



## Drugs, Biologics, and Dietary Supplements Regulations

### Policy

- Research at Children's Hospital that involves the investigational use of drugs, biologics, and dietary supplements must conform to Food and Drug Administration (FDA) regulations, as well as to Department of Health and Human Services (DHHS) regulations and State regulations (94C MGL 8).
- FDA regulations have additional requirements for clinical investigations that involve the use of an approved product or biologic if it is used in a manner for which it is not approved. There are also additional FDA requirements for investigators. The FDA regulations for investigational drugs are outlined in 21 CFR 312, and for investigations of biological products in 21 CFR 600.
- State regulations (94C MGL 8) require the registration of investigators who use investigational and Schedule II drugs in research protocols.

### Purpose

To describe the various regulatory mechanisms for obtaining, testing, and using drug and biologic products in compliance with federal and State regulations.

### Procedures

#### Investigational New Drug (IND) Exemption

Federal law prohibits the distribution of a new drug or biologic until the FDA reviews the clinical data and determines that the product is safe to use and is effective for a specified indication. Investigators/sponsors who wish to test a new product must acquire an exemption before any testing may begin unless the research is determined to be exempt from IND review and submission.

The following criteria are used to determine whether your protocol is exempt from an IND:

- Clinical investigations of a drug product that is lawfully marketed in the United States, provided that **all** of the following conditions apply:
  1. The study is not intended to be reported to the FDA as a well-controlled study in support of a new indication or use; or support any significant change in the drug's labeling;

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2. The study is not intended to support a significant change in the advertising for a prescribed drug;
  3. The study does not involve a change in route of administration, dosage level, patient population, or other factors that significantly increases the risks associated with use of the drug product;
  4. The study complies with IRB evaluation and informed consent requirements;
  5. The study sponsor and/or investigator do not represent in a promotional context that the drug is safe and effective for the purposes in which it is under investigation;
- Drugs intended solely for testing in vitro or in laboratory research animals, provided the drug labels and shipments comply with FDA regulations.
  - Clinical investigations involving the use of a placebo provided that investigators do not involve the use of a new drug.
  - Certain in vivo bioavailability and bioequivalence studies in humans (generic drugs). FDA regulations state that INDs are required for in vivo bioavailability or bioequivalence studies in humans if the test product is a radioactively labeled drug product, is a cytotoxic drug product, or contains a new chemical entity.

Still, situations arise when studies could be exempt from IND submission, even though they do not meet the criteria above. These types of exemption are granted usually because there is significant information about these treatments already in the literature. For example, when a drug has been used clinically off-label regularly for the treatment of the studied condition and there is significant information in the literature about this use. In this situation the FDA is the one who determines that your protocol is exempt. If you still have any doubts whether your study requires an IND or not, contract the appropriate department at FDA

Complete IND information must be submitted with any protocol submitted to the Committee on Clinical Investigation (CCI) that involves an investigational drug or biologic. Investigators are required to submit IND information provided by the sponsor, or if the investigator is also the sponsor a copy of the letter from the FDA that assigns the IND. This will be required as part of the protocol application. The CCI will not release a final approval until all IND information is complete. Protocol administrators will be responsible for making sure this information is obtained prior to release of the approval notification and informed consent document. If there is any question as to whether an IND is required, the CCI may require, as part of the review and approval process, that the investigator contact a Children's Hospital regulatory affairs specialist or the FDA to discuss the protocol and to determine if an IND is required.

Investigators who propose to use investigational or marketed drugs for unapproved indications must also follow FDA regulations 21 CFR 50, 56 and 312. For the most part, the FDA regulations are the same as DHHS regulations 45 CFR 46. The regulations are the same with regard to IRB organization, composition, procedure,

record keeping, and criteria for approval of research protocol and informed consent documentation. There are additional determinations that must be considered for protocols that involve the use of investigational products.

For all investigations subject to IND regulations, the investigator is required to be knowledgeable about the requirements of FDA regulations and must be listed on a 1572 Form in order to administer an investigational product. At the time of continuing review the Committee may request additional documentation to be certain the investigator is following the IND requirements. If the investigator holds the IND, a copy of the annual report to the FDA may be requested. In addition whenever a protocol that involves an IND is randomly selected for a review by the EQuIP program, all case report forms, adverse event reports, drug dispensation, data and safety monitoring reports and informed consent documents will be reviewed to be certain the investigator complied with FDA requirements regarding sponsor requirements.

## **Use of a Marketed Drug or Biologic in a Manner for Which it is not Approved**

### **"Off Label Use"**

When the FDA approves a drug or biologic it also includes the indications for which it is approved. Variance from the intended use is referred to as "off label use." Good medical practice and patient interest require that physicians use commercially available drugs and biologics in a knowledgeable way and with sound judgment. If a physician uses a product for an indication that is not in the approved labeling, he or she has the responsibility to be well informed about the product, and to base its use on firm scientific rationale and sound medical evidence. Use of a product for an individual patient in this manner may be considered "medical practice" and does not require submission of an IND or a protocol to the CCI. This may be considered "off label use."

### **"Investigational Use"**

The investigational use of a marketed drug or biologic involves the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test product is to develop information about the product's safety or efficacy, submission of a protocol to the CCI is required. This is usually performed as a protocol with a hypothesis for a group of defined patients. In this situation the intent is not solely to treat one patient but to look at a group of patients to answer a specific, predetermined set of questions. In addition, an IND will be required from the FDA. An IND may not be required in accordance with the exempt criteria listed above

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires submission to the FDA for an IND, the investigator is advised to the regulatory affairs specialist or the FDA directly to determine if this is required. The CCI may require that an investigator contact the FDA or regulatory affairs specialist if this has not been done at the time of CCI review. If the FDA or regulatory affairs specialist indicates that an IND is not required, documentation of contact with the FDA or regulatory affairs specialist is required. This may be either a

written notification from the or documentation of contact, including who was contacted, the phone number, the time of the call, and a summary of the information provided.

## **Expanded Access of Investigational Drugs**

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, test articles may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, a life-threatening, or a debilitating condition, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects, or the thoroughness and scientific integrity of product development and marketing approval.

## **Open Label Protocol or Open Protocol IND**

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued to enable the subjects and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective CCI review of the protocol and informed consent.

## **Treatment IND**

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) the trial sponsor is actively pursuing marketing approval.

A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

## **Parallel Track**

The FDA's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol

that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective CCI review and informed consent.

## **Dietary Supplements**

The FDA has finalized rules that define the types of statements that may be made concerning the effects of dietary supplements on the structure or function of the human body. The increased use of supplements has led to an increase in research. The FDA requires research that involves dietary supplements, that is undertaken for the Purpose of investigating the effects of prevention, cure, mitigation, or diagnosis of disease, to abide by IND requirements before testing may begin. The investigator is to check with the FDA when developing a protocol that involves the use of dietary supplements. The CCI may also require that the FDA be contacted, if the investigator has not already done so.

## **Massachusetts Regulations (94C) for Registration of Investigational Drugs and Schedule II Drugs In Research**

Massachusetts law requires the registration of investigators who use investigational and Schedule II drugs in research protocols. The law requires that any investigator who is using either an investigational drug, as defined by FDA regulations, or a Schedule II drug as part of a research protocol must register and obtain a license as a researcher from the Commonwealth of Massachusetts..

To facilitate compliance with the law, the State has determined that Department Chairs may opt to assume responsibility for the registration of all research investigators within their departments. Children's Hospital registers and obtains a license for any department that engages in research that involves investigational and Schedule II drugs in research protocols. The license is obtained in the name of the Department Chair. In addition to the information required for the license, the State requires a current copy of the Department Chair's Massachusetts Medical License, Massachusetts Controlled Substance Practitioner Registration (if any), and the Drug Enforcement Administration Controlled Substance Registration. The license is renewed annually. The Clinical Investigation Office maintains a database of all approved protocols that fall under the State regulations. The Office is responsible for maintaining updated licenses, and pays the fee required to do so. If an investigator is uncertain whether a license exists for his or her department, he or she should contact the Clinical Investigation Office.

## **Dispensing and Storage of Investigational Drugs and Drugs Used in Research Protocols**

All investigational drugs and drugs used for research protocols must be stored and dispensed from the pharmacy, and used only under the direct supervision of the PI. Investigational drugs must be shipped to the pharmacy and should not be stored in offices and clinic areas. Industry sponsored studies may require inspection of the pharmacy's Investigational Drug Study Area before Children's Hospital is used as a study site.

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In all cases where study drugs are to be dispensed, the PI or a designee must contact the Pharmacy's Investigational Drug Study Service (ext. 2014 or 6803) to make arrangements for shipping location, storage, dispensing instructions, compounding, blinding procedures, record keeping, and other areas of pharmacy involvement. It is recommended that this be done as early as possible to avoid delays.

For further information as to whether FDA involvement and an IND are required, investigators are asked to call the following phone numbers:

Drugs:	301 827 4573
Biological Blood:	301 827 3518
Biological Vaccine:	301 827 0648
Biological therapeutic:	301 594 2860
Nights and Weekends:	301 594 0095

(Information taken from FDA, Office of Health Affairs Information Sheets, 1998 update.)

## Related Content

## Document Attributes

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