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
Kristen Foss, PhD, RAC
Regulatory Affairs Scientist

PART 2: IND Preparation and Maintenance
Stephanie Pierce, PhD
Regulatory Affairs Scientist
Office of Regulatory Affairs and Quality

Bruce Burnett, PhD, RAC (US, EU)  
Director of Regulatory Affairs And Quality

Sarah Gemberling, PhD, RAC  
Regulatory Affairs Scientist

Stephanie Pierce, PhD  
Regulatory Affairs Scientist

Amanda Parrish, PhD, RAC  
Director of Regulatory Affairs and Quality

Erika Segear Johnson, PhD, RAC  
Associate Director, Regulatory Affairs

Daniel Tonkin, PhD, RAC  
Regulatory Affairs Scientist

Jessica Chapman, PhD  
Regulatory Affairs Scientist

Kristen Foss, PhD, RAC  
Regulatory Affairs Scientist

Kelly Lindblom, PhD  
Regulatory Affairs Scientist

Dan Ozaki, M.P.H.  
Manager Quality Assurance

Audrey Perry  
Regulatory Document Specialist

Susan Nagorski  
Staff Assistant  
Training Program Coordinator

Not Pictured: Leiza Capiz, Patrick Killela, Shauna Anderson
How to Reach Us…

- **Website:** [http://medschool.duke.edu/ORAQ](http://medschool.duke.edu/ORAQ)

- **Email:** ORAQ@dm.duke.edu
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

- Mission is to provide researchers with the tools and resources necessary to find the successful pathway from discovery to clinical implementation of new and innovative drugs, biologics, and medical devices.

- Website: www.regardd.org
ReGARDD Regulatory Contacts

- **NC TraCS:**
  - **Amanda Wood, BS, CCRP** – IND/IDE Program Coordinator, amanda_wood@med.unc.edu, (919) 843-9445
  - **Marie Rape, RN, BSN, CCRC** – Associate Director, TraCS Regulatory Service, marie_rape@med.unc.edu, (919) 966-6844
  - **Diana Severynse-Stevens, PhD** – Director of Drug Development in Global Health Technologies, RTI International, dianastevens@rti.org, (919) 541-5903
    - [https://tracs.unc.edu/index.php/services/regulatory](https://tracs.unc.edu/index.php/services/regulatory)

- **Wake Forest:**
  - **Heather Hatcher, PhD** – IND/IDE Navigator, hhatcher@wakehealth.edu, (336) 716-3993
    - [https://ctsi.wakehealth.edu/regulatory-guidance](https://ctsi.wakehealth.edu/regulatory-guidance)
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
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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?

- A new drug or biological drug that is used in a clinical investigation (21 CFR 312.3)
  - 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 request to FDA for authorization to administer an investigational drug (or biologic) to humans.

- Such authorization must be secured prior to interstate shipment of any new drug that is not lawfully marketed in the US as a drug for the purpose of conducting clinical investigations.

- Not all clinical investigations using investigational drugs require an IND.
  - May be **exempt** from requiring an IND if exemption criteria are met.
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Lawfully Marketed Drugs

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

- However, it is important to note there are some drug products/active ingredients that 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.
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.
The Test Article can either be:

- Not legally marketed in the US as a drug, which makes it an Investigational Drug and requires an IND.
- Legally marketed in the US as a drug, which makes it a Lawfully Marketed Drug.

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.

Drugs@FDA: FDA Approved Drug Products

Search by Drug Name, Active Ingredient, or Application Number

Pembrolizumab

Browse by Drug Name

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9

Drug Approval Reports by Month

About Drugs@FDA | FAQ | Glossary | Contact Us
Drugs@FDA: FDA Approved Drug Products

Biologic License Application (BLA): 125514
Company: MERCK SHARP DOHME
Drug Name(s):
- KEYTRUDA (PEMBROLIZUMAB)

Medication Guide

- Products on BLA 125514
- Approval Date(s) and History, Letters, Labels, Reviews for BLA 125514
- Labels for BLA 125514
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage (1.1) 12/2015
Indications and Usage (1.2) 10/2016
Indications and Usage (1.3) 08/2016
Dosage and Administration (2.1, 2.3) 10/2016
Dosage and Administration (2.4) 08/2016
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7) 10/2016

INDICATIONS AND USAGE

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:
- patients with unresectable or metastatic melanoma. (1.1)
- patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC. (1.2)
- patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2)
- patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.3)

DOSAGE AND ADMINISTRATION

- Melanoma: 2 mg/kg every 3 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks. (2.3)
- HNSCC: 200 mg every 3 weeks. (2.4)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Embryofetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (reported in ≥20% of patients) were:
- fatigue
- pruritus
- diarrhea
- decreased appetite
- rash
- dyspnea
- constipation
- nausea

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2016
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 (including drug combinations)
  - Off-label use is common and allowed in the practice of medicine and often is the standard of care.
* Assuming no marketing application or change in advertising is planned
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FDA Regulations and Guidance on IND Exemptions

- 21 CFR Part 312.2(b) – 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](http://tinyurl.com/nqkbkd)

  - [http://tinyurl.com/2g7z7kv](http://tinyurl.com/2g7z7kv)
FDA Regulations and Guidance on IND Exemptions

- When is an IND not needed for investigations involving drugs?
  
  - Some clinical studies using lawfully marketed drugs
  
  - Some studies using in vitro diagnostic biological products (blood grouping serum, reagent red blood cells, anti-human globulin)
  
  - Studies using drugs only in vitro or in laboratory research animals
  
  - Some clinical studies using radioactive or cold isotopes
  
  - Some clinical bioavailability or bioequivalence studies
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))
FDA Regulations and Guidance on IND Exemptions

- Five criteria must all be met if a study can be considered exempt from requiring an IND

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.
FDA Regulations and Guidance on IND Exemptions

- Evaluate risks associated with the changes in:
  - Patient Population
  - Route of Administration
  - Dose
  - Drug Combinations
  - Drug Modification
Change in the 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
Route of Administration…

“For example, there could be a significant increase in risk if marketed drug for oral administration is converted to a dosage form that is to be administered by injection or intravenous, intrathecal, or inhalation route”

- [http://tinyurl.com/2g7z7kv](http://tinyurl.com/2g7z7kv)
Dosage...

- “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](http://tinyurl.com/2g7z7kv)
Drug Combinations. . .

- Remember – the use of 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.”

- [http://tinyurl.com/nqkbkd](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](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 FDA to get an IND Exemption?

YES

-or-

NO
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.”

- This statement is found in both FDA Guidance documents on IND Exemptions.
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 risk 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
    - Forms 1571, 1572, 3674
    - Letters of Authorization (if applicable)
    - Reprints from the literature (2-3 references are acceptable)
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)
Informal Process for Obtaining Exemption

- Call 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.
- You should receive a decision within two weeks.
- Response may be verbal or written from FDA.
## How to Determine Appropriate FDA Review Division

<table>
<thead>
<tr>
<th>Center for Drug Evaluation and Research (CDER)</th>
<th>Center for Biologics Evaluation and Research (CBER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs and some biologics (e.g., protein therapeutics, monoclonal abs)</td>
<td>Biologics</td>
</tr>
<tr>
<td>Small molecules</td>
<td>Large molecules</td>
</tr>
<tr>
<td>Generally synthetic</td>
<td>Derived from living organisms</td>
</tr>
<tr>
<td>Analytically simple</td>
<td>Analytically complex (e.g., gene therapy; vaccines; cell, blood and tissue products)</td>
</tr>
</tbody>
</table>
How to Determine Appropriate FDA Review Division

- For studies reviewed by CDER, select review division based on the indication/therapeutic area in your study.
  - CDER website has descriptions of therapeutic areas reviewed by each review divisions within the Office of New Drugs.

- CBER has three product offices.
  - Office of Blood Research and Review
  - Office of Vaccines Research and Review
  - Office of Tissues and Advanced Therapies

CDER: [https://tinyurl.com/lyuojbl](https://tinyurl.com/lyuojbl)   CBER: [http://tinyurl.com/nvcb7xz](http://tinyurl.com/nvcb7xz)
How to Determine Appropriate FDA Review Division

Office of Drug Evaluation I - Division of Cardiovascular and Renal Products (DCaRP)

The Division of Cardiovascular and Renal Products (DCaRP) regulates and reviews Investigational New Drug (IND) applications and marketing applications for drug and biologic products for the treatment of cardiovascular conditions and diseases, such as acute coronary syndrome, congestive heart failure, hypertension, peripheral arterial disease, pulmonary hypertension, and cardiac arrhythmias, as well as for drug and biologic products for the treatment of kidney diseases and conditions, such as acute and chronic renal failure, end-stage renal disease, lupus nephritis, nephrotic syndrome, and dialysate products used in hemodialysis and peritoneal dialysis.

- **Director:** Norman Stockbridge, M.D., Ph.D.
- **Deputy Director:** Stephen Grant, M.D.
- **Deputy Director for Safety:** Mary Ross Southworth, Pharm.D.
- **Chief, Project Management Staff:** Ed Fromm, R.Ph.
- **Safety Regulatory Project Manager:** Lori Wachter, R.N., B.S.N.
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Specific Issues

- Endogenous Compounds
- Live Organisms
- Dietary Supplements
- Tobacco Products
- 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 (treat, diagnose, cure, mitigate. . . )

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

- A tobacco product is any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product.
  - Include electronic nicotine delivery systems (e-cigarettes)
Can a Tobacco Product Study Require an IND?

- A tobacco product will be regulated as a drug under 2 circumstances:

  1. The product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, or
     - Examples include use in the cure/treatment of nicotine addiction (e.g., smoking cessation), relapse prevention, or relief of nicotine withdrawal symptoms.
  2. The product is intended to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.
     - Examples of structure/function claims commonly and legally claimed from to March 21, 2000 include satisfaction (including of addiction), pleasure, enjoyment, and refreshment.

https://tinyurl.com/yccgrpq9
Tobacco Products

- Tobacco product studies that do not require an IND may submit an Investigational Tobacco Product Application (ITP).
- Reviewed by FDA’s Center for Tobacco Products

Examples:
- Assessing smoker preference for cigarettes of varying nicotine levels
Research with Noncommercial Intent

- The IND regulations apply to investigations regardless if the intent of the study is commercial or non-commercial.
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An investigator plans to study an anti-flu drug to treat flu symptoms in children.

The drug INFLUN is currently approved in the US in the pediatric setting, given as an injection (IM).

In the proposed study, INFLUN will be administered via intranasal drops.

A compounding pharmacy will receive the INFLUN vials and create the nasal drops for use in this study.
Scenario #1

- Can this study be considered for an IND exemption (i.e., is the study using a lawfully marketed drug)?

- What is off label in this case?

- What kind of documentation would you provide to the IRB and/or FDA?
Scenario #2

- An investigator plans to conduct a trial to assess the effectiveness of Folic Acid for the treatment of depression.

- Folic Acid manufactured by Company X is legally marketed as a drug to treat osteoporosis.

- Folic Acid manufactured by Company Y is legally marketed as a dietary supplement.

- The investigator is using Folic Acid capsules from Company Y for the study.
Scenario #2

Can this study be considered for an IND exemption?

YES

-or-

NO
An investigator plans to study the effectiveness of a combination of three FDA approved drugs (Drugs A, B, & C) in colon cancer patients.

Drug A and Drug B are approved to be given in combination for the treatment of colon cancer.

Drug C is FDA approved for breast cancer.

The investigator is planning this study based on a previously published study assessing the effect of the therapeutic cocktail of Drugs A, B, & C in breast cancer patients.
Scenario #3

- Can this study be considered for an IND exemption?

- How many things are off-label in this example?

- What kind of documentation would you provide to the IRB and/or FDA in support of the IND exemption criteria?
An investigator plans to conduct a trial to study structural and functional changes that occur in the eye after exposure to ragweed extract.

The ragweed extract is an FDA approved drug for use in the skin prick test to diagnose allergies.
Scenario #4

- Can this study be considered for an IND exemption?
- What is off-label in this case?
- What kind of documentation would you provide to the IRB and/or FDA?
Questions on IND Exemptions?
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Assuming no marketing application or change in advertising is planned

Test Article

Not legally marketed in the US as a drug

Investigational Drug

Requires an IND

Pre-IND Meeting?

Legally marketed in the US as a drug

Lawfully Marketed Drug

Need an IND?

On-label

IND not required*

It depends!

Off-label
Pre-IND Meetings

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

1. **Submit Pre-IND meeting request to appropriate FDA Division**
2. **Date, time, location, and list of FDA participants provided to sponsor**
3. **FDA determines whether to grant meeting. If denied, reason provided**
4. **Submit Pre-meeting briefing package to FDA**
   - (1 month before meeting)
5. **FDA sends written responses to questions**
   - (24-48 hours before meeting)
6. **Meeting held and minutes distributed**
   - (within 60 days from FDA receipt of request)
Before Making the Meeting Request

- Identify specific, well-phrased questions
- Decide if you want to request a face-to-face meeting, teleconference, or written responses
- Begin preparing the meeting Briefing Package
  - Must submit at least 1 month before meeting
- Identify appropriate FDA review division based on therapeutic area that will be studied in your IND
Meeting Request Letter

- Product information and proposed indication
- Specific objectives and expected outcomes
- Proposed agenda
- Draft list of questions
- Sponsor attendees and FDA staff requested to attend
- Approx. date for submitting the briefing package
- Suggested meeting dates and times

- Template available on ORAQ website: http://tinyurl.com/he64vq5
Meeting Briefing Package

- Product information and proposed indication
- Brief statement summarizing the purpose of the meeting
- Proposed agenda
- Final list of questions
- **Provide information relevant to the discussion topics**
  - Manufacturing information
  - Preclinical study plans
  - Clinical study protocol

- Template available on ORAQ website: [http://tinyurl.com/he64vq5](http://tinyurl.com/he64vq5)
FDA Pre-Meeting Response

- Preliminary written responses from FDA internal meeting will be sent to the applicant ~1-2 days before the meeting.
- Review responses thoroughly and identify questions and issues for discussion at the meeting.
- Decide to proceed with meeting or cancel meeting if responses are acceptable.
Pre-IND Meeting Day

- 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 their minutes
- FDA responsible for providing the official minutes within 30 days
Pre-IND Question #1

In which of these situations can you request a Pre-IND meeting with FDA?

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

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

C) You want to know if the dosing schedule in your proposed clinical protocol is acceptable to FDA.

D) All of the above
Pre-IND Question #1

In which of these situations can you request a Pre-IND meeting with FDA?

A) You want to know if your proposed manufacturing plan and release specifications for your product are acceptable to FDA.
B) You want to know if your proposed nonclinical studies will be adequate to support your planned clinical study.
C) You want to know if the dosing schedule in your proposed clinical protocol is acceptable to FDA.
D) All of the above
Pre-IND Question #2

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

A) After you have conducted your preclinical safety studies
B) Before you have made any major manufacturing or preclinical decisions
C) Before you have made any major manufacturing or preclinical decisions and you have a clinical protocol/protocol synopsis
D) One month before your grant application is due
Pre-IND Question #2

- When is the **best** time to request a Pre-IND meeting?
  
  A) After you have conducted your preclinical safety studies
  
  B) Before you have made any major manufacturing or preclinical decisions
  
  C) Before you have made any major manufacturing or preclinical decisions and you have a clinical protocol/protocol synopsis
  
  D) One month before your grant application is due
Questions on Pre-IND Meetings?
It’s Time For A Break
The Investigational New Drug (IND) Workshop

PART 2: IND Preparation and Maintenance

Stephanie Pierce, PhD

Regulatory Affairs Scientist
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
- CTD and Electronic Submissions
- IND Maintenance
- Financial Disclosure
- 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, and under whose immediate direction a drug is administered or dispensed.
Definitions: Types of INDs

- Commercial IND
  - Ultimate goal is to obtain marketing approval
- Sponsor-Investigator IND (Investigator-Initiated IND)
  - Primarily research-driven
  - Goal is publication
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
- CTD and Electronic Submissions
- IND Maintenance
- Financial Disclosure
- 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
7. Chemistry, Manufacturing and Control Data (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 Content for Sponsor-Investigator

It is best practice to ‘follow the script’ and maintain these standard headings…

Why??
Original INDs Received by CDER

Link: https://tinyurl.com/ydah54xe
Is there a drug label or LOA to support your IND?

- FDA-Approved Drug – off label use
  - Use drug label to support IND
    - https://www.accessdata.fda.gov/scripts/cder/daf/

- Unapproved Drug – from company
  - Letter of Authorization (LOA) to support IND

- Unapproved Drug – you control manufacturing
  - Sponsor is responsible for all information
What is a Letter of Authorization?

- This is a letter from a sponsor (company) stating that confidential information from their submission (IND, IDE or DMF) can be used in support of your submission.
- Thus, the FDA has “permission” to reference the named materials in support of your IND.
- Get copies of the letters to include in your submission.
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. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover sheet
12. Form 3674

Can refer to drug labeling or to letter of authorization (cross reference letter) for Sections 5 and 7-9
Do you need a Letter of Authorization?

- For use of an investigational (not lawfully marketed) drug from an outside source?
  - Probably

- For use of a lawfully marketed drug?
  - Probably Not
Scenario 1

- Drug TCZ is approved for use in rheumatoid arthritis.
- An investigator at UNC would like to conduct a clinical trial of TCZ in type 1 diabetes.
- The drug manufacturer will be providing the investigational product from their commercial supply.
- FDA required an IND.
- Will a letter of authorization be required?
  • ?
Scenario 2

- Drug TCZ is approved for use in rheumatoid arthritis.
- An investigator at Duke University would like to conduct a clinical trial of TCZ in type 1 diabetes.
- The drug manufacturer will be providing the product from their investigational supply.
- FDA required an IND.
- Will a letter of authorization be required for the IND?
  - ?
IND Format & 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
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information
11. Biosimilar User Fee Cover Sheet
12. Form 3674
Section 6 - Protocols

- Can submit more than one
- Things that go in this section... 
  - Protocol (Section 6.1)
  - Informed Consent (Section 6.2)
  - CVs for principal investigator(s) and Form FDA 1572(s) (Section 6.3)
    - Agreement between investigator and sponsor
IND Format and Content

1. Form 1571 (cover sheet)
2. Table of Contents
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6. Protocols
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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”
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
- Full panel of animal studies are required before submission of marketing application
  - Will need to perform IND enabling toxicity studies: GLP Safety Studies
- If product has already been in humans before, pharm/tox studies may not be necessary*
IND Format and Content

1. Form 1571 (cover sheet)
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6. Protocols
7. Chemistry, Manufacturing and Control Data (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 not be any previous human experience if drug is completely new
- May be able to refer to published literature
  - Same indication
  - Different indication
  - Different route of administration
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
- CTD and Electronic Submissions
- IND Maintenance
- Financial Disclosure
- Expanded Access
Forms

- 1571 (Section 1)
  - Agreement between FDA and Sponsor
- 1572 (Section 6.3)
  - Agreement between Investigator and Sponsor
- 3674 (Section 12)
  - Certification of registration at [http://clinicaltrials.gov](http://clinicaltrials.gov)

Make sure you have the right version!

[http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm](http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm)
Key components of the Form FDA 1571

<table>
<thead>
<tr>
<th><strong>1. Name of Sponsor</strong></th>
<th><strong>2. Date of Submission (mm/dd/yyyy)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. Sponsor Address</strong></th>
<th><strong>4. Telephone Number (Include country code if applicable and area code)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address 1 (Street address, P.O. box, company name c/o)</td>
<td></td>
</tr>
<tr>
<td>Address 2 (Apartment, suite, unit, building, floor, etc.)</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>State/Province/Region</td>
</tr>
<tr>
<td>Country</td>
<td>ZIP or Postal Code</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)</strong></th>
<th><strong>6. IND Number (If previously assigned)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7. (Proposed) Indication for Use</strong></th>
<th><strong>Is this indication for a rare disease (prevalence &lt;200,000 in U.S.)?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Does this product have an FDA Orphan Designation for this indication?</strong></th>
<th><strong>If yes, provide the Orphan Designation number for this indication:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes □ No</td>
<td></td>
</tr>
</tbody>
</table>

**Continuation Page for #5**

**Continuation Page for #7**
Key components of the Form FDA 1572

<table>
<thead>
<tr>
<th>Key Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractual agreement between an Investigator and the Sponsor</td>
<td>Investigator agrees to conduct investigation in accordance with all applicable regulatory requirements.</td>
</tr>
<tr>
<td>Name of person responsible for conducting the investigation and their credentials</td>
<td>Should submit when you have information to update.</td>
</tr>
<tr>
<td>Listing of the facilities and labs that are participating in the investigation</td>
<td>Must submit a 1572 for each site (if it’s a multi-site study).</td>
</tr>
<tr>
<td>Listing of the IRB responsible for reviewing/approving study</td>
<td></td>
</tr>
<tr>
<td>Listing of additional Sub-Investigators</td>
<td></td>
</tr>
</tbody>
</table>

**Example of Form FDA 1572**

**1. NAME AND ADDRESS OF INVESTIGATOR**

<table>
<thead>
<tr>
<th>Name of Clinical Investigator</th>
<th>Address 1</th>
<th>Address 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED**

- Curriculum Vitae
- Other Statement of Qualifications

**3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED**

<table>
<thead>
<tr>
<th>Name of Medical School, Hospital, or Other Research Facility</th>
<th>Address 1</th>
<th>Address 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY**

<table>
<thead>
<tr>
<th>Name of Clinical Laboratory Facilities</th>
<th>Address 1</th>
<th>Address 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Key components of the Form FDA 3674


## Certification of Compliance

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

### SPONSOR / APPLICANT / SUBMITTER INFORMATION

<table>
<thead>
<tr>
<th>1. Name of Sponsor/Applicant/Submitter</th>
<th>2. Date of the Application/Submission Which This Certification Accompanies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Address</th>
<th>4. Telephone and Fax Numbers (Include country code if applicable and area code)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address 1 (Street address, P.O. box, company name c/o)</td>
<td>(Tel):</td>
</tr>
<tr>
<td>Address 2 (Apartment, suite, unit, building, floor, etc.)</td>
<td>(Fax):</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>State/Province/Region</th>
<th>Country</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)

For **Devices:** Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
# Form FDA 3674

## Certification Statement / Information

<table>
<thead>
<tr>
<th>9. CHECK ONLY ONE OF THE FOLLOWING BOXES (See instructions for additional information and explanation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.</td>
</tr>
<tr>
<td>□ B. I certify that the requirements of 42 U.S.C. § 282(i), Section 402(i) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.</td>
</tr>
<tr>
<td>□ C. I certify that the requirements of 42 U.S.C. § 282(i), Section 402(i) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.</td>
</tr>
</tbody>
</table>


NCT Number(s): ____________________  ____________________  ____________________  ____________________  ____________________  ____________________
Which clinical trials must be registered?

“Applicable Clinical Trials” if it meets all four criteria:

- Interventional studies (drugs, biologics, or devices)
- Phase 2 – 4 (not Phase 1)
- US FDA jurisdiction (e.g., IND/IDE or US site)
- Studies initiated after September 27, 2007, or still ongoing as of December 26, 2007
Other reasons to register your trial

- For Applicable Clinical Trials – Ensure compliance with Section 801 of the FDAAA
- 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
# Deadline(s) for Registering Trials

<table>
<thead>
<tr>
<th>Reason for registering</th>
<th>Registration timeline</th>
<th>Update</th>
<th>Have to report results?</th>
<th>Results required</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT (FDAAA)</td>
<td>No later than 21 days after enrolling first patient</td>
<td>12 months</td>
<td>Yes</td>
<td>Within 12 months of primary completion date</td>
</tr>
<tr>
<td>To publish (ICMJE)</td>
<td>Prior to enrollment</td>
<td>6 months</td>
<td>Encouraged</td>
<td></td>
</tr>
<tr>
<td>Funding requirement (NIH)</td>
<td>No later than 21 days after enrolling first patient</td>
<td>12 months</td>
<td>Yes</td>
<td>Within 12 months of primary completion date</td>
</tr>
</tbody>
</table>

**Your institutional policies may be different than this table, please check!!**
IND Content for Sponsor-Investigator

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. Prev Human Exp
10. Additional Info
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance (Form 3674)
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
- CTD and Electronic Submissions
- IND Maintenance
- Financial Disclosure
- Expanded Access
Filing the IND

- Cover Letter
- 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
Cover Letter

Month xx, 200x

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn. Jane Doe, MD

RE: Initial Investigational New Drug Application
Serial 0000

Dear Dr. Doe:

Please find enclosed three copies of this initial application for a Sponsor-Investigator IND. The sponsor for this IND will be John Duke, MD, Duke University.

The initial study protocol for use under this IND is entitled "A Phase I Trial of Deoxyribodismutase in Humans". The Principal Investigator for this study will be Josephina Duke, MD.

If there are any questions regarding this submission, please contact myself or Jacob Durham, at (919) 68x-xxxx or at jdurham@notes.duke.edu. Mr. Durham can act on my behalf on any issue relating to this IND.

Sincerely,

John Duke, MD
Duke University Medical Center
Address, Box xxxx
Durham, NC 277xx
(919) 68x-xxxx phone
(919) 68x-xxxx fax
jduke@duke.edu

Date of submission
Or CBER
Submissions go to the Central Doc Room
Address to the Division Director for Initial IND
Include the type of submission and serial number in the subject line
Summarize the content of your submission
List alternate contact person

May ask questions or request comments from the FDA
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 important information such as assigned review division, IND number, division contact, and official FDA date of receipt
- The official date of receipt starts a 30 day clock for the FDA to review the IND.
  - Multidisciplinary review team - Includes 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 and/or the alternate contact 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
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- Expanded Access
Electronic Submissions to FDA - eCTD

- CTD – Common Technical Document
- Common format developed by International Conference on Harmonisation to eliminate need for reformatting of applications to different countries
- Commercial INDs must be submitted electronically in May 2018.
IND Format & Content - CTD

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

- Module 2 – Summary

- Module 3 – Quality (CMC)

- Module 4 – Safety (Pharm/Tox)

- Module 5 – Efficacy (Clinical)
Outline for Part 2: Preparation and Maintenance of an IND

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Caring for and Feeding Your IND
IND Maintenance

Form FDA 1571: Box 11

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

- Four kinds...

1. New Protocol
2. Change in Protocol
3. New Investigator
4. PMR/PMC Protocol

From Form FDA 1571: Box 11

Protocol Amendment(s)
- New Protocol
- Change in Protocol
- New Investigator
- PMR/PMC Protocol
What Is a Protocol Amendment?

- A protocol amendment is an IND submission that contains new or updated information concerning the clinical study protocol(s).

- Amend the IND to ensure that the clinical investigation is conducted in accordance with the protocol(s).
Implementing Protocol Amendments

- Submit protocol amendments to FDA **before** implementation of changes.
- Protocol amendments may be implemented after submission to FDA and following IRB approval.
- Submit a request for comment and include specific questions, if applicable.
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.
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.
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.
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.
IND Maintenance

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

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

<table>
<thead>
<tr>
<th>Protocol Amendment(s)</th>
<th>Information Amendment(s)</th>
<th>Request for</th>
<th>IND Safety Report(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] New Protocol</td>
<td>[ ] Chemistry/Microbiology</td>
<td>[ ] Meeting</td>
<td>[ ] Initial Written Report</td>
</tr>
<tr>
<td>[ ] Change in Protocol</td>
<td>[ ] Pharmacology/Toxicology</td>
<td>[ ] Proprietary Name Review</td>
<td>[ ] Follow-up to a Written Report</td>
</tr>
<tr>
<td>[ ] New Investigator</td>
<td>[ ] Clinical</td>
<td>[ ] Special Protocol Assessment</td>
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<tr>
<td>[ ] PMR/PMC Protocol</td>
<td>[ ] Statistics</td>
<td>[ ] Formal Dispute Resolution</td>
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<tr>
<td></td>
<td>[ ] Clinical Pharmacology</td>
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</tbody>
</table>
Information Amendments

- Five kinds...
  - Select review discipline to which submission applies

1. Chemistry/Micro
2. Pharm/Tox
3. Clinical
4. Statistics
5. Clinical Pharmacology

From Form FDA 1571: Box 11

Information Amendment(s)
- Chemistry/Microbiology
- Pharmacology/Toxicology
- Clinical
- Statistics
- Clinical Pharmacology
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.
Content and Format Requirements

- 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

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

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

### Protocol Amendment(s)

<table>
<thead>
<tr>
<th>Amendment</th>
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<tbody>
<tr>
<td>New Protocol</td>
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<tr>
<td>Change in Protocol</td>
</tr>
<tr>
<td>New Investigator</td>
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<tr>
<td>PMR/PMC Protocol</td>
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</table>

### Information Amendment(s)

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### 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 Safety Reports

- Two kinds. . .
  1. Initial Written Report
  2. Follow-Up to a Written Report

From 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

<table>
<thead>
<tr>
<th>Type of SAE</th>
<th>FDA Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected fatal or life-threatening adverse drug experience</td>
<td>7 calendar days</td>
</tr>
<tr>
<td>Serious and unexpected adverse drug experience</td>
<td>15 calendar days</td>
</tr>
<tr>
<td>New findings that suggest significant risk to human subjects</td>
<td>15 calendar days</td>
</tr>
<tr>
<td>Follow-up reports</td>
<td>As relevant information is available (no later than 15 calendar days after sponsor receives info)</td>
</tr>
</tbody>
</table>
How to Prepare IND Safety Reports

- Submit via [Form FDA 3500A (MedWatch)] or in a narrative format or CIOMS form.
- 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.
Case Studies: IND Safety Reports
Scenario 1

- A study coordinator reported that a 38-year-old female patient developed vestibular toxicity manifested by nystagmus, nausea, and vomiting as well as myasthenia and memory loss following overdose of an investigational product NOPAIN while enrolled in a Phase III study. The overdose was estimated as 100x the prescribed dose to be received in a 24-hour time frame.

- The patient received supportive care and did not require hospitalization.

- The investigator did not characterize the event as life-threatening but evaluated the event as possibly related to the overdose. The patient recovered from the event without sequelae and was withdrawn from the study.
Scenario 1

From the Investigator’s Brochure for NOPAIN:

- “The investigational product is a new type of calcium channel blocker, which is considered by the sponsor to be a revolutionary way to treat neurological pain. The NOPAIN Investigators’ Brochure describes the reported events of vestibular toxicity, myasthenia, and memory loss as being possibly related to the use of NOPAIN at higher doses. The sponsor is in the processing of compiling information for the NDA submission. Phase III trials are ongoing in one country in the EU and in the US.”
Scenario 1

- Is this case Serious?
- Is this case Expected or Unexpected?
- Is this event Study Related?
- How and when would you report this event to the FDA?
Scenario 1

- What would be the FDA reporting timeline if the subject also experienced an unexpected AE following the overdose of NOPAIN, such as a seizure, that resulted in inpatient hospitalization but it was not life-threatening?

- What would be the FDA reporting timeline if the investigator determined that the seizure was unexpected and life-threatening?
Scenario 2

- A female patient was really tired and ingested 40 mg of investigational “SleepMore” to try and get some rest.
- She was admitted to the ICU with severe bradycardia (bpm 20-40) and a prolonged QT interval.
- The patient was treated with atropine and the bradycardia resolved.
- The QT interval normalized two weeks later.
- The reporting physician assessed the event as life-threatening and possibly related the SleepMore.
Scenario 2

From the Investigator’s Brochure for SleepMore:

- The SleepMore IB states that conduction abnormalities have been reported, including bradycardia and a prolonged QT interval, which have resolved quickly upon discontinuation of the product.

- The case was not submitted as an IND Safety Report; however, in your monthly review, questions arose as to whether this was of greater severity than is described in the IB.
Scenario 2

- Is this case Serious?
- Is this case Expected or Unexpected?
- Is this event Study Related?
- How and when would you report this event to the FDA?
IND Maintenance

Form FDA 1571: Box 11

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

- Due within 60 days of the anniversary of the IND effective date

Example:
- Effective date: January 20, 2017
- Report due: March 21, 2018

From Form FDA 1571: Box 11
Content for an Annual Report

- Individual Study Information
  - Basic Study Information
  - Enrollment Data
  - Results
Content for an Annual Report

- Individual Study Information
- Summary Information
  - Most frequent and serious adverse events
  - Summary of all IND safety reports
  - Subjects who died during participation
  - Subjects who dropped out due to an adverse event
  - New information regarding the action of the drug
  - List of preclinical studies
  - Summary of CMC changes
Content for an Annual Report

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
Content for an Annual Report

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator’s Brochure
Content for an Annual Report

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator’s Brochure
- Significant Protocol Updates
Content for an Annual Report

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator’s Brochure
- Significant Protocol Updates
- Update on Foreign Marketing Developments
Content for an Annual Report

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator’s Brochure
- Significant Protocol Updates
- Update on Foreign Marketing Developments
- Log of Outstanding Business
Annual Reports for Multiple Protocols Under One IND

- Information must be provided for each active protocol.
- Duplicate the same sections below for each protocol:
  - Individual Study Information
  - Summary Information
  - Update to General Investigational Plan
  - Update to Investigator’s Brochure
  - Significant Protocol Updates
  - Update on Foreign Marketing Developments
  - Log of Outstanding Business
The End of an IND

- **Withdrawal** - Initiated by the sponsor
  - If withdrawn for safety reason, IRB must be notified
- **Inactive Status** – Initiated by FDA or sponsor
  - 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
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
- CTD and Electronic Submissions
- IND Maintenance
- Financial Disclosure
- Expanded Access
Financial Disclosure

- Eliminating bias and preserving the integrity of the data in a marketing application
- 21 CFR Part 54 - Applicants who submit a marketing application are required to submit information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation
Financial Disclosure

- Maintain complete and accurate records concerning investigator financial interests:
  - Any financial arrangement where the value of the compensation could be influenced by the outcome of the study
  - Any significant payments of other sorts
  - Any proprietary interest in the tested product
  - Any significant equity interest in any sponsor
Financial Disclosure Forms

- Sponsor’s responsibility to collect financial disclosure information from the investigator
- Clinical investigators must provide financial information to the sponsor
  - Must update this information if changes occur during the study and for one year following the completion of the study
- These forms are never submitted to INDs (only with marketing applications)
Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
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Expanded Access

Expanded Access IND

- Mechanism that can be used to gain “access” to investigational drugs for treatment use under an investigational new drug application (IND).
  
  (treatment use, compassionate use)

- May also be used for access to an approved drug when availability has been limited by a risk evaluation and mitigation strategy (REMS).

- Primary goal is treatment as opposed to research
Expanded Access Regulations

- Expanded Access
  - Individual patients, including emergencies
  - Intermediate-sized patient populations
  - Large populations under a treatment IND/protocol
Expanded Access Regulations

- 312.305 – Requirements for all expanded access uses
  - Patient(s) must have serious or immediately life-threatening disease/condition and no comparable or satisfactory alternative therapy.
    - Immediately life-threatening means that there is a reasonable likelihood that death will occur within a matter of months or that premature death is likely without treatment.
    - Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.
  - Potential benefit justifies potential risks, and potential risks are not unreasonable in the context of disease/condition
  - Access will not interfere with clinical investigations to support marketing approval of the expanded access use
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
Procedural
Individual Patient Expanded Access: Form 3926

- Form 1571 seen as overly complicated and a poor fit for physicians submitting an individual expanded access new IND
  - 1571 designed for commercial applications
- Form 3926 created to simplify form and reduce attachments and time burden
- Can be used for emergency use
- Letter of authorization still required
**Individual Patient Expanded Access: Form 3926**

<table>
<thead>
<tr>
<th><strong>DEPARTMENT OF HEALTH AND HUMAN SERVICES</strong></th>
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<tbody>
<tr>
<td><strong>Food and Drug Administration</strong></td>
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</tr>
<tr>
<td><strong>Investigational New Drug Application (IND)</strong></td>
</tr>
<tr>
<td><em>(Title 21, Code of Federal Regulations (CFR) Part 312)</em></td>
</tr>
</tbody>
</table>

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.

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)
IND Format & Content – Expanded Access

- Individual-patient IND (30 day review, AR) [http://tinyurl.com/muzd2c](http://tinyurl.com/muzd2c)
  - Cover letter and cover sheet
  - Patient History
  - Proposed Treatment Plan
  - CMC & Pharm/Tox (LOA)
  - Informed Consent
  - Investigator Qualification Info (1572/CV)

- Emergency Single-Patient IND (EIND) [http://tinyurl.com/k2tskkkh](http://tinyurl.com/k2tskkkh)
  - Checklist and eligibility tool available on FDA website

- Intermediate Size Population IND

- Treatment IND
Questions?

- Check out our website: [http://medschool.duke.edu/ORAQ](http://medschool.duke.edu/ORAQ)
- Or contact the Office of Regulatory Affairs and Quality (ORAQ) by emailing: [ORAQ@dm.duke.edu](mailto:ORAQ@dm.duke.edu)