FDA-regulated Research: Myth vs. Reality

Part 1: Drugs

Office of Responsible Research Practices
September 10, 2020
Continuing Education Credits

Attendance at this event is approved for 2.00 contact hours each of clinical research-related education on applications for Maintenance for ACRP’s CCRC®, CCRA®, CPI®, or ACRP-CPC® certification designations.

• Complete program evaluation via BuckeyeLearn

Q&A during the session

• Use the Zoom chat feature to send your Qs to Sandra Meadows

Introducing Controverted Issues, a new blog from ORRP!

• After the session, we will post a summary of most common questions and answers to we don’t cover

• Subscribe at http://go.osu.edu/IRBblog
Today’s presenters

Paul Montesanti, BA, CIP
• Senior IRB Protocol Analyst
• Email: Montesanti.2@osu.edu

Erin Odor, MA, CIP
• QI Specialist – Regulatory, Education, and Policy Analysis
• Email: odor.3@osu.edu
Today’s attendees

Experience with FDA-regulated drug research

- Brand new: 48%
- Getting there: 30%
- Reinforce my understanding: 22%

Primary role in research

- Principal investigator: 41%
- Regulatory: 12%
- Research coordinator: 4%
- Student researcher: 3%
- Other: 40%
After this session, you will be able to:

• Explain common regulatory terms in the context of FDA-regulated drug studies

• Assess which regulations apply to clinical investigations involving drugs, including when an Investigational New Drug Application (IND) is required

• Identify and complete Buck-IRB application sections and documents required for FDA-regulated drug research

• Recognize how and when to consult the FDA
Drug studies reviewed by OSU

• Audit: 295 initial submissions, Jan – May, 2020
  • ~10% identified as drug studies in Buck-IRB (excludes eIND)
  • 54% had at least one error

• Common errors
  • Drug listed in wrong section ("approved" vs. "investigational")
  • Not all drugs (or devices) listed
  • Device study misidentified as drug study
  • Insufficient justification for IND exemption
  • Incomplete/inadequate documentation
Understanding FDA oversight of research is difficult.

**Reality: It can be!**

- Research discussed in multiple place in FDA regs
- Not one-size-fits all
- Guidance docs revised/updated at any time
- FDA-specific terminology

But we’re here to help!
Helpful Resources

Tools, IND templates, YouTube videos
http://www.regardd.org

FDA IND guidance

Guidance for Clinical Investigators, Sponsors, and IRBs
Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND

New ORRP tools for drug-related research
FDA-specific regulatory terms

- FDA-regulated (product, study)
- Clinical investigation/research
- Human subject
- Sponsor
- Exempt (from which parts)
- Drug
- Investigational New Drug (IND) application
FDA Overview
FDA history

- Oldest comprehensive consumer protection agency in the U.S. federal government
- 1906 Pure Food and Drugs Act: prohibited interstate commerce in adulterated and misbranded food and drugs
- 1938 FD&C Act gave the FDA greater authority to regulate drugs, devices, foods, and other products
What does FDA regulate?

- Foods (including dietary supplements & food/color additives)
- Drugs
- Biologics
- Medical devices
- Radiation emitting products
- Cosmetics
- Veterinary products
- Tobacco products

= FDA-regulated products
Today:
Oversight of Human Subjects Research

The Big Picture

Office for Human Research Protections (OHRP)
Common Rule
45 CFR 46

Food and Drug Administration (FDA)
21 CFR 50 & 56
21 CFR 312 (drugs)

Institutional Human Research Protection Program (HRPP)
FDA & Human Subjects Research

FDA’s perspective: protect subjects & ensure data integrity

- 21 CFR 50: informed consent
- 21 CFR 56: IRB review

**FDA-regulated study** means a study subject to 21 CFR 50 & 56

Additional requirements for certain studies

- 21 CFR 312: drug studies
- 21 CFR 812: medical device studies
FDA & Human Subjects Research

Implications of FDA-regulated research

• Requires continuing review by IRB
• Additional informed consent language
• No electronic consent options at Ohio State currently (21 CFR 11)
• As of 2017: FDA allows a waiver of consent for certain minimal risk research
FDA regulations apply only to studies of drugs, biologics, and medical devices.

**Reality:**
The informed consent and IRB requirements may apply to clinical investigations of *any* FDA-regulated product.
Two steps for drug studies

Is the study FDA-regulated?

Involves FDA-regulated *product*

+ Clinical investigation involving human subjects

= Subject to 21 CFR 50 & 56

Does the study require an IND?

Involves *unapproved drug product*

OR

Involves approved drug product that *does not meet* exemption criteria

= Subject to 21 CFR 312/requires IND
What do you think?

Which of the following **products** is NOT regulated by the FDA?

A. Ibuprofen = Drug
B. Adult diapers = Medical device
C. Sunscreen = Cosmetic AND drug
D. Daily multivitamin = Food (dietary supplement)
E. They are all FDA-regulated products
Summary

• “FDA-regulated product”: a drug, device, or other product under FDA’s jurisdiction
• “FDA-regulated study”: a clinical investigation subject to FDA’s informed consent & IRB requirements
• Next, we’ll talk about how to determine if you have an FDA-regulated study
Step 1: Clinical investigation involving drug
FDA Oversight Algorithm

Does the activity involve a drug?

Is the activity a clinical investigation?

Is the activity exempt from FDA’s IRB requirements?
I know a drug product when I see one.

Reality: While that may be true for many products, FDA considers *intended use* when determining if a test article meets the definition of a drug.
What is a drug?

A drug means an article that is:

- Recognized by the FDA as an approved drug;

- Intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease; or

- Not a food or dietary supplement, but is intended to affect the structure or any function of the body

Note: The primary difference between the definition of a drug and a medical device is that the former achieves its primary intended purposes through chemical action or is dependent upon being metabolized.
# Clinical Investigation

## Studies to evaluate a product’s…

<table>
<thead>
<tr>
<th>Disease claims (all products)</th>
<th>Structure/function claims (any product except food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment of migraine with aura</td>
<td>Use to regrow hair on top of the scalp</td>
</tr>
<tr>
<td>Ability to stop hangovers before they begin</td>
<td>Mechanism of action</td>
</tr>
<tr>
<td>Ability to help open breathing passages when they are constricted</td>
<td>Pathogenesis (e.g., live organisms such as virus, bacterium, fungus)</td>
</tr>
<tr>
<td>Effect on symptoms of diarrhea</td>
<td>Impact on bowel regularity</td>
</tr>
<tr>
<td>Ability to lower cholesterol</td>
<td>Ability to maintain cholesterol in healthy individuals</td>
</tr>
</tbody>
</table>
Traditional types of Drugs

Rx drugs

OTC drugs

Many biologics (e.g., blood, vaccines, HGT)

Some combination products
Non-Traditional types of Drugs

Foods

Dietary supplements & botanicals

Tobacco products

Cosmetics & essential oils

Source: FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND
FDA Review Algorithm

Does the activity involve a drug?

Is the activity a clinical investigation?

Is the activity exempt from FDA’s IRB requirements?
FDA definitions

Clinical Investigation

“Any use of a drug except for the use of a marketed drug in the course of medical practice.” (21 CFR 312.3(b))

“All experiment that involves a test article and one or more human subjects that
• must meet requirements for prior submission to FDA […]” or
• “the results of which are intended to be submitted to or held for inspection by the FDA as part of an application for research or marketing permit” (21 CFR 56.102(c))
FDA definitions

**Human subject**

“An individual who is or becomes a participant in research, either as recipient of the test article or as a control.” (21 CFR 56.102(e))

*Note: This includes biospecimens (and possibly data) regardless of identifiability.*

*Photo credit: FDA Photos Flickr*
Drug clinical investigations: common types

- **Any use of unapproved drug**
- **Approved drug, administration dictated by protocol***
- **Observational study, results to FDA (e.g., Phase IV trial)**

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*Protocol determines route, dose, timing, and/or randomization; drug may or may not be “standard of care”*
What do you think?

Does the use of cranberry juice to treat urinary tract infections (UTIs) meet the definition of a drug?

A. Yes, because cranberry juice is recognized by the FDA as an approved drug product
B. Yes, because “treatment of UTI” is a disease claim
C. No, because “treatment of UTI” is a structure/function claim, which does not apply to food products
D. No, because food products are excluded from the definition of drugs as long as they are already available for purchase
What do you think?

Does the following study meet the definition of a clinical investigation subject to FDA’s IRB regulations (i.e., an FDA-regulated study)?

- Psychology researchers are interested in the short-term effects of Pepto-Bismol on mood. Participants will complete a baseline questionnaire, be given a standard dose of Pepto-Bismol, and complete a final mood questionnaire 15 minutes later.

A. Yes, because an approved drug product is administered outside of medical practice

B. Yes, because Pepto-Bismol is the object of the study

C. No, because the study is not evaluating a disease or structure/function claim

D. No, because data will not be submitted to FDA in support of a marketing application
FDA Review Algorithm

Does the activity involve a drug?

Yes

Is the activity a clinical investigation?

Yes

Is the activity exempt from FDA’s IRB requirements?
Exempt studies

The following clinical investigations are EXEMPT from FDA’s IRB & consent requirements

1. Food: Taste and quality evaluations and consumer acceptance studies of wholesome foods without additives or if food ingredient(s) are GRAS

Compare to Common Rule exemptions

Remember, “exempt” in this context means exempt from 21 CFR 50 & 56—NOT exempt from IND requirements or any other regulations!

Note: Certain emergency treatment uses of test articles are also exempt from FDA’s IRB & informed consent requirements
Recap

Step 1: Is my study a clinical investigation?

- Subject to informed consent (waiver allowed) (21 CFR 50) and IRB oversight (21 CFR 56)
- Limits exemptions from IRB compared to Common Rule
- Requires continuing review by IRB
- Requires specific informed consent language
- MAY require additional oversight (IND)
- May also be subject to Common Rule

Not sure if your study involves a drug or is a clinical investigation? Ask FDA!
Step 2: Does the study require an IND?
My study is a clinical investigation of a drug. Now what?

Is the study FDA-regulated?

Involves FDA-regulated product +
Clinical investigation involving human subjects = Subject to 21 CFR 50 & 56

Does the study require an IND?

Involves unapproved drug product OR
Involves approved drug product that does not meet exemption criteria = Subject to 21 CFR 312/requires IND
IND Overview video from ReGARDD
My study is a clinical investigation of a drug. Now what?

Study needs an IND
(subject to 21 CFR 312)

Study is IND exempt
(exempt from 21 CFR 312)
Definitions

What is an Investigational New Drug?

“A new drug or biological drug that is used in a clinical investigation”

Includes:

• Biological product(s) used *in vitro* for diagnostic purposes
• Off-label use of marketed drug(s)
Definitions

What is “off-label use” of a marketed drug?

Any use that differs from approved labeling, such as:

- Indication(s) for use
- Patient population
- Route of administration
- Dose
- Drug combination
- Drug modification

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**Example of Highlights for a Fictitious Drug**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Indicon safely and effectively. See full prescribing information for Indicon.

**INDICON** (cholinesterase) CAPSULES

Initial U.S. Approval: 2000

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**WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS**

See full prescribing information for complete boxed warning. Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Indicon immediately if any of the following occur:

- Neutropenia/agranulocytosis (5.1)
- Thrombotic thrombocytopenic purpura (5.1)
- Aplastic anemia (5.1)

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**RECENT MAJOR CHANGES**

- Indications and Usage, Coronary Stenting (1.2)
- Dosage and Administration, Coronary Stenting (2.2)

**INDICATIONS AND USAGE**

- Indicon is an adenine dinucleotide (ADP) antagonist platelet aggregation inhibitor indicated for:
  - Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
  - Reducing the incidence of subsequent coronary stent thrombosis, when used with aspirin (1.2)

**Dosage and Administration**

- Stroke: 50 mg once daily with food (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at [phone & Web address] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Anticongulants: Discontinue prior to switching to Indicon (5.3, 7.1)
- Phenyltin: Elevated phenyltin levels have been reported. Monitor levels (7.2)

**USE IN SPECIFIC POPULATIONS**

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/200X
Definitions

What is an Investigational New Drug Application (IND)?

An IND is a request for FDA authorization to administer an investigational drug or biological product to humans

- Oversight to ensure safety of participants & assure quality of scientific evaluation
- All drug studies require an IND unless they meet exemption criteria
- IND and IRB approval must be in place before study begins
Myth vs. Reality

Only industry-sponsored research requires an IND.

Reality:
Marketing/commercialization is just one factor in determining whether an IND is needed.

About half of INDs approved each year are submitted by industry; the other half are investigator-initiated!
Two types\(^*\) of INDs

- **Commercial INDs**
  - Manufacturer/org holds IND
  - Usually large-scale study
  - Commercial intent
  - Lengthy IND application

- **Research INDs**
  - Investigator-initiated study
  - Non-commercial intent (e.g., improve tx)
  - Shorter IND application
  - Most common IND type

\(^*\)Excludes emergency INDs and treatment INDs
IND exemption

Who determines if a study is exempt from IND requirements?

• The FDA

• The sponsor with confirmation from the IRB

Definition: “Sponsor” in FDA context

“A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.”

• Unrelated to funding; rather, outlines specific responsibilities
IND exemption

Clinical investigations of drugs are exempt from IND requirements if all of the following are true:

• The product is lawfully marketed in the U.S. as a drug

• If used “off-label” (route of administration, dose, patient population, etc. differs from approved labeling) in the investigation, the use does not significantly increase risk (or decrease acceptability of risk) associated with the drug product

• The investigation will not be reported to FDA to support a change in labeling or advertising

• The investigation does not promote the drug as safe or effective for the purposes for which it is under investigation (e.g., in the consent form)

Remember, IND exempt studies are still subject to FDA’s IRB requirements
Determining IND exemption: 3 Questions

1. Marketed in US as a drug?
   - Yes
   - No

2. Used per label?
   - Yes
   - No

3. Off-label use increases risk?
   - Yes
   - No

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

Chart adapted from ReGARDD’s IND Workshop
What do you think?

Can the following study be considered for IND exemption?

- **Aim:** evaluate the effectiveness of reduced-dose nasal spray flu vaccine
- **Study population:** healthy adults (approved population for vaccine)
- **Administration:** lower dose than approved, given twice (more frequently than approved)

A. Yes, because the vaccine is already approved for the indication being studied (prevention of flu)
B. Yes, if the IRB agrees that the change in dosage and frequency does not significantly increase the risks associated with the drug
C. No, because the change in dosage and frequency is off-label use
D. No, because vaccine studies always require an IND
What do you think?

Can the following study be considered for IND exemption?

- Aims: assess the effectiveness of Folic Acid for 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 this study.

A. Yes, if the IRB agrees that the off-label use (administering folic acid for unapproved indication) does not significantly increase the risks associated with the drug
B. Yes, because the product from Company X (not used in study) is legally marketed as a drug
C. No, because the product from Company Y (used in study) is not legally marketed as a drug
D. No, because the use is off label

Source: ReGARDD's IND Workshop
So you need an IND...

IND components

• Cover letter
• FDA Forms (1571, 1572, 3674)
• Table of contents
• Introductory statement/general investigational plan
• Chemistry, manufacturing info
• Pharmacology & toxicity info
• Investigator’s Brochure
• Clinical Protocol
• Summary of previous human experience with the investigational drug
So you need an IND…

Typical IND timeline for novel drugs (Commercial IND)

What about Research INDs?
• Before submitting study in Buck-IRB
• As soon as you have a solid draft of the protocol
It’s better to designate my study as IND exempt and let the IRB tell me whether I need to contact the FDA.

**Reality:**
Only in clear-cut situations. FDA are the experts. The IRB often requests more info to assess IND exemption criteria—and may ask you to consult the FDA anyway, which delays the IRB review process further.
IRB Submission & Review Process

- Buck-IRB submission
- IRB screening with ORRP staff
- IRB Review Expedited or Full Board
- Study approved to begin

Clarifications may be requested
So you need an IND…

Use resources to complete the IND submission to FDA

• Ohio State resources:
  • Center for Clinical and Translational Science (CCTS)
  • Drug Development Institute (DDI)
• ReGARDD.org
  • IND Template for Investigator-Initiated Research INDs with video walk-through
  • IND Workshop recording
• FDA page for Investigator-Initiated Research INDs

Remember: the IND must be approved *before* the IRB can approve the clinical investigation!
Overview of FDA response & IND timeline from ReGARDD
Recap

Step 2: Does my study require an IND?

- Terms we learned in this section
  - Sponsor
  - Investigational New Drug
  - Investigational New Drug Application (IND)
  - “Off-label” vs. “on-label” use
  - IND exempt
- How to evaluate IND exemption criteria
- IND submissions: components & timeline

Next, we’ll look at Buck-IRB application requirements for drug studies & review tools for investigators
Application requirements for drug studies (OSU)
Who reviews drug studies?

- National Cancer Institute-sponsored clinical trials – NCI Central IRB (CIRB)
- Most industry-initiated clinical trials → Western IRB (WIRB)
- All other clinical investigations →
  - Most: Ohio State Biomedical IRB or Cancer IRB
  - Some may be reviewed by external IRBs
Drug studies reviewed by OSU

• **Common errors**
  • Drug listed in wrong section ("approved" vs. "investigational")
  • Insufficient justification for IND exemption
  • Incomplete/inadequate documentation (package inserts, IBs, IND #)
  • Not all drugs (or devices) listed
  • Misidentified as drug study; actually subject to device regs
Components of application

- **Buck-IRB pages:**
  - Summary, background, and objectives
  - Research methods and activities – Check "Drugs or biologics"
  - Drugs page (1 for each agent)
  - Risks, harms, and discomfort (include risks of agent(s) in study)
Tools

- Flowchart
- Scenario table
- Buck-IRB example pages
DECISION TREE: COMMON DRUG RESEARCH SCENARIOS

If your study involves administering a drug product or has aims related to drug products, use the decision tree to determine which of the five most common drug research scenarios applies to your research and whether or not an IND may be required. Please note, the decision tree does not account for every possible scenario or IND exemption.

1. “Drug” means any article that is (1) recognized by the FDA as an "approved drug," (2) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or (3) not a food or dietary supplement, but is intended to affect the structure or any function of the body. In the context of FDA-regulated clinical investigations, drugs include not only prescription and over-the-counter drug products, but also biologicals, blood, dietary supplements, cosmetic, and tobacco products when the intended use in the clinical trial meets the definition above.

This decision tree is provided for educational purposes only and should not be considered an official regulatory document.
# Scenarios

## Buck-IRB Cheat Sheet: FDA-Regulated Drug Research

This cheat sheet reflects the five most common drug research scenarios. It does not account for every possible scenario or IND exemption.

<table>
<thead>
<tr>
<th>Scenario #</th>
<th>Description &amp; example</th>
<th>FDA regulatory oversight</th>
<th>Buck-IRB Application Pages</th>
<th>Required documentation and documents that should reflect drug information</th>
</tr>
</thead>
</table>
| Scenario D1 | Drug(s) not administered per protocol may or may not be focus of research  
Examples: Exercise intervention in ex-smokers currently using nicotine patch (drug) vs. current smokers  
Comparison of three commonly prescribed antibiotics following surgery, treating physicians (not researchers) determine appropriate dose/drug for their patients | Clinical investigation: No* IND: No* | Required  
• None  
As applicable*  
• Funding & Financial Conflicts (if support provided by drug manufacturer)  
• Participant Population (if drug(s) are related to eligibility criteria)  
• Confidentiality of Data (if drug manufacturer will receive study data) | Required  
• Protocol  
As applicable  
• Consent form (should not include risks of drugs) |
| Scenario D2 | Approved drug(s) administered and:  
• the use is dictated by protocol  
• used according to label (“on label”)  
• may or may not be focus of research  
Examples: Lidocaine administered during research biopsy; lidocaine not focus of research  
Comparison of three commonly prescribed antibiotics following surgery; participants are randomized to one of three drugs | Clinical Investigation: Yes IND: No* | Required  
• Research Methods & Activities  
• Drugs or Biologics  
• Drugs (Supplemental Questions)  
• Alternatives to Study Participation  
• Risks, Harms, and Discomforts  
As applicable*  
• Funding & Financial Conflicts (if support provided by drug manufacturer)  
• Participant Population (if drug(s) are related to eligibility criteria)  
• Confidentiality of Data (if drug manufacturer will receive study data)  
• Monitoring (if greater than minimal risk) | Required  
• Approved labeling for each drug (package insert, generic drug monograph)  
• Protocol  
• Consent form  
As applicable  
• Recruitment materials  
• Subject materials/instructions, etc. |
## Scenarios

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<tbody>
<tr>
<td><strong>Scenario D3</strong></td>
<td>Approved drug(s) administered and:</td>
<td>Clinical investigation: Yes</td>
<td>Required:</td>
<td>Required:</td>
</tr>
<tr>
<td></td>
<td>- the use is dictated by protocol</td>
<td>IND: Yes</td>
<td>Research Methods &amp; Activities</td>
<td>Approved labeling for each drug (package insert, generic drug monograph) or Investigator’s Brochure</td>
</tr>
<tr>
<td></td>
<td>- used “off label” (different indication, dose, route of administration, population, or drug combination)</td>
<td></td>
<td>Drugs or Biologics</td>
<td>IND Documentation: FDA IND “study may proceed letter” (for investigator-initiated studies) or IND# on protocol (if sponsor is external to Ohio State)</td>
</tr>
<tr>
<td></td>
<td>- off-label use significantly increases the risk or decreases the acceptability of the risk of the drug product</td>
<td></td>
<td>Drugs (Supplemental Questions)</td>
<td>Protocol</td>
</tr>
<tr>
<td></td>
<td>Example: Participants receive experimental (“off-label”) combination therapy of two approved drugs where drug interactions are unknown</td>
<td></td>
<td>Alternatives to Study Participation</td>
<td>Consent form</td>
</tr>
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<td></td>
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<td>- Recruitment materials</td>
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<td></td>
<td>Monitoring (if greater than minimal risk)</td>
<td>- Subject materials/instructions, etc.</td>
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<tr>
<td><strong>Scenario D4</strong></td>
<td>Approved drug(s) administered and:</td>
<td>Clinical investigation: Yes</td>
<td>Required:</td>
<td>Required:</td>
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<td>- use dictated by protocol</td>
<td>IND: No*</td>
<td>Research Methods &amp; Activities</td>
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<td>Documentation of IND exemption from FDA (if available) or explanation of how study meets IND exemption criteria</td>
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<td>Example: Participants receive experimental (“off-label”) combination therapy of two approved drugs where off-label use is widely recognized as standard of care and/or where existing literature suggests low risk of adverse drug interactions</td>
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<td>Unapproved drug(s) administered; may or may not be object of study</td>
<td>Clinical investigation: Yes IND: Yes</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td><strong>Examples:</strong> First-in-human study of novel drug therapy Evaluation of cranberry juice as treatment for urinary tract infection Unapproved formulation of approved drug (e.g., compounded at commercial pharmacy/homemade formulation) is administered</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td><strong>Required</strong></td>
<td></td>
<td></td>
<td>Investigator’s Brochure for each unapproved drug</td>
</tr>
<tr>
<td></td>
<td>• Research Methods &amp; Activities  • Drugs or Biologics  • Drugs (Supplemental Questions)  • Alternatives to Study Participation  • Risks, Harms, and Discomforts</td>
<td></td>
<td></td>
<td>IND Documentation: FDA IND “study may proceed letter” (for investigator-initiated studies) or IND# on protocol (if sponsor is external to Ohio State)</td>
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<td><strong>As applicable</strong></td>
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<td>Protocol</td>
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<td>• Funding &amp; Financial Conflicts (if support provided by drug manufacturer)  • Participation Population (if drug(s) are related to eligibility criteria)  • Confidentiality of Data (if drug manufacturer will receive study data)  • Monitoring (if greater than minimal risk)</td>
<td></td>
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<td>Consent form</td>
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<td>Recruitment materials</td>
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<td>Subject materials/instructions, etc.</td>
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Buck-IRB example pages

For information on the staged approach to restarting human subjects research, read Guidance and FAQs.

New updates have been made to Buck-IRB. See the Buck IRB Updates page for a list of what is new.

These are your active and in progress studies sorted by your role. You may search for a specific one by entering text in the input below. To easily search for any submissions that are currently pending a team member’s signature (not necessarily your own), type “signatures” in the Find a Study input below for a listing. Otherwise, studies that are pending signatures will be denoted with a ✓ icon.

Show 0 studies
What do you think?

Which scenario does this correspond to?

- An investigator wishes to study a drug for ataxia. The drug is legally marketed to treat ataxia, but the investigator wishes to study the drug by injection as opposed to pill form (the currently approved route of administration). In the investigator's opinion, the use of this drug via this route does not significantly increase risks to subjects.

Which scenario does this correspond to?

A. Scenario 1
B. Scenario 2
C. Scenario 3
D. Scenario 4
What do you think?

Which scenario does this correspond to?

• An investigator wishes to compare two cohorts of participants undergoing standard of care treatment for myocarditis. Participants will take either enalapril or captopril as directed by their physician. Both drugs are legally marketed to treat myocarditis. The investigator does not intend to submit study data to the FDA for a labeling change. Which scenario does this situation correspond to?

A. Scenario 1
B. Scenario 2
C. Scenario 3
D. Scenario 4
What do you think?

Which scenario does this correspond to?

- An investigator wishes to study a new drug to treat Gastroesophageal reflux disease (GERD) in adults who have had the disease for at least one year. While the drug has yielded promising results in animal models, it has not yet been tested in humans. Data will be submitted to the FDA in anticipation of potential marketing approval. Which scenario does this situation correspond to?

A. Scenario 2
B. Scenario 3
C. Scenario 4
D. Scenario 5
How and when to contact FDA
 Myth: The FDA is difficult to work with

Reality: They want to help! And should be consulted early.
Why contact the FDA?

• You're unsure if the research involves a drug product
• You are unsure if your research requires an IND
• You think the research is IND-exempt, but the IRB disagrees or is unsure
• Grant/funder requires documentation of IND exemption
CDER divisions are organized by therapeutic intent.

How to contact - drugs

Office of Responsible Research Practices

Contacting FDA
How to contact - drugs

The Division of Neurology I (DNI) regulates and reviews Investigational New Drug (IND) applications and marketing applications for drug and biologic products for the treatment of neurodegenerative disorders, movement disorders, and neuromuscular disorders, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, muscular dystrophy, amyotrophic lateral sclerosis, and spasticity.

**Director:** Eric Bastings, M.D (Acting)
**Deputy Director:** Teresa Buracchio, M.D. (Acting)
**Deputy Director for Safety:** Alice Hughes, M.D.
**Safety Regulatory Project Manager:** TBD

**Regulatory Operations**
**Chief of Project Management Staff:** Jacqueline Ware, Pharm.D. (Acting)

**Contact Us**

**Mailing Address:**
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology (DN I)
10903 New Hampshire Avenue, Silver Spring, MD 20993
Building 22, Suite 4346
**Phone:** (301) 796-2250
**Fax:** (301) 796-9842

CDER divisions are organized by therapeutic intent
How to contact - Biologics

There are three CBER divisions

• Blood products
• Vaccines
• Tissues and advanced therapies (HGT, cell therapy)
IND exemption
Formal vs. Informal
IND exemption
Formal vs. Informal

- Both formal and informal inquires can be made to determine if the use of a drug in a research study is IND exempt
- Formal determination: Final, in writing
- Informal: May be phone call or email; IRB may still disagree.
Formal inquiries have all of the following features:

- They are in writing (can be paper or electronic).
- They can pose a question of any level of complexity.
- The inquirer is seeking a formal written response or FDA determines that a formal written response should be given (i.e., that the inquiry cannot be answered informally).
- The documentation contains enough detail to permit FDA to provide a formal response concerning the applicability of the IND regulations to a planned clinical investigation (e.g., a study protocol, information about the drug product).
Formal

- This is similar to submitting an IND application
- Make sure to indicate in the cover letter if you think the study may be IND exempt
- FDA will provide a letter documenting IND exemption or you will have an IND
Informal inquiries have the following features:

- They can be communicated either orally or in writing (written communication includes email, fax, or other written correspondence).
- They can pose only relatively uncomplicated questions about a planned clinical investigation that FDA can answer based on somewhat limited information.
- The inquirer is not seeking a formal written response.
Informal

- Contact the appropriate CDER review division and ask for an informal exemption
- Faster than doing a full IND submission
- If study is IND exempt, documentation may not be provided – may just be an email or phone call – IRB still has to agree.
- FDA might require you to do an IND submission or request further information
Example

Investigator/sponsor wants to test a legally marketed drug to treat myocardial inflammation. However, the investigator wants to test this drug in children. The drug is currently legally marketed for use with adults, but is sometimes used clinically with children.

If the investigator is unsure what regulations apply, which division do we contact?

A. Immunology and inflammation
B. Cardiology, hematology, endocrinology, and nephrology
C. Neuroscience
D. Office of blood products
Contacting FDA

Example slide/case study

Office Organization

- Office of New Drugs – Immediate Office
- Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) – Cardiology and Nephrology, Diabetes, Lipid Disorders, and Obesity, General Endocrinology, Nonmalignant Hematology
- Office of Immunology and Inflammation (OII) – Dermatology and Dentistry, Gastroenterology, Hepatology and Nutrition, Pulmonology, Allergy and Critical Care, Rheumatology and Transplant Medicine
- Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPRUM) – Pediatric and Maternal Health, Rare Diseases and Medical Genetics, Urology, Obstetrics and Gynecology
- Office of Infectious Diseases (OID) – anti-infective products; antiviral products, transplant and ophthalmology products.
- Office of Neuroscience – neurology products, psychiatric products, anesthesia, analgesia and addiction products
- Office of Nonprescription Drugs (ONPD) - nonprescription products (marketed under Over-the-counter (OTC) monographs and under NDAs).
- Office of Oncologic Diseases (OOD) - oncology products; non-malignant hematology products; issues related to hematology oncology toxicology.
- Office of Specialty Medicine (OSM) - drug products used in the image-based diagnosis and monitoring of diseases as well as ophthalmology products
Pre-IND consultation

Pre-IND consultation: “Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the biologic or drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.”
Pre-IND consultation

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 sends written responses to questions. (24-48 hours before meeting)
4. FDA determines whether to grant meeting. If denied, reason provided.
5. Submit Pre-meeting briefing package to FDA. (1 month before meeting)
6. Meeting held and minutes distributed. (within 60 days from FDA receipt of request)
Resources
Links

- **General information**: druginfo@fda.hhs.gov

- **Office of new drugs (CDER divisions that can answer questions regarding drugs and INDs/perform pre-IND consultations are listed here)**: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs

- **CDER offices and divisions**: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-offices-and-divisions

- **FDA drug database**: https://www.fda.gov/drugs/drug-approvals-and-databases/about-drugsfda


- **Office of new drugs contact sheet**: https://www.fda.gov/media/78312/download
Handout/FAQ

- Links to CDER, CBER, ORRP web site, REGAARD
- CDER: https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder
- CBER: https://www.fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber
- ORRP: http://orrp.osu.edu/irb/
- REGAARD: http://regardd.org/
Questions?

"We’ve considered every potential risk except the risks of avoiding all risks."