

University of Pennsylvania  
Patient-Oriented Research Certification Program

GCP Module:  
FDA Regulations for  
Clinical Research  
*(Print Version)*

- Overview of the FDA
- Investigational New Drug (IND) Research
- Medical Device Studies (IDE)
- Resources at Penn



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Patient-Oriented Research Certification Program developed and maintained by:  
Office of Human Research  
School of Medicine  
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[www.med.upenn.edu/ohr](http://www.med.upenn.edu/ohr)

## Introduction

Not sure whether or not you need to file an IND to conduct your study? Think your study might be exempt? You're not alone. The language in the Code of Federal Regulations and the Food and Drug Safety Act is difficult to interpret and often misunderstood. **Many researchers make the mistake of not filing an IND** when by regulation, they are required to do so.

The immense scope and breadth of the FDA regulations is often underestimated by researchers. To put this into perspective, consider the following questions:

### When do FDA regulations apply to my research?

FDA-regulated human subject research includes all human subject research that is conducted using an **FDA-regulated product** - whether or not there is an Investigational New Drug (IND) application in place.



### What does the FDA regulate?

Food, Drugs, Biologics, Medical Devices, Radiation-Emitting Products, Dietary/Nutritional Supplements, Cosmetics, and Veterinary Products.

## Overview of the FDA

### Highlights of FDA History

The evolution of the FDA, covered in Module I of this certification program (Historical Perspectives), is embedded with a history of tragedies involving the use and research of drug products. While tragic, these events underscore the absolute necessity of FDA regulations governing clinical research. The FDA regulations around investigational drugs and devices covered in this module were developed with an intention of protection of human subjects in clinical trials.



**Trigger:** Sulfanilamide distributed by Massengill without safety testing, resulting in 100+ deaths, many of whom were children



**Action:** Federal Food, Drug and Cosmetic Act (1938)

- Required new drugs to be tested for safety
- Initiated NDA (New Drug Application) to be filed with FDA prior to marketing
- Required adequate labeling for safe use



**Trigger:** Nearly 300 deaths result from sulfathiazole tablets; tablets were tainted with the sedative, Phenobarbital

**Action:** Beginnings of Good Manufacturing Practices (1941)

	<p><b>Trigger:</b> Fatal Blood dyscrasias associated with chloramphenicol</p> <p><b>Action:</b> Development of large-scale system for adverse reaction reporting (1957 - 1963)</p> <ul style="list-style-type: none"> <li>• Voluntary system in conjunction with:</li> <li>• American Society of Hospital Pharmacists</li> <li>• American Association of Medical Record Librarians</li> <li>• American Medical Association</li> </ul>
	<p><b>Trigger:</b> Thalidomide (Kevadon) distributed in US for investigational use (1958 - 1962)</p> <ul style="list-style-type: none"> <li>• Original FDA application had not been approved due to insufficient safety data</li> <li>• Clinical "investigation" drug were passed out as samples to patients</li> <li>• Discovery in 1962 of thousands of birth defects in Western Europe from Thalidomide</li> </ul> <p><b>Action:</b> Kefauver-Harris Amendments (1962); Addressed use of drugs in clinical trials</p> <ul style="list-style-type: none"> <li>• Requirement of informed consent by subjects</li> <li>• Required pre-clinical safety data with animals</li> <li>• Strict control of accountability and distribution of investigational drugs</li> </ul>

*What Does the FDA Regulate?*

The FDA is the federal agency responsible for ensuring that foods are safe, wholesome and sanitary; human and veterinary drugs, biological products, and medical devices are safe and effective; cosmetics are safe; and electronic products that emit radiation are safe. The FDA also ensures that these products are honestly, accurately, and informatively represented to the public.

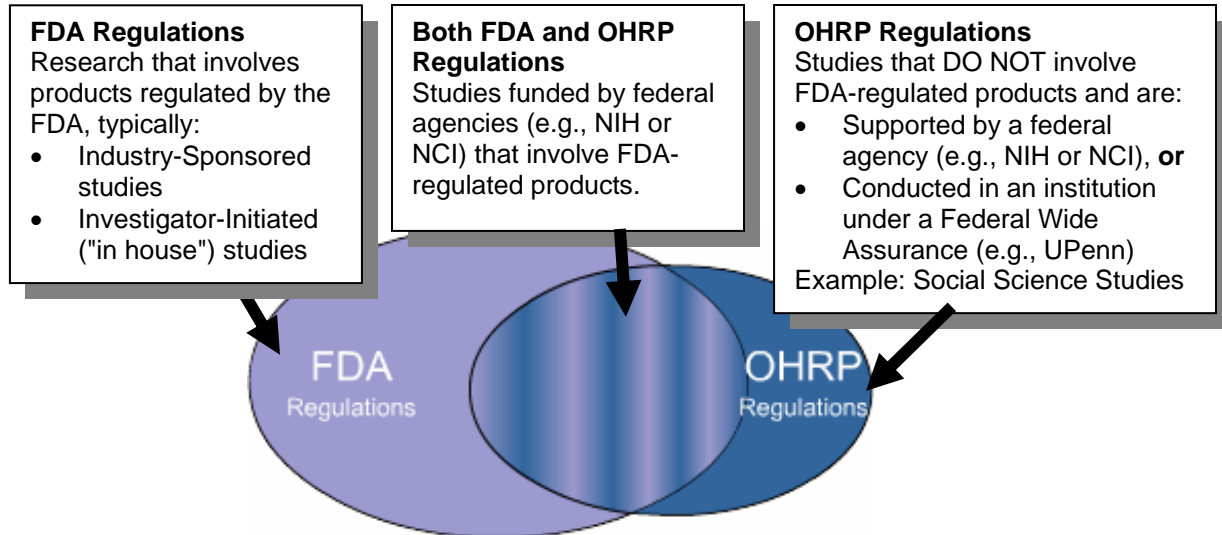
<b>Biologics</b>	<ul style="list-style-type: none"> <li>• Product and manufacturing establishment licensing</li> <li>• Safety of the nation's blood supply</li> <li>• Research to establish product standards and develop improved testing methods</li> </ul>
<b>Veterinary Products</b>	<ul style="list-style-type: none"> <li>• Livestock feeds</li> <li>• Pet foods</li> <li>• Veterinary drugs and devices</li> </ul>
<b>Drugs</b>	<ul style="list-style-type: none"> <li>• Over-the-counter and prescription drug labeling</li> <li>• Drug manufacturing standards</li> <li>• Cosmetics</li> <li>• Safety</li> <li>• Labeling</li> <li>• Product Approvals</li> </ul>
<b>Cosmetics</b>	<ul style="list-style-type: none"> <li>• Safety</li> <li>• Labeling</li> <li>• Product Approvals</li> </ul>
<b>Foods</b>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Safety of all food products (except meat and poultry)</li> <li>• Bottled water</li> </ul>
<b>Medical Devices</b>	<ul style="list-style-type: none"> <li>• Pre-market approval of new devices</li> <li>• Manufacturing and performance standards</li> <li>• Tracking reports of device malfunctioning and serious adverse reactions</li> </ul>
<b>Radiation-Emitting Electronic Products</b>	<ul style="list-style-type: none"> <li>• Radiation safety performance standards for: microwave ovens, TV receivers, diagnostic x-ray equipment, cabinet x-ray systems (such as baggage x-rays at airports), laser products, ultrasonic therapy equipment, mercury vapor lamps, and sunlamps</li> <li>• Accrediting and inspecting mammography facilities</li> </ul>

### FDA vs. OHRP

The role and authority of the FDA is often confused with that of the DHHS (Department of Health and Human Services) and its many branches, especially NIH (National Institutes of Health) and OHRP (Office of Human Research Protections). NIH is primarily a funding agency, not a regulatory agency. OHRP is a regulatory agency governing clinical research that is federally funded.

Many researchers incorrectly assume that because their research is funded by NIH or is conducted in an academic center, that FDA regulations do not apply. However, the FDA has responsibility for clinical investigations of FDA-regulated products:

- Irrespective of **study funding**
- Irrespective of study **location** within the U.S. (e.g., whether academic or other)
- Irrespective of whether for **commercialization/marketing** or for **scientific knowledge**



**Read each scenario below. For each scenario, check the box of each regulatory agency to which the study must adhere. Then check your ANSWERS ON PAGE 14.**

Scenario	FDA	OHRP
A study of a drug for a new indication in which Penn is one site of a multi-site study. The pharmaceutical company is sponsoring the trial.	<input type="checkbox"/>	<input type="checkbox"/>
A study of a new cancer vaccine at Penn. The study is funded through a grant from the National Cancer Institute.	<input type="checkbox"/>	<input type="checkbox"/>
A survey study of Penn medical students studying the effects of sleep deprivation on academic performance.	<input type="checkbox"/>	<input type="checkbox"/>
A study of ultrasound equipment to diagnose auditory canal disturbances. The study was initiated by the Penn investigator and funded through departmental funds.	<input type="checkbox"/>	<input type="checkbox"/>

## *Three Types of Authorities Empowered to the FDA*

### **Procedural Law (Legislative Authority)**

This refers to the process by which the FDA "makes rules" by soliciting and incorporating public comments.

The process involves:

1. Publishing draft versions of all regulatory and guidance document development
2. Soliciting comments from the public on these draft versions
3. Reviewing, assessing, and publishing comments
4. Finalization of ruling/guidance

The current list of FDA dockets awaiting comments can be found at:

<http://www.fda.gov/ohrms/dockets/DOCKETSCLOSE/Commentsdue.htm>

### **Substantive Law (Executive Authority)**

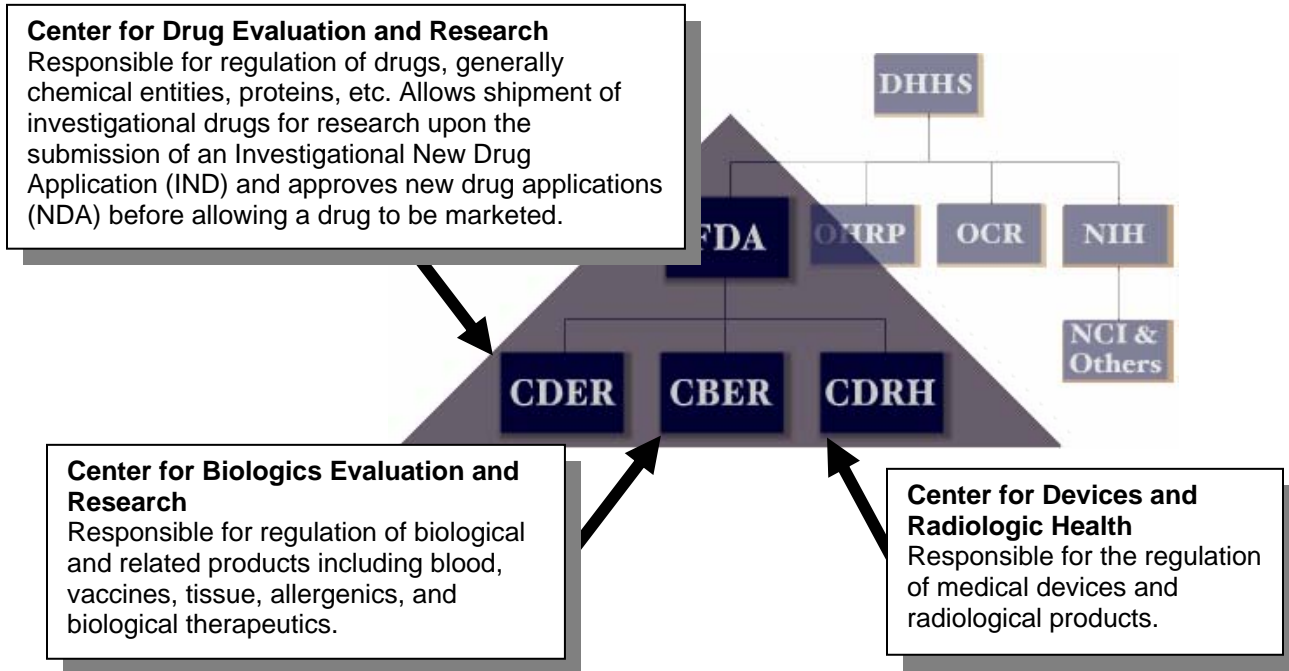
This is the "rule-making". Title 21 of the CFR is considered "rules" or regulation. This means that the FDA writes regulations with the **force of law**, judges whether the law has been followed, and assigns penalties based on their assessment of the severity of the infraction. Violation of FDA regulation can be considered a criminal offense.

### **Interpretive Law (Judicial Authority)**

This facet of FDA authority is represented primarily through the development and publishing of **Guidance Documents**. Guidance documents are generally provided as "advice", or methods by which the regulations can be met. Although they are technically "guidance" and not law, they are used by the courts to interpret the law. FDA's position on the use of guidance is that a researcher is free to use other means to fulfill the requirements of the law if they have an equal or better process than that which is detailed in the Guidance documents.

## FDA Centers

Currently, the FDA is divided into three centers relevant to clinical research. Each of these centers regulates different types of products.



## Investigational New Drug (IND) Research

### Clarifying the "New" in IND

One of the FDA's primary mechanisms for ensuring the safety of research subjects is through **Investigational New Drug (IND)** filing requirements. The term IND can be misinterpreted, leading researchers to conclude that if the drug they are studying is already approved by the FDA, it is not a "new" drug. **THIS IS INCORRECT!**

There are many issues to consider in determining if a drug being investigated is "new". The FDA approves a drug as safe with any or all of the following specifications (these indications are spelled out in the Investigational Brochure or in the PDR):

- Route of administration
- Dose/duration
- Form of the drug (e.g., capsule vs. tablet)
- For specific medical conditions
- With concomitant medications or medical conditions



A study that uses a “**new**” **aspect of the drug** (e.g., different indication, dose, population, etc.) usually requires the filing of an IND. For **any investigator-initiated biomedical research** being conducted, the researcher should consult with OHR (Office of Human Research) to determine whether or not an IND application needs to be filed. In attempting to determine whether or not an IND is required, the following points are considered:

- Preclinical Data
- Properties of the Study Drug
- How the Data Will Be Used

### *Assessing Preclinical Data*

All FDA-approved drugs have undergone **some** preclinical safety testing. However, the scope of the testing was dependent on the proposed/intended use. For example, a drug approved for short term or single-use administration would not necessarily have undergone any long-term safety or carcinogenicity studies.



It is important to compare your intended use of a study drug with the FDA-approved uses of that drug. The assessment should take into consideration whether the following potential preclinical studies were done and/or applicable to your intended use of the drug:

- Carcinogenicity studies
- Mutagenicity studies
- Teratogenicity studies
- Embryotoxic studies
- Drug Absorption/Distribution/Metabolism studies
- Pharmacokinetic/Pharmacodynamic studies
- Chronic/Long-term safety studies

You may conclude that it would be unsafe to use the study drug as you intended without first conducting preclinical safety studies.

#### **Example 1**

Finasteride was originally developed as a treatment for benign prostatic hypertrophy and therefore only intended for men. Would the following preclinical testing be important?

- Determine whether or not the drug is distributed in body fluids
- Determine whether or not there are embryonic or teratogenic effects.

#### **Example 2**

Tylenol was originally developed as an oral tablet. To develop Tylenol as a rectal suppository, what preclinical testing would be important?

- Determine the pharmacokinetic properties of absorption
- No preclinical studies required because Tylenol is sold over-the-counter

**Example 1 Answer (Finasteride for men):**

*Even though Finasteride was only intended for use in men, it was found to distribute in many body fluids, including semen. The drug was also found to be highly teratogenic (caused malformations in external genitalia of male offspring in rats). Had these preclinical studies NOT been done, pregnancies of female sexual partners of treated males may have been put at risk. This risk is so high that the drug labeling includes a warning against women coming in contact with crushed or broken tablets.*

**Example 2 Answer (Tylenol as rectal suppository):**

*Since the rectal mucosa has markedly different absorptive properties than the gastrointestinal tract, it was important to study pharmacokinetic properties in animals prior to introducing this route of administration to humans. It was found that a markedly different formulation of Tylenol was necessary to achieve the same pharmacokinetic and therapeutic profile as the oral formulation.*

**Properties of the Study Drug**

Another factor to consider when determining the need for an IND is how the study drug will be physically modified for the purposes of the study. This may actually place the subject in a situation of unanticipated risks.



**Changing the Form of the Drug**

Some drugs have an encapsulation or coating that can be a protectant or can have special properties that determine the location and rate at which the drug is absorbed.

**Question 1:** I am conducting a trial that involves Coumadin. Is it okay to crush the pills for the purpose of blinding?

**Question 2:** I am conducting a trial that involves Niaspan. Is it okay to crush the pills to put in a gelatin capsule for the purpose of blinding?

**Answer to question 1:**

*No! Coumadin is very unstable in high humidity, which is why the pills are coated. Crushing of these caplets can change them chemically and result in unanticipated safety risks and a lack of efficacy.*

**Answer to question 2:**

*No! Niaspan pills are formulated to control the rate of absorption of the drug to reduce side effects and maintain consistent drug delivery over a 24-hour period. Crushing the Niaspan pill (such as one might do to put a drug in a gelatin capsule for study blinding) would cause the drug to be absorbed much more rapidly. This would lead to significant side effects, a markedly shortened duration of drug delivery, and wide variations in peak drug concentration.*

## Manufacturing Issues

Good Manufacturing Practices (GMP) dictate that proper controls are in place to ensure the product is safe, the stability is known, and that the product's storage or delivery system is effective. These regulations are just as important as regulations on clinical drug development in the protection of human patients/subjects.

### Example 1

I want to study the use of a cytotoxin in a psoriasis study, where the patients are seen in a dermatologist's office. What issues should the research team consider?

#### Issues to Consider

*A cytotoxin, as its name implies, is highly toxic. The direct handling of this drug in a dermatologist's office would not only have potentially unacceptable toxicities in that setting, but it might also expose the research team, who are not familiar with the safe handling of cytotoxins, to be at increased risk.*

### Example 2

How important is it to maintain the original drug packaging provided by the manufacturer?

#### Issues to Consider

*The packaging of some drugs is very important to preserve its chemical composition. Some drugs are in blister packs, for example, because they decompose when they come in contact with air. Another example is drugs stored in dark glass bottles to prevent degradation by exposure to light.*

## How the Data Will Be Used

Another consideration when determining if an IND is needed has to do with the way the study data will be utilized. This is important, because the results of your study may be used to **change the labeling or marketing of a drug**. Also, if your intention (or someone supplying funds) is to **influence prescribing habits**, there is a possibility that an IND may be required. In both cases, a larger population of patients could be placed at risk.



Interestingly, even if the on-site investigator is not intending to submit the results of the study to the FDA, the **sponsor may have intentions** of doing so. For example, in an investigator-initiated study that is receiving funds and/or supplies of a study drug from a pharmaceutical company, there may be a contract with the company that gives the company the ability to use the study data in a filing with the FDA. If that is the case, the study would need to be conducted under an IND.

### *IND Decision Tool*

The Office of Human Research has developed an IND Decision Tool, intended to assist the researcher in determining whether or not a particular study will need an IND, as well as educate the researcher about factors that influence this decision. The tool guides the researcher through a simple decision tree process to determine whether or not an IND is required for a particular study.

**It is suggested for this section that the user use the IND Decision Tool online at <http://www.med.upenn.edu/penn/ohr/ind> (choose **IND Decision Tool** under **Tools**). Read each study below and use the IND Tool to determine if an IND must be filed. ANSWERS ON PAGE 14**

#### **Scenario 1:**

Your study is investigating the use of a pain reliever that is approved for only oral administration. You intend to administer it rectally.  
Do you need to file an IND?

#### **Scenario 2:**

Your study is investigating the use of sunflower stems to reduce the effects of Rheumatoid Arthritis. If the results of the study are successful, you intend to submit an application to the FDA to market this new indication.  
Do you need to file an IND?

#### **Scenario 3:**

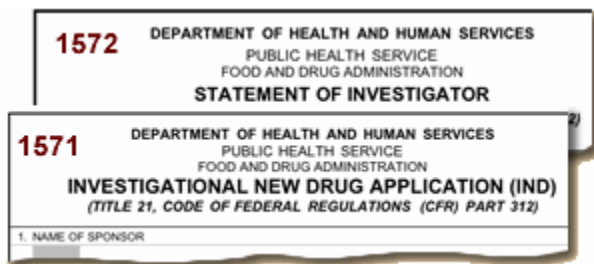
Your study is comparing the use of Prozac and Lexapro to treat depression. You intend to administer both drugs within the FDA-approved use. You do not have a contract with a pharmaceutical company, and do not plan on submitting these results to the FDA for a change in labeling. You hope to publish the results in JAMA.  
Do you need to file an IND?

## IND Submission

The purpose of the IND Submission is to gain FDA non-objection to studying the investigational agent in humans. The IND Submission to the FDA is prepared using FDA Forms 1571 and 1572.

Information required includes:

- Sufficient preclinical data, including toxicity data
- Details of the chemistry, manufacturing and controls to provide adequate quality control information for the production of the agent and to describe the mechanism of action of the agent
- Background and rationale for intended clinical use
- Proposed protocol for Phase I human use



Upon receipt of the IND submission by the FDA, the investigator may proceed with the clinical study 30 days after the receipt date on the FDA's IND acknowledgement letter (unless notified by FDA not to begin the study) OR on receipt of an IND approval letter from FDA.

## IND Holder Responsibilities

Once submitting an IND, the IND holder is responsible for:

- Selecting qualified investigators
- Ongoing monitoring of all studies submitted under the IND
- The validity of the data from all sites conducting research under the IND
- Maintaining adequate records of receipt, shipment, and disposition of the investigational drug
- For multi-site studies, ensuring that all sites are kept informed of adverse events and safety updates

The IND holder must notify the FDA of any of the following:

### ➤ Protocol Amendments

- Any changes to the protocol or any new protocols under the IND  
**Example:** An investigational imaging agent currently being studied under an IND for use in movement-related disorders. The investigator also wishes to study the use of this agent in individuals being treated for substance abuse. This new protocol would be submitted under the IND for the investigational imaging agent, therefore both protocols are conducted under one IND.
- Any new sub-investigators or changes to investigators (with a revised FDA Form 1572)

### ➤ Safety Data

- IND Safety Reports (refer to AE module)
- IND Annual Reports (includes a summary of all study findings and adverse events to date)

### ➤ Investigational Drug Updates

- Any changes to the chemistry, manufacturing, and controls  
**Example:** Changes in how the product is manufactured, quality testing of the product, or the chemical structure must be submitted to the FDA.
- Changes to the Investigational Brochure  
**Example:** New information regarding human or animal studies, or absorption, distribution, metabolism of the product should be revised in the IB, submitted to the FDA, and distributed to all the sites.

### ➤ Closing Out the IND

## Medical Device Studies (IDE)

An IDE is the medical device equivalent of an IND Application for drug studies. An Investigational Device Exemption application is required when the study poses a Significant Risk to participants. This categorization is determined by the IRB, although the FDA makes the ultimate decision in determining whether a device study poses a Significant or Non-Significant Risk.



The risk determination should be based on the proposed use of a device in a study, NOT on the device alone.

### NSR (Non-Significant Risk) Device Study

- For NSR Device Studies, the IRB can grant an IDE
- The study may begin immediately after IRB approval

### SR (Significant Risk) Device Study

An SR Device presents a potential risk to the health, safety, or welfare of a subject **and** is:

- An implant, **or**
- Used in supporting or sustaining human life, **or**
- Of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health, **or**
- Otherwise presents a potential serious risk to the health, safety, or welfare of a subject.

## Resources at Penn

### *Central IND Process*

In an attempt to develop a consistent approach to handling IND applications, the University of Pennsylvania School of Medicine has developed a central process for all IND matters, including:



- Determination/confirmation that a study is EXEMPT from filing an IND Application
- Correspondence/Interface with FDA on filing IND Applications

As such, all researchers who are conducting investigator-initiated studies that involve Biomedical research should consult with the Office of Human Research to be sure all IND issues are properly addressed and documented. Oncology studies conducted within the Abramson Cancer Center system can consult with the Administrative Director for Compliance and Monitoring for IND Exempt determinations.

General IND filing guidance and assistance is available to all investigators through the Office of Human Research.

### *Investigational Drug Service (IDS)*

The Investigational Drug Service (IDS) is available on a fee-for-service basis, for both inpatient and outpatient clinical trials. Services provided include, but are not limited to:

- Study initiation
- Inventory management and record keeping
- Preparation and dispensing
- Study closure

All clinical trials of an investigational agent are required to provide a certain amount of information to the IDS.



Questions relating to the information required or to arrange for the services of the IDS should be directed to:

Kenneth Rockwell, PharmD, MS  
Director, Penn-IDS  
(215) 349-8817

**Answers from activity on page 4.**

Scenario	FDA	OHRP	Rationale
A study of a drug for a new indication in which Penn is one site of a multi-site study. The pharmaceutical company is sponsoring the trial.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<b>This study will be primarily regulated by the FDA since it is studying an FDA-regulated product. Because it is being conducted at Penn, where a Federal Wide Assurance is in place with OHRP, it will also be regulated by OHRP.</b>
A study of a new cancer vaccine at Penn. The study is funded through a grant from the National Cancer Institute.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<b>This study will be primarily regulated by the FDA since it is studying an FDA-regulated product. Because it is being funded by a federal agency, it will also be regulated by OHRP.</b>
A survey study of Penn medical students studying the effects of sleep deprivation on academic performance.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<b>This study does not involve an FDA-regulated product, so is not regulated by the FDA. Because it is being conducted at Penn, where a Federal Wide Assurance is in place with OHRP, it will be regulated by OHRP.</b>
A study of ultrasound equipment to diagnose auditory canal disturbances. The study was initiated by the Penn investigator and funded through departmental funds.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<b>This study will be primarily regulated by the FDA since it is studying an FDA-regulated product. Because it is being conducted at Penn, where a Federal Wide Assurance is in place with OHRP, it will also be regulated by OHRP.</b>

**Answers from activity on page 10.**

Scenario	Answer
Your study is investigating the use of a pain reliever that is approved for only oral administration. You intend to administer it rectally. Do you need to file an IND?	<b>Yes. An IND is needed for this study because:</b> <ul style="list-style-type: none"> <li>• <b>it involves the use of a product for the purpose of mitigating the effects of a disease</b></li> <li>• <b>the results may be used in support of a new indication for labeling and/or marketing</b></li> </ul>
Your study is investigating the use of sunflower stems to reduce the effects of Rheumatoid Arthritis. If the results of the study are successful, you intend to submit an application to the FDA to market this new indication. Do you need to file an IND?	<b>Yes. An IND is needed for this study because:</b> <ul style="list-style-type: none"> <li>• <b>it involves the use of a product for the purpose of mitigating the effects of a disease</b></li> <li>• <b>the results may be used in support of a new indication for labeling and/or marketing</b></li> </ul> <p><b>Seemingly innocuous substances can have significant effects on humans. For example, digitalis/digoxin is made from the foxglove plant, opium from the poppy plant, and marijuana from the cannabis plant.</b></p>
Your study is comparing the use of Prozac and Lexapro to treat depression. You intend to administer both drugs within the FDA-approved use. You do not have a contract with a pharmaceutical company, and do not plan on submitting these results to the FDA for a change in labeling. You hope to publish the results in JAMA. Do you need to file an IND?	<b>No. An IND is not needed for this study because:</b> <ul style="list-style-type: none"> <li>• <b>the study drugs are being used within the FDA-approved indications</b></li> <li>• <b>the results will not be used in support of a new indication, or a change in labeling or advertising</b></li> </ul>

## Resources

The following references or web sites were used in development of this module.

### *Penn Resources*

1. Office of Human Research (<http://www.med.upenn.edu/ohr>)
2. Office of Regulatory Affairs, IRB  
(<http://www.upenn.edu/regulatoryaffairs/IRB.html>)
3. IDS: Investigational Drug Service (<http://www.uphs.upenn.edu/ids/index.shtml>)
4. IND Research (<http://www.med.upenn.edu/penn/ohr/ind/index.htm>)

### *Government Resources*

1. About the FDA (<http://www.fda.gov/opacom/hpview.html>)
2. Code of Federal Regulations, Title 21  
(<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm>)
3. FDA Center for Drug Evaluation and Research (<http://www.fda.gov/cder/>)
4. FDA Center for Devices and Radiological Health  
(<http://www.fda.gov/cdrh/index.html>)