation would you provide to the IRB and/or FDA in support of an IND exemption?
  - Any previous data evaluating the combination of these two drugs in humans and/or in animal models
  - Discussion of whether the drugs affect the same metabolic pathway and whether their risk profiles overlap

HCT/P Scenario

- An investigator plans to use peripheral blood stem cells (PBSCs) to treat Parkinson's disease, based on animal data that indicates that PBSCs can induce repair of neurologic tissue.
- The PBSCs will be collected from a related donor and infused into the subject on the same day.

Are the PBSCs minimally manipulated?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Is this use of the PBSCs homologous use?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

HCT/P Scenario

- From the FDA guidance “Regulatory Considerations for Human Cells, Tissues, and Cellular and TissueBased Products: Minimal Manipulation and Homologous Use”
  - https://tinyurl.com/ycspgtpk
- Hematopoietic progenitor cells “from cord blood are intended for intravenous infusion to treat cerebral palsy purportedly through the repair of damaged tissue in the brain through paracrine signaling or differentiation into neuronal cells. This is not homologous use because there is insufficient evidence to support that repair of neurologic tissue through paracrine signaling or differentiation into neuronal cells is a basic function of these cells in the donor.”

Will this PBSC study require an IND?

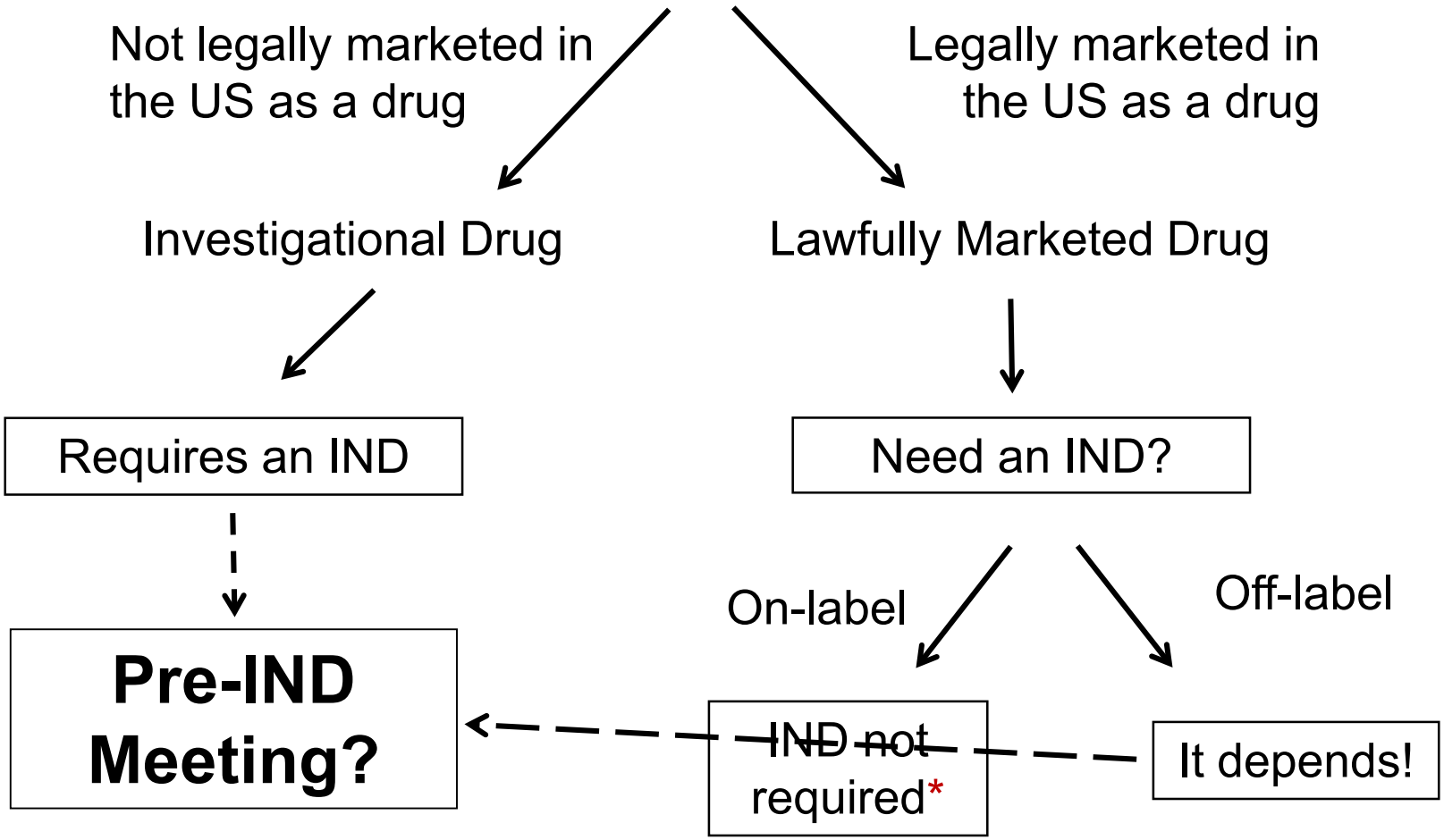
Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Questions on IND Exemptions?

Outline for Part 1: IND Exemption Studies and Pre-IND Meetings

- Definitions
- Products Not Lawfully Marketed as Drugs vs. Lawfully Marketed Drugs
- On-label vs. Off-label Use
- IND Exemptions
- FDA Review Process
- Specific Issues
- Case Scenarios
- Pre-IND Meetings

Test Article



** Assuming no marketing application or change in advertising is planned*

Pre-IND Meetings

- Method to receive feedback from FDA on your manufacturing plans, preclinical studies, and/or clinical study
- Can help prevent issues during review of the initial IND
- Most advantageous when using a non-FDA approved drug and you control the manufacturing, but also useful in other circumstances
- Best to have Pre-IND meeting <u>before</u> making major manufacturing and preclinical decisions
- Only one Pre-IND meeting per IND application

Pre-IND Meeting Request Process

Submit Pre-IND meeting request to appropriate FDA Division.

FDA determines whether to grant meeting. If denied, reason provided.

Date, time, location, and list of FDA participants provided to sponsor.

Submit Pre-meeting briefing package to FDA.

(1 month before meeting)

FDA sends written responses to questions.

(24-48 hours before meeting)

Meeting held and minutes distributed.

(within 60 days from FDA receipt of request)

Template Documents: https://tinyurl.com/he64vq5

Pre-IND Meeting

- Introductions to identify attendees
- Short introduction (2 min max)
- Bulk of time on questions and answers
- Prioritize questions
- Don’t hide concerns
- Don’t present data not included in the briefing package
- Everyone should take notes for debriefing
- At the end, summarize major decisions and action items

Post-Meeting Activities

- Debrief thoroughly with team immediately following meeting
- Document decisions
- Draft minutes ASAP
  - Minutes may be sent to FDA Project Manager
    - May use them to draft official minutes
- FDA responsible for providing the official minutes within 30 days

In which of these situations would it be appropriate to request a Pre-IND meeting with FDA?

You want to know if your proposed manufacturing plan and release specifications for your product are acceptable to FDA.

You want to know if your proposed nonclinical studies will be adequate to support your planned clinical study.

You want to know if the eligibility criteria in your proposed clinical protocol are acceptable to FDA.

All of the above

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

When is the best time to request a Pre-IND meeting?

Before you have made any major manufacturing or preclinical decisions

Before you have made any major manufacturing or preclinical decisions and you have a clinical protocol/protocol synopsis

After you have conducted your preclinical safety studies

One month before your grant application is due

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Questions on Pre-IND Meetings?

It's Time For A Break

The Investigational New Drug (IND) Workshop

PART 2: IND Preparation and Maintenance

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- IND Maintenance
- Expanded Access

Definitions

- **Sponsor:** An individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation
- **Investigator:** An *individual* who conducts a clinical trial, i.e. under whose immediate direction a drug is administered or dispensed
- **Sponsor-Investigator:** An *individual* who both initiates and conducts an investigation

Definitions: Types of INDs

- Commercial IND
  - Ultimate goal is to obtain marketing approval
- Research IND
  - Goal is publication
  - Generally sponsored by individual investigators, academic institutions, and non-profit entities

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- IND Maintenance
- Expanded Access

IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator's Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Information (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance (Form 3674)

IND Template:
https://tinyurl.com/he64vq5

IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. **Investigator's Brochure**
6. Protocols
7. **CMC**
8. **Pharm/Tox**
9. **Previous Human Experience**
10. Additional Information
11. Biosimilar User Fee Cover sheet
12. Form 3674

Refer to drug labeling or to letter of authorization if possible for Sections 5 and 7-9.

Let’s Practice…

Please open the following website on your phone/tablet:

pollev.com/oraq

If you are submitting an IND for a study using an FDA-approved drug off-label, you will most likely reference which of the following to support your IND?

Approved Drug Label

Letter of Authorization (LOA) from the manufacturer

Both A and B

Neither A or B. You will need to provide all information for all sections of the IND.

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

If you are submitting an IND for a study using an unapproved drug that will be provided by an outside company, you will most likely reference which of the following to support your IND?

Approved Drug Label

Letter of Authorization (LOA) from the manufacturer

Both A and B

Neither A or B. You will need to provide all information for all sections of the IND.

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

If you are submitting an IND for a Phase I study using a new drug that you have developed in your lab, you will most likely reference which of the following to support your IND?

Approved Drug Label

Letter of Authorization (LOA) from the manufacturer

Both A and B

Neither A or B. You will need to provide all information for all sections of the IND.

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Is there a drug label or LOA to support your IND?

- Off-label use of FDA-Approved Drug
  - Use drug label to support IND
    - https://www.accessdata.fda.gov/scripts/cder/daf/
    - https://dailymed.nlm.nih.gov/dailymed/index.cfm
- Unapproved Drug from outside company
  - Letter of Authorization (LOA) to support IND
- Unapproved Drug when you control manufacturing
  - You as the sponsor are responsible for providing all information in the IND application.

IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigator's Brochure
6. **Protocols**
   - 6.1 Protocol(s)
   - 6.2 Informed Consent
   - 6.3 Investigator and Facilities Data (Form 1572 and PI CV)
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Form 3674

IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigator's Brochure
6. Protocols
7. **Chemistry, Manufacturing, and Control Information (CMC)**
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance (Form 3674)

Section 7 – CMC

- Drug Substance (Active Pharmaceutical Ingredient)
  - Manufacturer & Raw Materials
  - Manufacturing Process
  - Analytical Testing (in-process and release)
  - Certification of Analysis (CoA)
- Drug Product (Final Product)
  - Manufacturer & Manufacturing Process
  - Analytical Testing and Specifications
  - Release Criteria and CoA
  - Stability Testing (Or Stability Plan)
  - Container Closure System
  - Labeling
    - “Caution: New Drug — Limited by Federal law to investigational use”

IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigator's Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Information (CMC)
8. **Pharmacology and Toxicology Data**
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance (Form 3674)

Section 8 – Pharm/Tox

- Adequate pharm/tox information involving animals or *in vitro* studies to demonstrate it is reasonably safe to conduct the proposed clinical trial
  - IND-enabling toxicity studies: GLP safety studies
  - Full panel of pharm/tox studies are required before submission of marketing application
- If product has already been in humans before, pharm/tox studies may not be necessary.

IND Format and Content

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5. Investigator's Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Information (CMC)
8. Pharmacology and Toxicology Data
9. **Previous Human Experience**
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance (Form 3674)

Section 9 – Previous Human Experience

- May be able to refer to published literature
  - Same indication
  - Different indication
  - Different route of administration
- May not be any previous human experience if drug is completely new

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- IND Maintenance
- Expanded Access

IND Format and Content

1. **Form 1571 (cover sheet)**
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigator's Brochure
6. **Protocols**
   - 6.1 Protocol(s)
   - 6.2 Informed Consent
   - 6.3 Investigator and Facilities Data **(Form 1572)**
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. **Form 3674**

Forms

- 1571 (IND Section 1)
  - Agreement between FDA and sponsor
- 1572 (IND Section 6.3)
  - Agreement between investigator and sponsor
- 3674 (IND Section 12)
  - Certification of compliance/registration: http://clinicaltrials.gov

Make sure you have the right version!

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

Which Clinical Trials Must Be Registered on ClinicalTrials.gov?

- "Applicable Clinical Trials" if it meets all four criteria:
  - Interventional studies
  - Evaluates an FDA-regulated drug, biologic or device
  - US FDA jurisdiction (e.g., IND/IDE, US site, or product manufactured in US)
  - Phase 2 – 4 (not Phase 1)

ACT Checklist: https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

Other Reasons to Register Your Trial

- To protect publication rights – Ensure compliance with ICMJE policy regarding trials registration
- For clinical trials funded in whole or in part by NIH – Ensure compliance with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

Deadlines for Registering Trials

Reason for registering	Registration timeline	Update	Have to report results?	Results required
ACT	No later than 21 days after enrolling first patient	12 months	Yes	Within 12 months of primary completion date
To publish (ICMJE)	Prior to enrollment	N/A	Encouraged	N/A
Funding requirement (NIH)	No later than 21 days after enrolling first patient	12 months	Yes	Within 12 months of primary completion date

Note: Your institutional policies may be different!

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
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Filing the IND

- Cover Letter
  - Template: https://tinyurl.com/he64vq5
- An original and two copies
  - Less than 3 copies may result in delays
  - Original in a grey ACCO-like report cover
  - 2 copies in different colors other than grey
  - Must be paginated uniquely throughout

Filing the IND

- Where to send the initial submission?

For a Drug (CDER):

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901 Ammendale Road
Beltsville, MD 20705-1266

For a Biologic (CBER):

U. S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Room
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

What happens after you submit?

- Sponsor receives IND Acknowledgement Letter
  - Contains the assigned review division, IND number, division contact, and official FDA date of receipt
- The official date of receipt starts a 30-day clock for FDA to review the IND.
  - Multidisciplinary review team (clinical reviewers, chemists, toxicologists, clinical pharmacologists, project managers, statistician, microbiologist)
- During review, the FDA's primary objective is to help protect the rights and safety of subjects.

What happens after you submit?

- An IND goes into effect:
  - (1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under 312.42; or
  - (2) On earlier notification by FDA that the clinical investigations in the IND may begin.
    - FDA does not routinely send letter stating that IND is in effect
    - This 30th day after receipt is your ‘effective date’!!
- Can legally begin your study once IRB approved.
- Best practice to try to confirm with FDA.

What if there are issues with the IND?

- If concerns are identified, the FDA review team will contact the sponsor with requests for information.
- Commitments in writing will often preclude a clinical hold. These would be submitted as an amendment to the IND.
- If concerns cannot be resolved within the 30-day period, FDA will place the study/IND on clinical hold.
- Clinical Hold
  - Subjects would be exposed to unreasonable or significant risk of illness/injury
  - IND application does not contain sufficient information needed to assess risks to subjects

What if there are issues with the IND?

- A Clinical Hold can be imposed by telephone or other means of rapid communication (or in writing).
  - Official letter will be received within 30 days
- The sponsor is expected to address the clinical hold comments in writing and submit a complete response to the IND.
  - Puts FDA on new 30-day clock
- Investigation may resume after FDA has notified the applicant that the investigation may proceed.
- When hold is lifted, verify the IND effective date.

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- IND Maintenance
- Expanded Access

Caring for and Feeding Your IND

IND Maintenance

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*:
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Form FDA 1571: Box 11

Maintenance of an IND includes any and all of the above types of submissions.

IND Maintenance – 1. Protocol Amendments

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

1

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Form FDA 1571: Box 11

IND Maintenance – 1. Protocol Amendment

- A protocol amendment is an IND submission that contains new or updated information concerning the clinical study protocol(s).
- Protocol amendments may be implemented after submission to FDA and following IRB approval.
- Submit a request for comment and include specific questions, if applicable.

1.1. New Protocol Amendments

- The sponsor is required to submit to FDA a protocol amendment containing the new protocol.
- Include a brief description of the differences between the new protocol and previous protocols.

1.2. Change in Protocol Amendments

- Submit a protocol amendment when changes to the existing protocol could significantly affect:
  - Safety of the subjects
  - Scope of the investigation
  - Scientific quality of the study
- The amendment should contain a description of the change and reference the submission that contained the original protocol.

1.2. Change in Protocol Amendments

- A protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by a change in protocol amendment and the reviewing IRB is also notified.

1.3. New Investigator Protocol Amendments

- Submit a protocol amendment when a new investigator is added to carry out a protocol.
- The amendment should include:
  - The new investigator's CV and Form FDA 1572
  - The IRB approval letter from the new site
- FDA should be notified within 30 days of the investigator being added to the study.

Let’s Practice…

Please open the following website on your phone/tablet:

pollev.com/oraq

In which situation is it most important to give FDA time to respond to a protocol amendment before putting an IRB-approved protocol change in place?

Altered inclusion/exclusion criteria to improve recruitment

Revised schedule of events table for better clarity for study coordinator

Added additional laboratory analyses on blood samples already collected per protocol

Accelerated dose escalation plan

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

IND Maintenance – 2. Annual Reports

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report (2)
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Form FDA 1571: Box 11

- Due within 60 days of the anniversary of the IND effective date
  - Effective date: January 20, 2017
  - Report due: March 21, 2018

IND Maintenance: Annual Report Content

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator's Brochure
- Significant Protocol Modifications
- Foreign Marketing Developments
- Log of Outstanding Business

IND Maintenance – 3. Information Amendments

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*:
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s) 3

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Form FDA 1571: Box 11

IND Maintenance: 3. Information Amendments

- Any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports.
- Submit information amendments as needed but, if possible, not more than every 30 days.

IND Maintenance: 3. Information Amendments Content and Format

- Any information amendment submitted under an IND application is required to bear prominent identification of its contents.
  - *"Information Amendment: Pharmacology-Toxicology"*

- Information amendments should contain the following:
  - A statement of the nature and purpose of the amendment
  - An organized submission of the data in a format appropriate for scientific review

IND Maintenance: 4. IND Safety Reports

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

4

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Form FDA 1571: Box 11

Safety Reporting Requirements

- Submit IND safety reports for the following:
  - Serious and unexpected adverse events associated with the use of the study drug
  - Any clinically important increase in the rate of occurrence of a serious adverse event associated with the study drug
  - Findings from other studies that suggest a significant risk in humans
  - Findings from animal or *in vitro* testing that suggest a significant risk in humans

IND Safety Reports: Serious Adverse Drug Experience

- Any adverse drug experience occurring at any dose that results in any of the following outcomes:
  - death
  - a life-threatening adverse drug experience
  - inpatient hospitalization or prolongation of existing hospitalization
  - a persistent or significant disability/incapacity
  - or a congenital anomaly/birth defect.
- Other important medical events that require medical or surgical intervention to prevent one of the outcomes listed above.

IND Safety Reports: Unexpected Adverse Drug Experience

- Any event in which the specificity or severity of which is not consistent with the current investigator brochure (IB) or package insert
- Or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the current IND

IND Safety Reports: Adverse Event Associated with the Use of the Drug

- Any event in which there is a reasonable possibility that the drug caused the adverse event.
- "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.
- Sponsor must evaluate available evidence and make a judgement about the likelihood that the drug caused the AE.

Timelines for IND Safety Reports

Type of SAE	FDA Timeline
Unexpected fatal or life-threatening adverse drug experience	7 calendar days
Serious and unexpected adverse drug experience	15 calendar days
New findings that suggest significant risk to human subjects	15 calendar days
Follow-up reports	As relevant information is available (no later than 15 calendar days after sponsor receives info)

How to Prepare IND Safety Reports

- Submit via Form FDA 3500A (MedWatch) or in a narrative format.
- Include a brief narrative describing the adverse event and any other relevant information.
- Identify all safety reports previously submitted to the IND concerning similar adverse events.
- Submit IND safety reports to all of the sponsor's INDs under which the drug is being administered.

Let’s Practice…

Please open the following website on your phone/tablet:

pollev.com/oraq

Safety Reporting Scenario #1

- An investigational drug is administered via an intramuscular injection in a clinical study for patients with type I diabetes. The IB indicates the drug may cause peripheral numbness and a mild rash that resolves within a few days.
- A study subject reported peripheral numbness and a rash near the injection site within a few hours after the drug was administered.
- The following day, the subject reported to the emergency room with a fever, low blood pressure, and worsening rash. The patient was admitted to the hospital.
- Following treatment, the patient recovered from the event without sequelae and was withdrawn from the study. The investigator assessed the event as not life-threatening.

Is this event serious?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

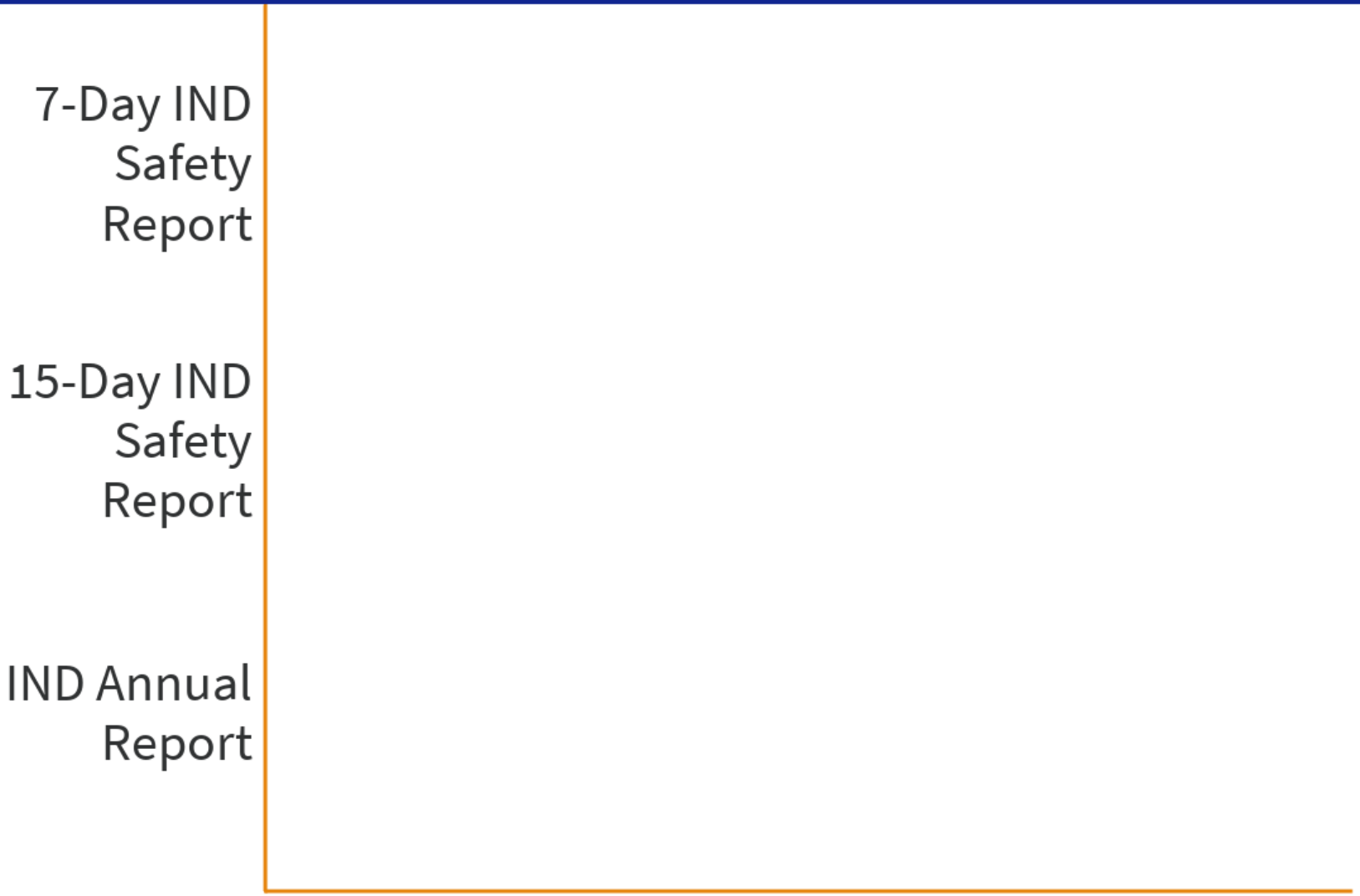
Is this event unexpected based on the information in the IB?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Is the event related to the study drug?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

How and when should this event be reported to the FDA?



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What would be the reporting timeline if the numbness became widespread and led to difficulty breathing, which became life threatening?

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Safety Reporting Scenario #2

- In a clinical study for asthma patients, an investigational drug is administered twice daily via a nebulizer for a period of 60 days. The IB lists throat irritation, chest pain, and dizziness as possible adverse reactions of the drug.
- After receiving the drug for two weeks, a study subject developed a mild case of pneumonia.
- The patient did not require hospitalization but received supportive care and made a full recovery.
- The investigator evaluated the event as not serious but possibly related to the use of the drug.

Is this event serious?

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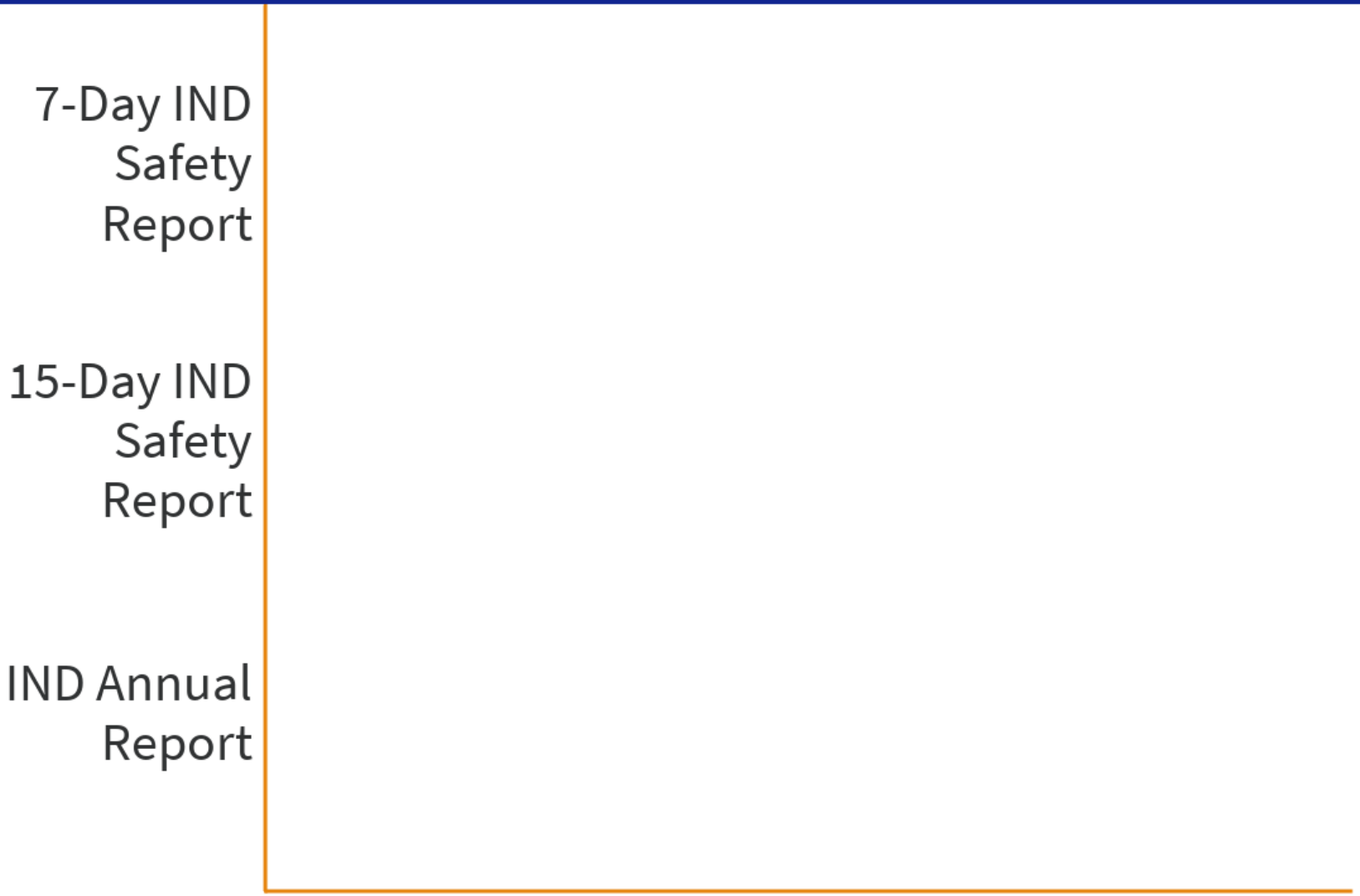
Is this event unexpected?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

Is this event related to the study drug?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

How and when should this event be reported to the FDA



Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

What would be the reporting timeline if the pneumonia worsened and became life threatening?

Start the presentation to see live content. Still no live content? Install the app or get help at **PollEv.com/app**

The End of an IND

- Withdrawal – Initiated by the sponsor
  - If withdrawn for safety reason, IRB must be notified
- Inactive Status – Initiated by sponsor or FDA
  - FDA may inactivate IND if no subjects are entered into clinical studies in 2 years or an investigation remains on clinical hold for >1 year (or sponsor can request this action)
  - A sponsor is not required to submit an annual report
  - An inactive IND can be reactivated via a protocol amendment
  - INDs inactive for > 5 years may be terminated by the FDA

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

The End of an IND

- Termination – Initiated by the FDA
  - Based on safety issues, deficiencies in the IND or in the conduct of an investigation
  - Sponsors usually have a chance to respond

Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- IND Maintenance
- Expanded Access

Expanded Access

- The use of investigational drugs outside of a clinical trial for treatment purposes
- Also known as “compassionate use” or “treatment use”
- Primary goal is <u>treatment</u> as opposed to <u>research</u>

Expanded Access Requirements

- FDA requirements for expanded access use:
  1. Patient(s) must have **serious** or **immediately life-threatening** disease/condition and no comparable or satisfactory alternative therapy
  2. Potential benefit justifies potential risks, and potential risks are not unreasonable in the context of disease/condition
  3. Access will not interfere with clinical investigations to support marketing approval of the expanded access use
- Must also have approval from drug company and IRB

Categories of Expanded Access

- Expanded access for **individual patients**, including emergency use (21 CFR 312.310)
- Expanded access for **intermediate-size patient populations** (21 CFR 312.315)
- Expanded access for **large patient populations,** i.e. Treatment IND/protocol (21 CFR 312.320)
- Any of these requests can be submitted as a new IND or as a new protocol under an existing IND

When can treatment begin?

- Expanded Access Protocol

Review Timelines	
Individual Patient (emergency)	Upon verbal authorization*
Individual Patient (non-emergency)	Once submitted to FDA
Intermediate-size Population	Once submitted to FDA
Treatment Protocol	30 days after submission

- Expanded Access IND

Review Timelines	
Individual Patient (emergency)	Upon verbal authorization*
Individual Patient (non-emergency)	30 days after submission
Intermediate-size Population	30 days after submission
Treatment IND	30 days after submission

* Written report needs to be sent to FDA within 15 working days of verbal authorization.

Individual Patient Expanded Access: Form 3926

- Streamlined alternative for submitting an IND for individual patient expanded access, including for emergency use
- Form 1571 seen as overly complicated and a poor fit for physicians requesting individual patient expanded access
- Letter of authorization still required
- Informed consent requirements apply

Individual Patient Expanded Access: Form 3926

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Individual Patient Expanded Access
Investigational New Drug Application (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0814
Expiration Date: April 30, 2019
See PRA Statement on last page.

1. Patient's Initials

2. Date of Submission *(mm/dd/yyyy)*

3.a. Initial Submission

☐ Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.

3.b. Follow-Up Submission

☐ Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.

Investigational Drug Name

Physician's IND Number

4. Clinical Information

Indication

Brief Clinical History *(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)*

5. Treatment Information

Investigational Drug Name

Name of the entity that will supply the drug *(generally the manufacturer)*

FDA Review Division *(if known)*

Treatment Plan *(Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)*

Individual Patient Expanded Access: Form 3926

- Box 10a: Request for waiver of additional IND requirements
- Box 10b: Request to obtain IRB chair concurrence as opposed to full IRB review and approval

10.a. Request for Authorization to Use Form FDA 3926

☑ I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

10.b. Request for Authorization to Use Alternative IRB Review Procedures

☑ I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

Individual Patient Expanded Access

Individual Patient Expanded Access Applications: Form FDA 3926

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2016
Updated October 2017
Procedural

Thank you!

Questions?
Please contact us at
ORAQ@duke.edu

ORAQ website:
http://medschool.duke.edu/ORAQ