Drugs, Biologics, and Dietary Supplements Regulations

Policy

- Research at Boston Children's Hospital that involves the investigational use of drugs, biologics, and dietary supplements must conform to Food and Drug Administration (FDA) regulations, 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.
- The FDA regulations for investigational new drug (IND) requirements are outlined in 21 CFR 312. Regulations on drug products can be found in 21 CFR 314 and regulations on biological products are 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 pertaining clinical investigations.

Procedures

Investigational New Drug (IND) Application and Exemptions

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA. The IND regulations are detailed in ***21 CFR 312***.

There are commercial and research (non-commercial INDs).

FDA classifies that there are three IND types:

1. An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose

studying an unapproved drug, or an approved product for a new indication or in a new patient population.

2. ***Emergency Use IND*** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR *312.23* or *21 CFR 312.34.* It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
3. ***Treatment IND*** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Exemptions from IND Requirements

Federal regulations also allow for certain types of studies to be exempt from the IND regulations:

A. Per 21 CFR 312.2, Clinical investigations of a drug product that is lawfully marketed in the United States may be exempt from the requirements of the IND regulations, 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;

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; and

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.

When research involves the use of a drug other than the use of a marketed drug in the course of medical practice, the regulations also provide for additional exemptions from the IND regulations:

B. A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:

- Blood grouping serum
- Reagent red blood cells
- Anti-human globulin

- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.

- The diagnostic test is shipped in compliance with 21 CFR 312.160

C. A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

(See ***21 CFR 312.2*** for a full description of exempt categories)

It is the responsibility of the Sponsor (including Sponsor-Investigator or Principal Investigator) to justify why a proposed study meets the requirements for exemption from the IND regulations. Boston Children's Hospital (BCH) Regulatory Affairs, in conjunction with the IRB, will determine whether the justification is sufficient to proceed, or whether confirmation by FDA is necessary.

Investigators are advised to review the FDA Guidance document, "Investigational New Drug Applications (INDs) —Determining Whether Human Research Studies Can Be Conducted Without an IND".

Process for Submitting an Investigational New Drug Application

It is the responsibility of the Sponsor-Investigator to submit an IND application to FDA for studies which must be conducted under an IND. The IND application must contain information in three broad areas:

1. Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. For many Sponsor-Investigator (or investigator-initiated INDs), this requirement can be met by submitting a Letter of Authorization cross-referencing a third party's regulatory application. Also included in the IND are data on any previous experience with the drug in humans.

2. Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug. For many Sponsor-Investigator (or investigator-initiated INDs), this requirement can be met by submitting a Letter of Authorization cross-referencing a third party's regulatory application.

3. Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

There are many resources available to assist Investigators who are submitting an IND to FDA. The FDA has developed a ***comprehensive website*** to assist with investigator-initiated INDs; there is information and tools available on the ***BCH Regulatory Resources*** website.

All Investigators seeking to submit an IND to FDA will first be required to participate in an internal review process during which a group of experts from across the hospital will meet with the Investigator (and his/her team) to review the proposed protocol, review

requirements of the institution and of sponsoring an IND, and provide recommendations for how the Investigator can meet his/her regulatory obligations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Information to be submitted with IRB Application

Complete IND information must be submitted with any protocol submitted to the IRB 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 IRB 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 IRB may require, as part of the review and approval process, that the investigator contact a Boston 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 and 56. 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.

At the time of a continuing review, if an investigator is the sponsor of an IND, a copy of the annual report to the FDA may be requested.

Responsibilities for Conducting a Study In Accordance with IND Regulations

Investigators: 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 FDA Form 1572 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. Responsibilities of an investigator participating in a study under an IND are detailed in ***Subpart D*** of 21 CRR 312.

Sponsor-Investigators: A Sponsor-Investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. A Sponsor-Investigator is responsible for all requirements as both a sponsor and an investigator. Regulatory responsibilities for investigators and sponsors are detailed in ***Subpart D*** of 21 CRR 312. Prior to approval of a protocol in which the IND is held by a Sponsor-Investigator, BCH Regulatory Affairs will conduct Sponsor responsibility training with Sponsor-Investigator. Please also see BCH Policy, "Requirements for Investigators Who are Also Considered Sponsors of New Drugs".

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 is it 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, s/he 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 IRB. This may be considered "off label use." The IND regulations do not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

"Investigational Use"

Approved drug and biologic products may also be utilized in clinical trials. 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 IRB 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.

FDA has stated that whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in 21 CFR 312.2(b) are met (see earlier section in this document). When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires an IND, the investigator is advised to speak to BCH Regulatory Affairs or to contact the FDA directly. The IRB may require that an investigator contact the FDA or BCH Regulatory Affairs if this has not been done at the time of IRB review, and documentation of the determination is required.

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 IRB 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 IRB 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. When a clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required. The investigator is advised to check with the BCH Regulatory Affairs or with the FDA when developing a protocol that involves the use of dietary supplements. The IRB 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. Boston 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 Boston Children's Hospital is used as a study site.

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.

Related Content

Document Attributes

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