Drugs

Small Business Assistance: Frequently Asked Questions on Drug Development and Investigational New Drug Applications

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Investigational New Drug Application

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INVESTIGATIONAL NEW DRUG PROCESS

An Introduction

This website is designed for individuals interested in bringing a drug to market. This may be an individual or pharmaceutical company, governmental agency, academic institution, or other type of organization.
The main purpose of an Investigational New Drug (IND) application is to provide the data showing that it is reasonable to begin tests of a new drug on humans. Also, 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.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

The IND is not an application for marketing approval.

Definitions

- Clinical investigation means any experiment in which a drug is administered or dispensed to one or more human subjects.
- Investigator means an individual under whose immediate direction the drug is administered or dispensed to a subject.
- Sponsor means a person who takes responsibility for and initiates a clinical investigation.
- Sponsor-Investigator means 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.

Types of INDs

- 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.

- 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 21CFR, Sec. 312.23 or Sec. 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.

- **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.

There are two IND categories:

- Commercial. These are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product.

- Research (non-commercial)

Emergency and Treatment INDs are also known as "Compassionate" INDs, but the term "Compassionate" is not in the IND regulations.

A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug. A sponsor shall not begin a clinical trial until the investigation is subject to an approved IND application. A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent.

### Phases of an Investigation

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. The three phases of an investigation are as follows:

**Phase 1** includes the initial introduction of an investigational new drug into humans. These studies are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. The total number of subjects included in Phase 1 studies is generally in the range of twenty to eighty.

**Phase 2** includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies usually involve several hundred people.
Phase 3 studies are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

INVESTIGATIONAL NEW DRUG APPLICATION

What are the FDA requirements for pre-clinical studies?

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

What is an Investigational New Drug Application?

In many ways, the investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

Do I need to submit an IND?

"Investigational use" suggests 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 article is to develop information about the product's safety or efficacy, submission of an IND may be required. However, the clinical investigation of a marketed drug or biologic does
not require submission of an IND if all six of the following conditions are met:

(1) it 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) it is not intended to support a significant change in the advertising for the product;

(3) it 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) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

(5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

(6) it does not intend to invoke 21 CFR 50.24.

Where do I get the necessary updated forms?

The forms needed are 1571 and 1572.

Are there instructions to help you fill out the forms?

Instructions for completing FDA forms 1571 and 1572

When will I be assigned an IND number?

An IND number will be assigned after the IND application is received by FDA.

When can I start clinical trials?

Unless you are contacted, you may begin trials thirty days after FDA receives your IND application.

Do I need to fill out a Statement of Investigator Form 1572?

Yes. Investigators may participate in an investigation only after they provide the sponsor with a completed, signed Statement of Investigator Form FDA 1572.

What is an Institutional Review Board?
Under FDA regulations, an Institutional Review Board (IRB) is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research.

Institutional Review Boards are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.

An IRB must be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of activities commonly conducted by research institutions. In addition to possessing the professional competence needed to review specific activities, an IRB must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. Therefore, IRBs must be composed of people whose concerns are in relevant areas.

**Does a physician, in private practice, conducting research with an FDA regulated product, need to obtain IRB approval?**

Yes. The FDA regulations require IRB review and approval of regulated clinical investigations, whether or not the study involves institutionalized subjects. FDA has included non-institutionalized subjects because it is inappropriate to apply a double standard for the protection of research subjects based on whether or not they are institutionalized. An investigator may be able to obtain IRB review by submitting the research proposal to a community hospital, a university/medical school, an independent IRB, a local or state government health agency or other organizations. If IRB review cannot be accomplished by one of these means, investigators may contact the FDA for assistance (Health Assessment Policy Staff 301-827-1685).

**Does a clinical investigation involving a marketed product require IRB review and approval?**

Yes, if the investigation is governed by FDA regulations [see 21 CFR 56.101, 56.102(c), 312.2(b)(1), 361.1, 601.2, and 812.2].
Do I need informed consent?

Yes. Investigators may involve a human being as a subject in research only after they have obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

What are the specific divisions and contacts in CDER who can answer my questions?

The Food and Drug Administration's Center for Drug Evaluation and Research is dedicated to ensuring that all persons involved in, or who depend upon, drug regulation have the information needed to develop, review, market, dispense, prescribe or use drugs safely and effectively.

Any of these individuals or groups may request information on specific drugs, guidance documents, publications, or general information such as a description of the drug approval process.

There are a number of ways consumers and industry representatives can communicate with or get reliable, current, and up-to-date information from the Center.

- The newest, and easiest, method for getting information is the Drugs section of FDA's web site.

- For more specific or complex drug inquiries, telephone the Drug Information Branch at (301) 796-3400 or send them an electronic mail message at druginfo@cdr.fda.gov.

Other sources of information include:

- FDA Office of Public Affairs, at 301-827-6250.

- Organization, Contact, and Meeting Information
In addition, consumers and industry representatives can contact:

- [CDER Ombudsman](mailto:CDER Ombudsman), Virginia Behr;
- FDA Freedom of Information Staff, (301) 827-6567;
- FDA MedWatch Office at 1-800-FDA-1088;
- [AIDS Clinical Trials Information Service](mailto:AIDS Clinical Trials Information Service), 1-800-TRIALS-A