

## **Clinical Investigations of New Drugs or Marketed Drugs: Investigational New Drugs (INDs) and Investigator-Sponsored INDs**

When research activities involve the clinical investigation of a drug (or biological or botanical drug product for human use), the investigator is required to provide the PHRC with information about the drug being investigated. The information provided must include compliance with FDA regulatory requirements for investigational new drug applications [21 CFR 312].

Before the research may begin, in addition to PHRC approval, investigators must also obtain approval of the institutional Research Pharmacy Committee/Investigational Drug Service where the research will be conducted. The PHRC is responsible for forwarding copies of protocol submissions requiring Research Pharmacy Committee/Investigational Drug Service review to the appropriate committee(s). Consultation with the Research Pharmacy/Investigational Drug Service prior to submission to the PHRC is recommended whenever the drug will be prepared inhouse or there are special storage/handling requirements.

### **Clinical Investigations of Drugs or Biological Products that are not Marketed**

The clinical investigation of a drug that is not marketed requires submission of an Investigational New Drug (IND) application to FDA. An IND can be issued to a company, a government agency such as NIH or NCI, or an individual investigator (sponsor-investigator). The clinical investigation of an investigational new drug may not begin until the IND goes into effect. FDA notifies the sponsor in writing of the date it receives the IND application.

An IND goes into effect 30 days after FDA receives the IND application, unless the FDA notifies the sponsor that the investigations described in the IND application are subject to a *clinical hold*. A *clinical hold* is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. Investigators are responsible for promptly notifying the PHRC whenever FDA issues a *clinical hold*.

An IND may also go into effect before the 30-day period when FDA notifies the sponsor that the clinical investigations may begin. The PHRC must ascertain that the IND has been issued and is not subject to a *clinical hold* before final approval can be given for the clinical investigation to begin.

In the event the PHRC has determined that an IND is required, but the FDA disagrees, the investigator will be asked to provide documentation of FDA's determination that an IND is not needed.

## **Clinical Investigations of Marketed Drugs or Biological Products**

The clinical investigation of a marketed drug requires submission of an Investigational New Drug (IND) application to FDA unless the clinical investigation meets all of the following conditions:

1. The clinical investigation is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2. The clinical investigation is not intended to support a significant change in the advertising for the product;
3. The clinical investigation does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The clinical investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5. The clinical investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
6. The clinical investigation does not intend to invoke 21 CFR 50.24 Exception from informed consent requirements for emergency research.

## **Clinical Investigations of Botanical Drug Products or Marketed Botanical Dietary Supplements**

The clinical investigation of a botanical drug product or marketed botanical dietary supplement requires submission of an Investigational New Drug (IND) application to FDA when it is being studied for its effects on diseases (i.e., to cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms).

### **Investigator-held INDs (Sponsor-Investigators)**

When an individual investigator holds an IND, s/he assumes all of the responsibilities of the sponsor. Therefore sponsor-investigators must be knowledgeable of the regulatory requirements found in 21 CFR Part 312 - Investigational New Drug Application and be familiar with FDA guidance documents. In addition, the PHRC requires first-time IND holders (with the exception of Emergency Use INDs) to review their responsibilities as sponsor-investigators with the Partners Human Research Quality Improvement Program (the QI Program) before final approval can be given for the clinical investigation to begin.

Sponsor-investigators are responsible for establishing recordkeeping and retention systems that comply with the requirements in Subpart D – Responsibilities of Sponsors and Investigators. The FDA may inspect sponsor-investigators' records at any time. During these inspections, FDA representatives hold sponsor-investigators to the same recordkeeping requirements as corporate or government sponsors. Establishing good recordkeeping systems before the clinical investigation begins will make FDA inspections easier and minimize the likelihood that the

inspection will result in issuance of Form FDA 483 citing observations of objectionable practices.

The QI Program has developed an IND-holder checklist as well as other relevant tools that will help investigators meet the FDA requirements for sponsor-investigators and be ready for an unexpected audit. The [IND-holder checklist](#) is available on the QI Program website. The QI Program staff is available to assist investigators with setting up recordkeeping systems and organizing regulatory documents. They can also advise investigators on proper study management and best practices. All sponsor-investigators are strongly encouraged to utilize the services of the QI Program.

### **Research Involving Drugs not Manufactured by a Licensed Pharmaceutical Co.**

When an individual or entity other than a licensed pharmaceutical company manufactures the drug being investigated, the PHRC and the Research Pharmacy Committee/Investigational Drug Service will rely upon FDA review of the chemistry, manufacturing, and control information contained in the IND Application. When an individual or entity other than a licensed pharmaceutical company manufactures the drug administered to human subjects and an IND is not required, the PHRC will request a Certificate of Analysis. The clinical investigation may not begin until the PHRC receives documentation of approval from the Research Pharmacy Committee/Investigational Drug Service and when applicable, the IND is in effect.

**For more information, refer to the FDA regulations, guidance documents and forms listed below:**

#### **Investigational New Drugs (INDs) and Marketed Drugs**

FDA Regulations: 21 CFR 312 – Investigational New Drug Application

[http://www.access.gpo.gov/nara/cfr/waisidx\\_04/21cfr312\\_04.html](http://www.access.gpo.gov/nara/cfr/waisidx_04/21cfr312_04.html)

FDA Information Sheet Guidance: “Off Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices

<http://www.fda.gov/oc/ohrt/irbs/offlabel.html>

FDA Information Sheet Guidance: Emergency Use IND

<http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency>

FDA Information Sheet Guidance: Treatment IND

<http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#treatment>

FDA FAQs: Frequently Asked Questions on Drug Development and Investigational New Drug Applications

<http://www.fda.gov/cder/about/smallbiz/faq.htm>

FDA Instructions: Information for Sponsor-Investigators Submitting IND Applications  
<http://www.fda.gov/cder/forms/1571-1572-help.html>

FDA Forms: 1571 Investigational New Drug Application and 1572 Statement of Investigator  
<http://www.fda.gov/opacom/morechoices/fdaforms/default.html>

### **Biological Products**

FDA Instructions: Information on Submitting an Investigational New Drug Application for a Biological Product  
<http://www.fda.gov/cber/ind/ind.htm>

FDA FAQs: Center for Biologics Evaluation and Research (CBER) Frequently Asked Questions  
<http://www.fda.gov/cber/faq.htm>

### **Botanical Products in Research**

FDA Guidance: Guidance for Industry, Botanical Drug Products  
<http://www.fda.gov/cder/guidance/4592fnl.pdf>

FDA FAQs: Frequently Asked Questions on Botanical Drug Product Development  
[http://www.fda.gov/cder/Offices/ODE\\_V\\_BRT/faq.htm](http://www.fda.gov/cder/Offices/ODE_V_BRT/faq.htm)

### **FDA Inspections**

FDA Information Sheet Guidance: FDA Inspections of Investigators  
<http://www.fda.gov/oc/ohrt/irbs/investigator.pdf>

FDA Warning Letters:  
<http://www.fda.gov/foi/warning.htm>