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## Part 1: Introduction

### Definition of an Investigational Product

ICH GCP defines an investigational product as,

“A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial” (ICH GCP 1.33).

This may include a marketed product that is being used in a different form than the one it was approved for, or a marketed product being used for an unapproved or new indication.

### Definition of an Investigational New Drug



The Code of Federal Regulations (CFR) defines an investigational new drug as:

"...a new drug or biological drug that is used in a [clinical investigation](#)."

In the U.S. Food and Drug Administration (FDA) regulations, an investigational new drug is any substance (such as a drug, vaccine or other biological product) for which FDA approval is being sought.

A drug may be considered “new” even if it has been in use for years if a change is proposed in its use, formulation, route of administration, use in patient population where risk would be increased, or packaging. For example, years ago the FDA approved a drug to treat high blood pressure. The manufacturer of the drug now wants to test it as a treatment for anxiety in adults. This new use of the drug would be considered investigational.

In a study protocol and other documents, an investigational new drug may be referred to as the “study drug,” “experimental product,” “experimental drug,” “new intervention,” or similar term. Investigational new drugs are regulated under CFR Title 21 Part 312 ([21 CFR 312](#)).

### Labeling of an Investigational New Drug

The labeling of an investigational new drug:

- Must include the following statement: “Caution: New Drug — Limited by Federal (or United States) law to investigational use.”
- Must not be false or misleading and should not imply that the drug is safe or effective for the investigational purpose.

### Control of an Investigational New Drug

An investigational new drug may be given to participants only under supervision by the [principal investigator](#) or by a sub-investigator. (Usually, the person supervising the administration of an investigational new drug is a physician.) The investigator cannot supply the investigational new drug to any person who is not authorized to receive it.

Research that involves the use of controlled substances must comply with U.S. Drug Enforcement Administration regulations ([21 CFR 1300-end](#)). When studying an investigational new drug that is considered a controlled substance, the investigator must take adequate precautions to prevent theft or diversion of the drug into illegal channels of distribution. Such precautions include storing the investigational new drug "in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited."

### Promotion of and Charging for Investigational New Drugs

Neither an investigator nor a [sponsor](#) may promote (that is, endorse or advertise) an investigational new drug as safe or effective for the investigational purpose. In addition:

- An investigational new drug cannot be distributed commercially or in a test market.
- An investigation cannot be prolonged “after finding that the results of the investigation appear to establish sufficient data to support a marketing application.” In other words, if there is good evidence that the investigational new drug is safe and effective, the study should be stopped and no other participants enrolled.
- Charging for an investigational new drug in a clinical trial is not permitted without approval from the FDA unless the drug is being provided for [treatment use](#).

## Part 2: Phases of Clinical Trials of Investigational New Drugs



Clinical trials of an investigational new drug are generally conducted in four phases, Phase 1 to Phase 4. Phase 0, or “exploratory” trials, also exist as small clinical trials (sometimes only a few participants) that involve dosing at a sub-therapeutic level. Phase 0 trials are not as prevalent as Phases 1-4. Each phase is designed to find out different information. Although the phases of a trial are usually conducted sequentially (one after another), they sometimes overlap.

Individuals may be eligible for studies in different phases, depending on their age, general condition, the type and stage of their disease, and previous therapy, if any.

## **Part 2: Phases of Clinical Trials of Investigational New Drugs**

### **PHASE 1 Trials**

Phase 1 trials are the first studies of an investigational new drug in humans. They are usually conducted in healthy volunteers. In some cases, Phase 1 trials may be conducted in individuals who have the disease the drug is intended to treat. Phase I trials generally involve between 20 and 80 participants.

Phase 1 trials are designed to:

- Make a preliminary determination of the drug's safety in humans.
- Identify some of the side effects associated with the drug's use.
- Begin to define a safe therapeutic (healing) dose range.

### **PHASE 2 Trials**

Phase 2 trials are usually conducted in individuals who have the disease the drug is intended to treat or are at high risk for developing the disease. Phase 2 trials are larger than Phase 1 trials but still relatively small, usually involving no more than several hundred participants.

Phase 2 trials are designed to:

- Begin to evaluate the drug's effectiveness in treating or preventing the disease or condition of interest.
- Determine the optimal dosing of the drug.
- Determine the common short-term side effects and risks associated with the drug.

### **PHASE 3 Trials**

Phase 3 trials are conducted after preliminary evidence from Phase 1 and 2 trials suggests that the investigational new drug is safe and effective. They usually include between several hundred and several thousand participants.

Phase 3 trials are designed to:

- Gather additional information about the drug's safety and effectiveness to evaluate whether its benefits outweigh its risks.
- Compare it to other commonly used treatments for the same condition (if available) or compared to a placebo. These studies can be performed in a blinded manner.
- Evaluate interactions with other treatments that may be used at the same time as the investigational new drug.
- Provide adequate information to determine the indication for which the drug will be labeled if it is approved for marketing as well as any limitations on the drug's use that should be stated in the labeling. For example, if there were insufficient information to show that a drug can safely be given to children, the labeling would restrict the drug's use to adults.

### **PHASE 4 Trials**

Phase 4 trials are conducted after the drug or treatment has been approved for marketing. They are designed to:

- Continue testing the drug or treatment to collect additional short-term safety information.

- Collect information about the effect of the drug or treatment in various populations.
- Collect information about side effects associated with long-term use of the drug.

## Part 3: Investigational New Drugs Requirements

### The Investigational New Drug Application

A [sponsor](#) who wishes to conduct a clinical trial that involves an investigational new drug must submit an Investigational New Drug application (IND) to the FDA. In IND studies, the IND holder is considered to be the sponsor.

#### [Information that must be provided in an IND](#)



Information that must be provided in an IND includes the following:

- The identity and contact information of the sponsor and the phase (or phases) of the trial.
- A commitment that an IRB will be responsible for initial and continuing review of the trial.
- The name of the drug, a list of its active ingredients, and its dosage and route of administration.
- The objectives and planned duration of the proposed clinical trial(s).
- A brief description of the plan for investigating the drug, including:
  - The reasoning behind the drug or the study,
  - The indication(s) to be studied,
  - The kinds of clinical trials to be conducted in the first year after the IND submission,
  - The estimated number of patients who will be given the drug in the clinical trial(s), and
  - Any serious risks that are anticipated on the basis of animal studies or previous human studies of this drug or related drugs.
- For most trials, a copy of the [investigator's brochure](#).
- A protocol for each planned study. (See related material summarized from [The Research Protocol module](#).)
- The identities and qualifications of all investigators. (As demonstrated in a Curriculum Vitae and Form FDA 1572. Click here for instructions on completing [Form FDA 1572](#).)
- The criteria for patient selection and exclusion and an estimate of the number of patients to be studied.
- A summary of previous experience with the drug in both animal and human studies, including (if relevant):
  - Previous INDs,
  - Experience with the drug in other countries,

- Known safety issues, chemistry and manufacturing information, and
- Dependence and abuse potential.

### When an IND Goes Into Effect



An IND is considered safe to proceed 30 calendar days after the FDA receives it unless:

- The FDA notifies the sponsor that the investigation described in the IND is subject to a [clinical hold](#), or
- The sponsor receives written permission from the FDA to begin the study before 30 days have elapsed.

At the sponsor's request, the FDA will provide advice on specific matters relating to an IND. Meetings between a sponsor and the FDA are frequently useful, and the FDA encourages such meetings to the extent that FDA resources permit.

### IND Exemptions for Studies of Lawfully Marketed Drugs

Studies of lawfully marketed drugs are exempt from the IND regulations if they meet all five of the criteria listed in [21 CFR 312.2\(b\)\(1\)](#). The first four of these criteria are straightforward and need no special comment.

- The study is not intended to support approval of a new indication or a significant change in the product's labeling.
- The study is not intended to support a significant change in the product's advertising.
- The study is conducted in compliance with [Institutional Review Board](#) (IRB) and [informed consent](#) regulations.
- The study will not be used to promote non-approved indications.

The final criterion, however, requires interpretation.

- The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.

It is the investigator's responsibility to determine whether an IND is necessary for a study that involves a marketed drug. A critical question in determining whether such a study is exempt from IND regulation is



whether the study “significantly increases the risk” associated with use of the drug.

If an investigator is quite sure that a drug study does not require an IND, he or she can simply not submit an IND application. If the investigator is doubtful about whether an IND is required, or wishes to have proof of the IND-exempt status of a study, the IND application can be submitted with an exemption from IND guidelines requested, and FDA staff will review the application to determine whether the study is exempt. The review is limited to critical safety concerns (dose, schedule, route, and patient population). If, after this limited review, the FDA determines that a study is exempt from the requirement for an IND, it performs no further review of the application. The FDA sends a letter to the sponsor giving notice of the exemption. Prior to submission of the application, the sponsor can also set up a pre-IND meeting with the FDA in order to discuss any questions or concerns.

### IND Protocol Amendments

The sponsor of an IND must submit a protocol amendment to the FDA:

- To describe any change in a Phase 1 protocol that significantly affects the safety of participants; or
- To describe any change in a Phase 2 or Phase 3 protocol that significantly affects the safety of participants, the scope of the investigation, or the scientific quality of the study.

The following are examples of changes that would require the submission of a protocol amendment to the FDA:

- An increase in drug dosage or in the duration of participants' exposure to the drug.
- A significant change in the study design, such as the addition or elimination of a control group.
- The addition of a new test or procedure to improve monitoring for, or to reduce the risk of, an adverse event, or the dropping of a test intended to monitor safety.
- The protocol amendment can be implemented at study sites after the amended protocol has been submitted to and approved by the reviewing IRB, and submitted to the FDA..

A protocol change that is intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided that:

- The FDA is subsequently notified of the change by a protocol amendment, and
- The reviewing IRB is also notified of the change in accordance with the IRB's rules.

### IND Safety Reports

Sponsors must promptly review and investigate all information they receive relevant to the safety of an investigational new drug that is received from any source, foreign or domestic, including information derived from:

- Clinical or epidemiological studies,
- Animal studies,
- Commercial marketing experience,
- Reports in the scientific literature,
- Unpublished scientific papers, and
- Reports from foreign regulatory authorities.

The sponsor must notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but not later than 7 calendar days after the sponsor's initial receipt of the information. Sponsors must provide written notification to the FDA and to all investigators participating in a trial within 15 calendar days of any adverse event that is:

- Both serious and unexpected, and
- Reasonably likely to have been caused by the investigational new drug.

Subsequent, appropriate follow-up information must also be submitted, as it becomes available.

The sponsor must also provide written notification of any finding from tests in laboratory animals that suggests a significant risk for human participants. The written notification must be provided as soon as possible and no later than 15 calendar days after the sponsor receives the information.

### IND Information Amendments and Annual Reports

A sponsor must file an information amendment to report essential information about the IND that is not within the scope of a protocol amendment, IND safety report, or annual report. The following are examples of information that requires the filing of an information amendment:

- New information about technical features of the drug, such as its toxicology or chemistry.
- Discontinuation of a clinical investigation.

Within 60 days of the first anniversary of the date the IND went into effect, and every subsequent year, a sponsor must submit a brief report of the progress of the investigation. This annual report must include:

- A brief summary of the status of each study in progress or completed.
- A summary of the most frequent and most serious adverse experiences.
- A summary of all IND safety reports submitted.
- A list of participants who died during participation in the investigation, with the cause of death for each participant.
- A list of participants who dropped out as a result of any adverse experience, whether or not the adverse experience is thought to be related to the investigational new drug.
- A summary of the general investigational plan for the upcoming year.
- An updated Investigator's Brochure, if available.
- A summary of any foreign market developments.
- A summary of any outstanding business with the FDA regarding the IND (i.e. a response to an FDA request for information).

## Part 4: Investigational New Drugs Responsibilities



### Responsibilities of Sponsors



Both sponsors and investigators who are involved in conducting a clinical trial under an IND filed with the FDA must accept and fulfill certain responsibilities.

Sponsors' responsibilities include:

- Selecting qualified investigators.
- Providing investigators with the information they need to conduct the investigation.
- Ensuring proper monitoring of the trial.
- Ensuring the trial is conducted according to the plan and protocols contained in the IND.
- Informing the FDA and all investigators of significant new adverse effects or risks that are reasonably likely to be caused by the investigational new drug.
- Maintaining proper records.
- Disposing of unused supplies of the investigational new drug.

Unless the sponsor is a sponsor-investigator, the sponsor does not actually conduct the investigation.

Based on GCP guidelines, other Sponsor responsibilities include (ICH GCP E6, 5.12; 5.13; 5.14):

- Ensuring that the Investigational Product is manufactured in accordance with Good Manufacturing Practices.
- Ensuring that Investigational Product is packaged in a way that prevents contamination and unacceptable deterioration during transport and storage.
- Supplying investigators/institutions with the Investigational Product.
- Having written procedures that include instructions on the handling and storage of Investigational product that sites should follow.

- Maintaining sufficient quantities of the Investigational Product used in the trial to reconfirm specifications should the need arise.

The above represent good examples of responsibilities the Sponsor may transfer to a Contract Research Organization (CRO), such as a clinical coordinating center. However, the ultimate responsibility for Investigational Product resides with the Sponsor. Any Investigational Product-related duties and functions that are transferred to and assumed by a CRO are specified in writing.

## Responsibilities of Investigators



Investigators' responsibilities include:

- Providing the sponsor with a completed, signed Statement of Investigator. (Form FDA 1572. [Click here](#) for instructions on completing this form.)
- Conducting the trial in accordance with the signed investigator statement, protocol, and applicable regulations.
- Protecting the rights, safety, and welfare of trial participants.
- Obtaining informed consent from all trial participants.
- Maintaining proper records.
- Furnishing all required progress reports, safety reports, financial disclosure reports, and a final report.
- Complying with Institutional Review Board review. and
- Ensuring the proper handling of controlled substances.

This topic is also discussed in the [Roles and Responsibilities module](#).

Based on GCP guidelines, other Investigator responsibilities include (ICH GCP E6, 4.6):

- Ensuring Investigational Product accountability
- Assigning duties for Investigational Products to a pharmacist or an appropriate individual who has the necessary license for dispensing
- Maintaining records of the Investigational Product from delivery at the site to dispensing to the participant as well as use by the participant, return by the participant, and reconciling all product prior to destruction.
- Ensuring that the Investigational Product is used in accordance with the approved protocol
- Explaining the correct use of the Investigational Product to each participant and checking at intervals that each participant is following instructions properly.

Click to view **Clinical Trial Network** related content

CTN



## Why is the regulation of investigational new drugs relevant to the Clinical Trials Network?

Studies performed within the NIDA Clinical Trials Network (CTN) that involve an investigational drug

must be carried out in accordance with the investigational new drug regulations.

The investigational new drug regulations are enacted to:

- Protect the safety of research participants,
- Ensure that participants are not exposed to experimental drugs or procedures unnecessarily, and
- Protect participants' rights.

It is important, however, that all members of the CTN — not only those involved with studies of investigational new drugs — understand the basics of these important regulations because the reasoning behind the investigational drug regulations applies to all research involving human participants, including the [International Council for Harmonization](#) Good Clinical Practice guidelines.

These principles are equally applicable to behavioral research, or to medication studies not requiring an IND, even though these studies do not involve an investigational new drug. Research participants should not be exposed to any experimental intervention unnecessarily, in an unsafe manner, or in a manner that fails to protect their rights.

Although behavioral studies and IND-exempt medication studies conducted in the CTN are not subject to the requirement to submit IND safety reports to the FDA, CTN members who conduct such studies must submit Adverse Event/Serious Adverse Event information and reports to the DSMB Medical Monitor at NIDA. All CTN members should be familiar with the similarities and differences in terminology and reporting requirements between reports required by NIDA and those required by the FDA.



[Read more...](#)

## Guidance Documents

The FDA has incorporated the concept of Good Clinical Practice (GCP) into agency guidance documents, which are intended to help researchers comply with GCP regulations. Guidance on Good Clinical Practice may be found in the following documents:

- [FDA's Good Clinical Practice: Consolidated Guideline \(April 1996\)](#)
- [Clinical Investigation of Medicinal Products in the Pediatric Population](#)
- [Choice of Control Group and Related Issues in Clinical Trials \(May 2001\)](#)
- [Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators \(2015\)](#)

Although these guidance documents are not binding, they reflect the FDA's current thinking about the interpretation of the regulations. Many guidance documents are available on the FDA's Website. ([Click here](#) for a list of available guidance documents.) Guidance documents are also published in the [Federal Register](#).

Guidance documents used internationally include both the:

- [International Conference on Harmonization](#) Good Clinical Practice guidelines E6, and
- [International Conference on Harmonization](#) Good Clinical Practice guidelines E8.

## Part 4: Investigational New Drugs Responsibilities

### Interactive: Investigational New Drugs

#### Users are instructed as follows:

The three investigators below are planning clinical trials that involve substance abuse treatment. Read about each of their trials, and then make a decision: Which Investigator needs to file an Investigational New Drug Application prior to initiating the study? Then, consider the feedback.

#### A) Dr. Alvin

Marketed drug with a change in the indication

Dr. Alvin's trial will see if participants taking a marketed drug, currently used to treat anxiety, will have any use for relapse prevention in adults with cocaine dependence. Dr. Alvin is planning a small pilot study first, using the drug at doses currently used clinically, but with a reduction in dosing frequency. If the results are good, a larger study will be planned.

#### B) Dr. Bluth

Two marketed drugs in a head to head comparison for the same condition

Dr. Bluth has been approached by a small pharmaceutical company to run a comparison study of two products, both currently marketed to help adults quit smoking. The company has just gained FDA approval of their drug and want to use the data from Dr. Bluth's study in advertisements and in a journal article.

#### C) Dr. Carey

Combination drug treatment for tobacco and stimulant dependence

Dr. Carey is planning a trial to determine if smokers who are currently receiving FDA-approved treatment for stimulant dependence can benefit from taking an FDA-approved treatment to help them stop smoking. The goal is to see if stopping a patient from smoking helps with their stimulant dependence. Dr. Carey is drafting a grant for NIH to hopefully support this study.

*Feedback: Which Investigator needs to file an Investigational New Drug Application prior to initiating the stud: (A) Dr. Alvin, (B) Dr. Bluth, or (C) Dr. Carey?*

#### A) Dr. Alvin

*Feedback:* Dr. Alvin is exempt from the IND application because the trial involves 1) a product lawfully marketed in the US 2) not intended to be reported to FDA as a well-controlled study in support of a label change 3) not intended to support a change in advertising for the drug 4) the study does not increase the risk associated with the use of the drug. Dr. Alvin will still need approval by the local IRB and ensure patients are consented. Dr. Bluth's trial requires an IND application because it is conducting a 'head to head' comparison study which, although within the approved labels for both drugs, will be used to make a significant change to the advertising for the drug. Therefore, A is an incorrect response.

**B) Dr. Bluth**

*Feedback:* Dr. Carey is exempt from the IND application because the trial involves 1) two products lawfully marketed in the US 2) not intended to be reported to FDA as a well-controlled study in support of a label change 3) not intended to support a change in advertising for the drug 4) the study does not increase the risk associated with each use of the drug. Dr. Alvin will still need approval by the local IRB and ensure patients are consented. Dr. Bluth's trial requires an IND application because it is conducting a 'head to head' comparison study which, although within the approved labels for both drugs, will be used to make a significant change to the advertising for the drug. Therefore, C is an incorrect response.

**C) Dr. Carey**

*Feedback:* Dr. Bluth must submit an IND application because, although the trial involves testing two legally marketed drugs within the approved label, the goal of the study is to make a significant change to the advertising materials used from the drug, by, hopefully, saying that drug X is better or safer than drug Y in helping patients stop smoking. Therefore, the correct response is B.

## Part 5: Summary of Key Points

- ICH GCP refers to an Investigational Product as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
- In FDA regulations, an investigational new drug is any substance (such as a drug, vaccine, or biological product) for which FDA approval is being sought.
- A drug may be considered “new” even if it has been in use for years if a change is proposed in its use, formulation, route of administration, or packaging.
- A sponsor who wishes to conduct a clinical trial that involves an investigational new drug must submit an Investigational New Drug application (IND) to the FDA. Lawfully marketed drugs are exempt from the IND regulations if they meet certain criteria.
- Behavioral studies (like the ones conducted in the CTN) are not subject to investigational new drug regulations. Moreover, certain medication studies may be IND-exempt. It is important, nonetheless, that all researchers understand these regulations. The principle that research participants should not be exposed to experimental interventions unnecessarily, in an unsafe manner, or in a manner that fails to protect their rights is equally applicable to all studies involving human participants.