



## **Sponsor-Investigator Frequently Asked Questions**

Harvard Catalyst Regulatory Foundations, Ethics, and Law Program

IND/IDE Subcommittee

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## Drugs

### Definitions

The following definitions appear in the Investigational New Drug Application regulations 21 CFR 312.3:

**Clinical investigation:** Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

**Contract research organization (CRO):** A person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA.

**FDA:** Food and Drug Administration.

**IND:** Investigational New Drug Application.

**Investigational new drug:** A new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. Also, "investigational drug" and "investigational new drug".

**Investigator:** An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub investigator" includes any other individual member of that team.

**Marketing application:** An application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

**Sponsor:** A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

**Sponsor-Investigator:** 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. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

**Subject:** A human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

## What is an IND?

An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. In addition, 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 may want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND Application 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 three IND types:

- An Investigator IND is submitted by an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed (Sponsor-Investigator). A sponsor-investigator 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. Often referred to as investigator-initiated IND, or sponsor-investigator IND.
- 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 21CFR312.23 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 for which there are no satisfactory alternative treatments, while the final clinical work is conducted and the FDA review takes place.

(Source: [FDA website](#))

## When can I use an IND for expanded access?

[21 CFR part 312 Subpart I](#) provides general requirements, describes criteria that must be met to authorize expanded access, lists requirements for expanded access submissions, and describes safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the investigational product. Under FDA's current regulations for investigational drugs (including biologics), there are three categories of expanded access:

- Expanded access for individual patients, including for emergency use;
- Expanded access for intermediate-size patient populations; and
- Expanded access for widespread use.

For more information, see FDA's Draft Guidance (2013) on Expanded Access to Investigational Drugs:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf>

## Does my study require an IND?

U.S. regulations require that an IND be in effect prior to the clinical study of an investigational drug/biologic product. "Investigational use" can mean a product not approved by FDA for any use, or it could also mean the use of an approved product in a way that is beyond its approved labeling (e.g., use, route of administration etc.). 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 is exempt from the IND submission requirement if all of the following conditions are met:

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

The regulations provide for additional exemptions from the IND regulations. See [21 CFR 312.2](#) for a full description of exempt categories.

It is the responsibility of the Sponsor (including sponsor-investigator) to justify why a proposed study meets the requirements for exemption from the IND regulations. Per FDA, sponsors who are uncertain if their proposed investigation meets the criteria for IND exemption may seek advice from the FDA [Review Division](#) responsible for the relevant therapeutic area of the proposed trial and/or their IRB. In some cases, FDA staff may be able to provide this advice through informal communications (e.g., phone conversation, e-mail). In other cases, FDA staff may request that the sponsor submit a summary of their proposed investigation in writing for FDA review before providing advice. In certain cases, FDA staff may advise the sponsor to submit **a full** IND application for the proposed investigation for FDA review. If during that review FDA concludes the IND application meets the criteria for exemption, the sponsor will be so notified.

A key reference tool in determining whether an IND is required is the FDA Guidance document, "[Investigational New Drug Applications \(INDs\) —Determining Whether Human Research Studies Can Be Conducted Without an IND](#)". Investigators are advised to review this document when determining whether an IND is needed.

## **A Note about "Off Label Use"**

*When the FDA approves a drug or biologic it also specifies the indications and parameters for/by which it can be used. 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 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 IRB. 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.*

***Please note that when intent and scope of prescribing practice goes beyond practice of medicine and is research focused (e.g., involves systematic data collection, analysis, and there is intention for future publication or change in label), the local IRB and/or FDA should be consulted to ensure an IND is not required.***

## **I want to ask FDA some questions before I submit my IND, what should I do?**

Open communication is encouraged between FDA and sponsors/investigators. Both formal and informal communication with FDA is possible. Informal communication may involve emailing or calling a known contact at FDA to ask a question that may be anticipated to be reasonably addressed easily. For more complex questions, or to engage FDA in discussions on multiple questions regarding a particular study or development program, you should request a formal meeting with FDA. Meetings are classified into three types, each having its own timeframes and submission requirements. For example, a meeting to discuss items related to an IND submission before the application is submitted, is called a **Pre-IND Meeting**, and is classified as a Type B meeting. In general, the wait for formal meetings with FDA can be anywhere from two to five months. Please refer to the FDA website on [interacting with FDA](#) and to the FDA Guidance, "[Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants](#)" for specific information on how to request a meeting with FDA.

## **How do I prepare an IND?**

It is the responsibility of the Sponsor (or sponsor-investigator) to submit an IND application to FDA for studies which are subject to the IND regulations. 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.

Specifically, per [21 CFR 312.23](#) the content of an IND should include:

- Cover Letter
- [Form 1571](#)
- [Form 1572](#)
- [Form 3674](#)
- Table of Contents
- Introductory Statement and General Investigational Plan
- Chemistry, Manufacturing, and Control Information
- Pharmacology Toxicology Information
- Investigator's Brochure
- Clinical Protocol(s)
- Summary of Previous Human Experience with the Investigational New Drug
- Additional Information, if applicable (e.g. drug dependence and abuse potential, pediatric studies, etc.)
- Other Relevant Information, if applicable or if requested by FDA

**Note:**

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.

[Key Reference Tools:](#)

[FDA's website](#) with detailed information on the requirements and process for submitting and maintaining Investigator-Initiated INDs

[Investigator's Checklist for IND Application Submission](#)

[IND Forms and Instructions](#)

## What do I need to do as a sponsor of an IND?

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. A sponsor-investigator is responsible for all regulatory requirements as both a **sponsor** and an **investigator**. Regulatory responsibilities for investigators and sponsors are detailed in [Subpart D of 21 CFR 312](#).

Responsibilities include for IND sponsors include: selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described in the [regulations](#).

## What is “monitoring”?

Sponsors are responsible for ensuring proper monitoring of the investigation and for selecting a monitor qualified by training and experience to monitor the progress of the investigation.

FDA has issued a guidance document, “[Guidance for Industry - Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring](#)” which assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products. This guidance acknowledges that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring and describes strategies for “monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively”.

## When do I need to submit an amendment to an IND?

A sponsor of an active IND is expected to update the application as new information is obtained on the investigational product. The following outlines the types of amendments to an IND application:

1. **Protocol Amendments** ([21 CFR 312.30](#))
  - **New Protocol:** Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor must submit to FDA a protocol amendment containing the protocol for the study. The study may begin once the sponsor has submitted the protocol to FDA for its review **and** the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review

and approval of the study. The sponsor may comply with these two conditions in either order.

- **Changes in a protocol:** A sponsor must submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples include:
  - Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.
  - Any significant change in the design of a protocol (such as the addition or dropping of a control group).
  - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

A protocol may be made once the sponsor has submitted the change to FDA for its review **and** the change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

***Note:** A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).*

- **New investigator:** A sponsor must submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added. Sponsors must collect and submit the 1572 and CV of the PI from each site.

## 2. **Information Amendments** ([21 CFR 312.31](#))

Sponsors are required to submit to FDA in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

- New toxicology, chemistry, or other technical information; or
- A report regarding the discontinuance of a clinical investigation
- Serious, related, unexpected, significant adverse events, or fatal, life-threatening events

## What do I include in an annual report?

Sponsors are required to submit an annual report to FDA providing a brief report of the progress of the investigation within 60 days of the anniversary date that the IND went into effect. The annual report must include:

- (a) Individual study information - A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:
  - 1. The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.
  - 2. The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.
  - 3. If the study has been completed, or if interim results are known, a brief description of any available study results.
- (b) Summary information. Information obtained during the previous year's clinical and nonclinical investigations, including:
  - 1. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.
  - 2. A summary of all IND safety reports submitted during the past year.
  - 3. A list of subjects who died during participation in the investigation, with the cause of death for each subject.
  - 4. A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.
  - 5. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
  - 6. A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
  - 7. A summary of any significant manufacturing or microbiological changes made during the past year.

- (c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under [312.23\(a\)\(3\)\(iv\)](#).
- (d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.
- (e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.
- (f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.
- (g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

### When do I need to let FDA know about an adverse event in my clinical trial?

IND Safety Reporting is detailed in [21 CFR 312.32](#).

The Sponsor (or sponsor-investigator) must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

**The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:**

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates

those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Written reports should be reported to the FDA via MedWatch 3500A. FDA expects fatal or life-threatening reports to be reported within seven days and any follow-up information as they become available. For additional information on safety reporting requirements, please refer to the FDA Guidance, "[Safety Reporting Requirements for INDs and BA/BE Studies](#)".

### **As the Sponsor-Investigator of a multi-centered study what documents am I required to maintain on-site and what documents do site investigators need to maintain?**

The sponsor-investigator of a multicenter must retain appropriate records for their role as Sponsor as well as their role as Investigator. [The Harvard Catalyst Regulatory Binder](#) is a template and guidance document for tracking documentation associated with studies involving human subjects and has specific information for FDA-covered research and sponsor-investigator-initiated research.

#### Sponsor records:

- Adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.
- Complete and accurate records showing any financial interest paid to clinical investigators by the sponsor of the covered study and all other financial interests of investigators subject to 21 CFR 54.

A sponsor shall retain these records for two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

#### Investigator records:

- Adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.
- Adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
  - Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for

example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

An investigator shall retain these records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

### **If I am working with a research pharmacy, do I still need to maintain drug accountability on site?**

According to federal regulations (21 CFR 312.57), a Sponsor (or sponsor-investigator) shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment. A sponsor shall retain these records for two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. If drug dispensation is being maintained by a research pharmacy include a note-to-file within the regulatory files indicating where this is being maintained and by whom. Operational practice may vary by site, but it is the sponsor-investigator's responsibility to ensure the appropriate tracking and use of the investigational product is being maintained for all study participants.

### **I do not plan to conduct any further research under my IND and I want to make my IND "inactive". What steps should I take?**

If no subjects are entered into clinical studies for a period of two years or more under an IND, or if all investigations under an IND remain on clinical hold for one year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. A sponsor is not required to submit annual reports to an IND on inactive status. Additional information about inactive status of an IND can be found in [21 CFR 312.45](#).

In addition, a sponsor may **withdraw** an active IND at any time. If an IND is withdrawn, FDA must be notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all drug must be returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 21 CFR 312.59. If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

Before you decide to inactivate or withdraw your IND, you should consider the following:

- Is data collection complete and data analysis final?
- Do you anticipate conducting a follow-up study?

When you are ready to inactivate or withdraw your IND, you should close out the study with the IRB before making the IND inactive with the FDA. Once the IRB protocol is closed, we recommend sending a report (same structure as the annual report) to the FDA updating them on what occurred during the last year under the IND as well as requesting that the IND become inactive.

## Biologics

### What is a biological product?

Biological products include a wide range of products such as vaccines, blood, and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids, or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available. (Source: [FDA](#)) How are biological products regulated?

The Center for Biologics Evaluation and Research (CBER) within FDA regulates a wide range of biological products, including

- allergenic extracts (e.g. for allergy shots and tests)
- blood and blood components
- gene therapy products
- devices and test kits
- human tissue and cellular products used in transplantation
- vaccines

The Center for Drug Evaluation and Research (CDER) within FDA regulates other categories of biological products mostly produced by biotechnology methods, including:

- monoclonal antibodies designed as targeted therapies in cancer and other diseases
- cytokines (types of proteins involved in immune response)
- growth factors (proteins that affect the growth of a cell)
- enzymes (types of proteins that speed up biochemical reactions), such as thrombolytics (used to dissolve blood clots)
- immunomodulators (agents that affect immune response)

(Source: [FDA](#))

**Note: Investigational uses of biologic products follow the same requirements and process under the IND regulations (21 CFR 312).**

## Devices

### Definitions

Below are some key device found in [FDA's Device Advice](#):

**Implant:** Implant is a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

**Investigation:** Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

**Investigational device:** Investigational device is a device, including a transitional device, that is the object of an investigation.

**Investigational device exemption (IDE):** IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

**Investigator:** Investigator is an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.

**Monitor:** When used as a noun, monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor, or a consultant to the sponsor, or an employee of or consultant to a contract research organization. When used as a verb "monitor" means to oversee an investigation.

**Premarket Approval (PMA):** A premarket approval means any premarket approval application for a Class III medical device, including all information submitted with or incorporated by reference therein. (21 CFR 814.3)

**Premarket Notification [PMN or 510(k)]:** 510(k) refers to the type of submission to FDA described under 21 CFR 807 Subpart E in which the applicant must establish that their device is substantially equivalent to a legally marketed device. This type of submission is used for most Class II devices and some Class I devices.

**Significant risk device (SR device):** Significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.

**Sponsor:** Sponsor is a person or other entity that initiates but does not actually conduct the investigation. An entity other than an individual (e.g., a corporation or an agency) which uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor, not a sponsor-investigator, and the employees are considered to be investigators. The sponsor of an IDE must be located in the United States (see 21 CFR 812.18).

**Sponsor-Investigator:** Sponsor-Investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

**Subject:** Subject is a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or who participates as a control. A subject may be in normal health or may have a medical condition or disease.

**Unanticipated adverse device effect:** Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

## What is a Medical Device?

A device is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

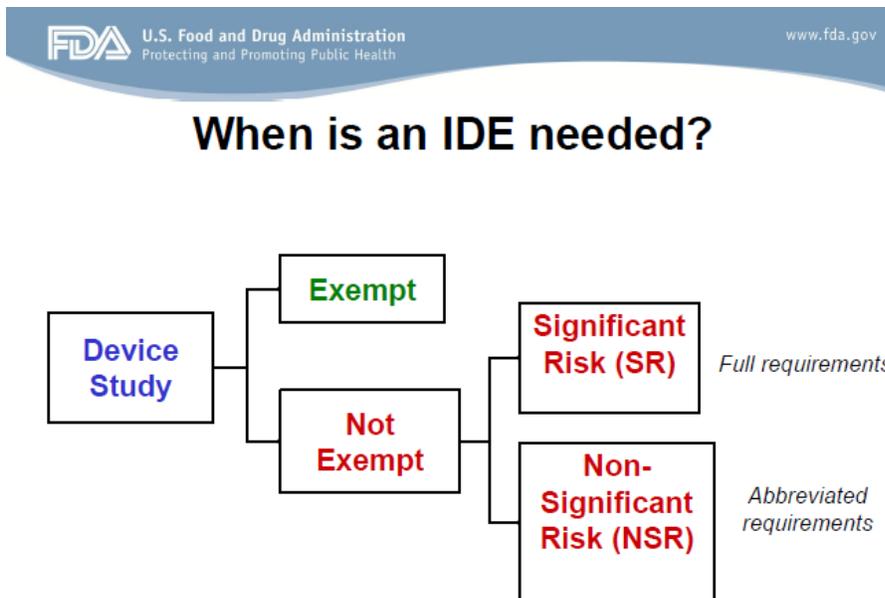
The FDA maintains the website [Device – Not a Device](#) which includes tools to help Sponsors/Investigators determine whether their product is a medical device.

## What is an IDE?

An IDE is an “Investigational Device Exemption” and allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.

## Does my medical device study fall under the IDE regulations?

This algorithm from FDA may help you determine when an IDE is needed.



### Exempt Categories:

Per [21 CFR 812.2\(c\)](#), these are categories of research that are exempt from the IDE regulations:

- Commercial devices used in accordance with labeling
- Diagnostic devices if the testing:
  - Is noninvasive,
  - Does not require an invasive sampling procedure that presents significant risk,
  - Does not by design or intention introduce energy into a subject, and
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- Testing of consumer preference, of a modification, or of a combination of devices, when not determining safety or effectiveness and not putting subjects at risk

- Veterinary devices or research on/with laboratory animals
- A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. (See also [FDA Guidance on Custom Devices](#))

Also exempt from the IDE regulations:

- Practice of medicine with legally marketed devices (for any indication)
- Basic physiological research
  - Applicable for studies investigating a physiological principle, with no intent to develop the device for marketing. The device is only used to address the research question. IRB approval and informed consent should still be obtained.

### **I am conducting a clinical study with a medical device. How can I determine whether this is a Significant Risk or a Non-Significant Risk study?**

The risk determination is important as it determines the IDE pathway. Significant risk (SR) device means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A Non-significant risk (NSR) device study is one that does not meet the definition for an SR device study.

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. The IRB may agree or disagree with a Sponsor's NSR assessment. If the IRB finds the device to be SR, it must notify the investigator. FDA is available to help the sponsor, clinical investigator, and IRB in making the risk determination. FDA is the final arbiter in deciding whether a device is SR or NSR.

Sponsors/Investigators are encouraged to review the FDA Information Sheet "[Significant Risk and Non-significant Risk Medical Device Studies](#)" for help determining risk.

## What are my responsibilities as an IDE sponsor?

Regulatory responsibilities for Sponsors and Investigators of SR and NSR risk studies differ.

Most notably, sponsors (or sponsor-investigators) of NSR device studies do not need to submit an IDE application to FDA; the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. Additionally, for NSR device studies there are abbreviated regulatory sponsor responsibilities (labeling, IRB review, consent, monitoring, reporting, prohibition on promotion).

For SR device studies, before the study can begin an IDE application must be first submitted to and approved by FDA. Responsibilities include: selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts [B](#) and [G](#).

Sponsors/Investigators are advised to review this [FDA website](#) which details IDE Responsibilities for sponsors of significant risk and non-significant risk device studies.

## I am the Sponsor-Investigator of a Significant Risk study. How do I submit an IDE application to FDA?

A sponsor of a SR device study must submit a complete IDE application to FDA. Note, there are no forms for an IDE application; however, an IDE application must include certain required information.

The sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained, that the investigation is scientifically sound, and that there is reason to believe that the device as proposed for use will be effective.

### Required Elements

The following information must be included in an IDE application for a SR device investigation. A sponsor cannot begin a significant risk device investigation until FDA and IRB approval are granted.

Three copies of a signed IDE application are required, and the application must include the following in the order provided (per 21 CFR 812.20):

1. Name and address of sponsor

2. A **report of prior investigations** must include reports of all prior clinical, animal, and laboratory testing of the device
3. An **investigational plan**
4. A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device
5. An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. Information that must be included in the written agreement are found in 21 CFR 812.43
6. Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study
7. A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available)
8. The name and address of any institution (other than those above) where a part of the investigation may be conducted
9. The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization
10. Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required.
11. Copies of all labeling for the device
12. Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR 50
13. Any other relevant information that FDA requests for review of the IDE application. Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference

FDA also has suggested content for original IDE application cover letters and a suggested format for IDE submissions available on its [IDE Application website](#). Also available on this website is an IDE application administrative checklist which Sponsors and sponsor-investigators should use prior to submitting their applications.

**Note:** An electronic copy (eCopy) is required to be submitted with all IDE submissions (other than compassionate and emergency use IDEs). An eCopy is defined as an exact duplicate of the paper submission, created and submitted on a compact disc (CD), digital video disc (DVD), or a flash drive. An eCopy is accompanied by a paper copy of the signed cover letter and the complete paper submission. An eCopy must follow pre-specified technical requirements. Sponsors and sponsor-investigators are advised to review FDA's Guidance, "[eCopy Program for Medical Device Submissions](#)" for details on how to submit a valid eCopy.

## **I have other questions about IDEs and Medical Devices, where can I learn more?**

Investigators are advised to review the FDA website, “[Device Advice: Investigational Device Exemptions](#)” for additional information.

## Multi-Topic

### Is there any guidance on how to prepare for an FDA Inspection?

The FDA provides guidance on preparing for an audit via their [Compliance Program Guidance Manual for FDA Staff](#), as well as the [Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors on FDA inspections of Clinical Investigators](#).

<http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf>  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>

Additional guidance is available here:

[http://catalyst.harvard.edu/pdf/regulatory/HowtoSurviveanFDAInspection\\_CindyMonahan.pdf](http://catalyst.harvard.edu/pdf/regulatory/HowtoSurviveanFDAInspection_CindyMonahan.pdf)

### What responsibilities can I delegate to my staff or a CRO?

Any transfers of responsibility must be documented in writing. If not all of the sponsor responsibilities are transferred, the writing should contain a comprehensive list of all responsibility areas and specific whether the sponsor has retained responsibility or transferred responsibility. The best way to ensure the sponsor and CRO are communicating and on the same page is to document all area. Examples of delegated responsibilities may include but is not limited to:

- Trial design and management, data handling and record keeping:
- Investigator Selection: appropriate, qualified investigators, trained in protocol and product
- Financing: document financial arrangements with investigators, secure adequate liability coverage
- Submissions to FDA:
- Communication with IRB for review and approvals
- Safety Monitoring and Reporting
- Monitoring: selection, training and oversight.
- Auditing: establishing an audit plan, selecting auditors and approving audit procedures.
- Dealing with non-compliance: prompt corrective action, including terminating investigators if needed
- Suspension or termination of a trial (if warranted)
- Trial Reporting: to IRB and regulatory authorities

## Can I communicate directly with the FDA or do I have to notify my IRB first, or both?

Institutional policies and procedures differ. Please contact your institutional regulatory representative or your IRB to determine whether there are specific requirements at your institution. If there are any conflicting information being provided by your IRB and FDA, please note the FDA has the final say. Sponsor-Investigators can arrange to have a pre-IND Meeting between the FDA and IRB Representatives if necessary.

## How are medical food or supplements classified?

A dietary supplement is defined, in part, as a product taken by mouth that is intended to supplement the diet and that contains one or more dietary ingredients. A dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required. For additional information, please refer to the FDA Guidance, "[Investigational New Drug Applications \(INDs\) —Determining Whether Human Research Studies Can Be Conducted Without an IND](#)".