Research Compliance Professional's Handbook, Third Edition
7 FDA-Regulated Clinical Research

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Introduction

The U.S. Food and Drug Administration ("FDA") oversees clinical trials involving drugs and medical devices under the Federal Food, Drug, and Cosmetic Act ("FDCA") and implementing regulations. This chapter describes the types of trials regulated by the FDA, the major regulations governing conduct of those trials, responsibilities of sponsors and investigators in performing FDA-regulated trials, what to expect from an FDA inspection of a clinical trial and how to respond.

Legal Framework

Among other things,[2] the FDCA prohibits the shipment of "adulterated" and "misbranded" drugs and devices in interstate commerce.[3] Drugs or devices that are not approved or cleared by the FDA, or that are approved or cleared but offered for a use that is inconsistent with their approved or cleared labeling, are traditionally thought of as adulterated or misbranded. The FDCA facilitates new drug and device development through provisions authorizing the FDA to issue regulations that permit and govern the investigational use of drugs and devices to study their safety and effectiveness before approval or clearance.[4] These regulations include:

- 21 C.F.R. Part 11 (Electronic Records; Electronic Signatures) [5]
- 21 C.F.R. Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards), which correspond substantially with the provisions of the Common Rule [6]
- 21 C.F.R. Part 54 (Financial Disclosures by Clinical Investigators) [7]
- 21 C.F.R. Part 312 (Investigational New Drug Application [IND])
- 21 C.F.R. Part 812 (Investigational Device Exemptions [IDE])

In addition to the FDCA and related laws and regulations, the FDA regularly issues industry guidance to facilitate compliance with legal and regulatory mandates. These guidance documents are not law but represent the agency's current thinking or policy on regulated activities, including clinical research.[8] They do not bind the FDA or the public and do not establish legally enforceable rights or responsibilities. To the contrary, a sponsor or investigator may employ an alternate approach provided its conduct complies with the requirements of all applicable statutes and regulations. Where a sponsor or investigator intends to follow an alternate approach, however, an advance meeting or discussion with the FDA may be prudent.

Importantly, while the laws and regulations referenced above govern the conduct of research involving investigational drugs and devices, they do not address the off-label use in clinical practice of approved or cleared drugs or devices. A practitioner who wishes to use an FDA-approved or cleared drug or device off-label should, however, be well informed about the product, base its use on firm scientific rationale and on sound medical

evidence, and maintain records of the product's use and effects.[9]

Sponsor and Investigator Responsibilities

A "sponsor" is an individual or organization who initiates but does not actually conduct a clinical investigation.[10] The sponsor is ultimately responsible for the proper conduct of the investigation. An "investigator," by contrast, is the individual who actually performs the investigation.[11] An individual who both initiates and performs an investigation is referred to as a "sponsor-investigator."[12] The FDA prescribes the responsibilities of sponsors and investigators in regulations governing clinical investigations and clarifies its approach in associated guidance posted to the agency's website.[13]

Sponsor Responsibilities

1. Generally

Sponsors are ultimately accountable for assuring that clinical investigations are conducted in accord with approved protocols, or "investigational plans," and with applicable laws and regulations.[14] For example, it is a sponsor's job to:

- Secure FDA approval of an IND, IDE or exemption if required, and comply with the requirements applicable to an IND or IDE
- Select qualified investigators and monitors and provide them with the information they need to conduct and monitor the investigation properly
- Ensure that the investigation is conducted in accordance with the general investigational plan and protocol
- Promptly inform the FDA, the IRB, and investigators of any significant new adverse effects or risks associated with the product
- Appropriately label investigational products
- Initiate, hold, or discontinue clinical trials as required
- Control the distribution and return of investigational products, including shipping only to authorized investigators
- Evaluate and report adverse experiences
- Maintain adequate records
- Submit progress reports and final study results
- Refrain from promotion and commercialization of investigational products, among other things

IND regulations explicitly allow a sponsor to transfer certain obligations to a contract research organization ("CRO"). IDE regulations do not explicitly include such a provision but CROs can be used with appropriate controls. In these cases, the sponsor's responsibilities are delegated under a written agreement and, while a CRO that signs such an agreement must comply with its obligations under the agreement and is subject to the FDA enforcement if it fails, this does not relieve the sponsor of its ultimate accountability.

2. Selecting Investigators

A sponsor must select study investigators who have sufficient training and experience; provide investigators with all the information necessary to properly conduct the study; ensure that the study is monitored properly and on a regular basis; ensure that investigators receive IRB review and approval before starting the study; and ensure that the investigator promptly informs the sponsor and IRB of any significant adverse events relating to the study.

The sponsor is encouraged to conduct a pre-study visit to each site to ensure that each investigator (i) understands the regulatory/specific requirements of the investigation; (ii) understands and accepts the obligations associated with conducting the study; (iii) has access to a suitable number and type of study subjects; and (iv) has adequate facilities to properly conduct the investigation.

A sponsor must secure and maintain a record of a signed agreement for each selected investigator that includes, at a minimum: (i) the investigator's curriculum vitae; (ii) a summary of the investigator's relevant experience; and (iii) a statement of the investigator's commitment to conduct the study in accordance with: all applicable regulations; FDA or IRB imposed conditions; and the investigational plan.

3. Selecting Monitors and Monitoring Investigations

The sponsor is responsible for assuring that the study is monitored properly on a regular basis and that study monitors, like investigators, are qualified to perform their assigned tasks on a study. In recent years, the FDA has begun recommending avoiding a "one size fits all" model of monitoring, where all sites receive similarly routine, on-site visits. It, instead, recommends moving towards a risk-based approach where sponsors and investigators work to risk-stratify facilities based on a variety of factors as may be especially evident by looking at trending conducted by a centralized location. [15] Depending on the nature of the study, the type of product being tested, and the scope of monitoring necessary to oversee its conduct, various professionals ranging from physicians to engineers to nurses may be qualified monitors. Considerations in determining the number of monitors and the level of expertise required include:

- The number of investigators conducting the study
- The number/location(s) of facilities
- The type of product being tested
- The complexity of the study
- The nature of the disease or condition being studied

Sponsors (or their appropriately authorized designees) must monitor clinical investigations periodically to ensure investigator compliance with the requirements of the study and applicable regulations. If an investigator does not comply, the sponsor must implement effective and timely remedial action to correct the non-compliance. Sponsors also must evaluate data regarding safety and effectiveness as it is gathered, make all appropriate reports to the FDA and suspend or terminate the study as required.[16]

Investigator Responsibilities

Investigator responsibilities are described in the IND and IDE regulations; in 21 C.F.R. Parts 50, 54, and 56 ; in contracts or forms they sign promising to properly conduct studies; and in local institutional policies.[17]

Investigators involved in IND studies make the following specific commitments in writing on Form FDA-1572, "Statement of Investigator":

- I agree to conduct the study(ies) in accordance with the relevant, current protocols(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 C.F.R. Part 50 and institutional review board (IRB) review and approval in 21 C.F.R. Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 C.F.R. § 312.64 .
- I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 C.F.R. § 312.62 and to make those records available for inspection in accordance with 21 C.F.R. § 312.68.
- I will ensure that an IRB that complies with the requirements of 21 C.F.R. Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 C.F.R. Part 312 .

No investigator may participate in an IND investigation until he/she provides the sponsor with a completed, signed "Statement of Investigator". No such formal document exists for IDE investigations but similar provisions are required as part of the "Investigator's Agreement".[18]

Regardless of whether an investigator has made a written commitment to comply with these standards, they reflect existing regulatory mandates in any event and so should be regarded as a minimum standard of conduct in virtually all situations.

INDs and IDEs

Sponsor and investigator responsibilities differ according to the type of "test article" (drug or device) under investigation. Drugs and devices are both generally products intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or intended to affect the structure or function of the body. Drugs act through metabolism or chemical reactions in or on the body.[19] Typical examples include medicines in the form of pills or solutions for ingestion or injection. Some cells, vaccines, and other biological medications derived from living beings are biologics regulated under the Public Health Service Act, but most also meet the definition of a drug, and therefore are subject to regulation by the FDA under the IND provisions if investigational.

Devices do not act through metabolism or chemical reaction; they include everything from pacemakers, stents, dental implants and artificial limbs to hospital beds to medical software applications.[20]

"Combination products" are those composed of any combination of a drug, a biological product, and a device.[21] Regulation of combination products is determined based on their "Primary Mode of Action" or "PMOA".21 The PMOA is the single mode of action that provides the most important therapeutic action of the combination product. Determination of the PMOA will result in a product being assigned to a "lead center" at the FDA that is responsible for determining requirements for the conduct of the investigation and is vested with primary reviewing responsibility for related studies.

Drug Trials

1. When is an IND Required?

An Investigational New Drug Application ("IND") enables a sponsor to ship in interstate commerce a new drug (i.e., one that has not been approved by the FDA or that will be used in a manner inconsistent with its approved labeling) for a clinical investigation. Studies involving investigational new drugs generally require an IND. Those involving lawfully marketed drugs, however, are exempt from IND requirements if all of the following criteria are met:

- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use or other significant labeling change.
- If the drug is a prescription drug, the investigation is not intended to support a significant advertising change.
- The investigation does not involve a route of administration, dosage level, a patient population or other factor that significantly increases the drug's risks (or decreases the acceptability of the risks).
- The investigation complies with institutional review board (IRB) and informed consent requirements (Parts 50 and 56).
- The investigation is conducted in compliance with the requirements of 21 C.F.R. § 312.7 , "Promotion and Charging for Investigational Drugs".

The following additional types of investigations also are exempt from IND requirements:

- Investigations of drugs intended solely for in vitro tests or for use in laboratory research animals, if they are shipped in accordance with 21 C.F.R. § 312.160 , "Drugs for Investigational Use in Laboratory Research

Animals or In-Vitro Tests"

- Investigations involving use of a placebo if they do not otherwise require submission of an IND
- Certain in vivo bioavailability studies [22]

By contrast, clinical investigations exempt from informed consent are not exempt from the requirements of Part 312.

2. What are the Phases of a Clinical Investigation?

Drug development proceeds through a number of different phases, each intended to gather different information about an investigational drug. Sponsor and investigator responsibilities vary somewhat depending on the phase of a given investigation. Figure 1 summarizes these phases:

Figure 1: Phases of a Drug Investigation

Phase	Description
0	Trials conducted early in product development, prior to Phase I, which involve very limited human exposure and have no therapeutic or diagnostic intent (*e.g.*, screening studies or microdose studies). Also known as "Exploratory IND Studies."
1	Studies typically designed to determine the metabolism and pharmacologic actions of a drug in humans, and the side effects associated with increasing doses; secondary objectives may be to gain early evidence on effectiveness. Focus is on pharmacokinetics and pharmacological effects.
2	Controlled clinical studies conducted to evaluate the effectiveness of a drug for a particular indication or indications in patients with the disease or condition under study and to determine common short-term side effects and risks associated with the drug.
3	Expanded controlled and uncontrolled trials, performed after preliminary evidence suggesting effectiveness has been obtained. Phase 3 trials are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
4	Studies performed after the FDA grants marketing approval, also referred to as "post-marketing studies" or "post-market surveillance studies." The FDA may ask or require sponsors to perform certain post-marketing studies to gather additional information about a drug's risks, potential benefits, and optimal use concurrent with marketing approval.

3. IND Applications

Unless a proposed drug study is exempt from IND requirements, a sponsor must file an IND with the FDA and receive FDA approval (or allow thirty days to elapse without FDA notification of a clinical hold) before initiating a study of an investigational new drug. The IND application must include:

- Cover sheet (Form FDA-1571) [23]
- Table of contents

- Introductory statement and general investigational plan
- Investigator's brochure
- Protocols for all planned studies to be conducted under the IND
- Chemistry, manufacturing, and control ("CMC") information
- Pharmacology and toxicology information
- Information about previous human experience with the investigational drug
- Additional information for INDs involving products with drug dependence and abuse potential; radioactive products; or products to be tested in pediatric populations
- A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or design and their potential as controlled clinical trials to support drug marketing

Detailed requirements are described at 21 C.F.R. § 312.23 . The FDA also has published guidance describing the limited preclinical support required for exploratory IND studies.[24]

A sponsor may ship an investigational new drug to investigators named in the IND application thirty days after the FDA officially receives the IND provided that no additional information requests or other correspondence have been issued by the FDA. Investigational new drugs may be shipped earlier upon receipt of explicit FDA authorization to ship. Researchers may not administer investigational new drugs to human subjects prior to the effective date of the IND.

At any time after an IND study has been initiated, the FDA may institute a clinical hold and request modification of the IND; terminate the study based on deficiencies in the IND or how the study is being conducted; or inactivate the IND if no subjects have been enrolled in the study for two or more years or if all investigations under the IND remain on clinical hold for one or more years. Sponsors who receive notification of clinical holds should promptly inform all investigators of the holds and assure the investigators notify their respective institutional review boards. Investigations subject to a complete clinical hold may not proceed unless and until the FDA lifts the hold; those subject to partial holds must comply with any imposed restrictions.[25] The FDA alternatively may communicate, either verbally or in writing, identify IND deficiencies or request additional data or information at any time during the application process or the clinical investigation itself. Prompt and complete response to such communications is essential to maintaining a positive working relationship with the FDA and avoiding unnecessary holds.

Once an IND is in effect, a sponsor must amend it as needed to ensure that the clinical investigation is conducted according to protocols included in the application. If a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor must submit an amendment using a Form FDA-1571. The new study may begin after the protocol has been submitted to the FDA for its review and approved by the responsible IRB. Protocol amendments may be initiated only as follows:

- For changes intended to "eliminate apparent immediate hazard to subjects," the changes may be implemented immediately provided that the FDA is promptly notified by an amendment and the reviewing IRB is notified within five (5) working days.
- For other changes to Phase 1 studies that significantly affect subject safety and for changes to Phase 2 or 3

studies that significantly affect subject safety, scope of the investigation, or its scientific quality, the sponsor must submit the changes to the FDA for review and receive approval from the responsible IRB prior to implementation.

- Changes in investigatorship also must be addressed through protocol amendments, except in the case of treatment protocols performed under 21 C.F.R. § 312.34 .

Sponsors are subject to additional reporting requirements in connection with INDs, as follows:

- IND safety reports must be made to the FDA and all participating investigators for any serious and unexpected adverse experiences associated with use of the drug, as well as findings from tests in laboratory animals that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity. Safety report requirements are described at 21 C.F.R. § 312.32(c) .

- Annual reports must be made within sixty days of the anniversary of the IND's effective date, describing the progress of the investigation and additional information specified in the regulations. Requirements for annual reports are identified at 21 C.F.R. § 312.33 .

- Other essential information relevant to an IND, such as new toxicology, chemistry, or other technical information; or notice of suspension or termination of an investigation, must be reported in an "information amendment" as described at 21 C.F.R. § 312.31 .

4. Early and Expanded Access

The FDA has developed special mechanisms to facilitate access to promising therapeutic agents where no satisfactory alternative treatments exist and standard IND requirements may result in unnecessary and counterproductive delays. These mechanisms are designed to ensure that human subject protection and the scientific integrity of the product development process are not compromised.

- **Single Patient INDs for Emergency Use.** Emergency use (also known as compassionate use) is the use of an investigational drug with a human subject in a life-threatening (or severely debilitating) situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. This exemption from prior IRB review and approval is limited to a single use. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. The FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

  IRBs may, but are not required to, establish procedures requiring notification prior to an emergency use. Notification does not substitute for approval, but rather is used solely to initiate tracking to ensure the investigator files a report within five days. Expedited approval is not permissible for emergency use; full board approval is required unless the requirements for an exemption as described above are met and it is not possible to convene a quorum within the time available.[26]

  Regardless of local IRB policies, the emergency use of an investigational drug requires an additional IND or amendment.[27] If the intended subject does not meet the criteria of an existing study protocol, or if an approved protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug can be made available for the emergency use under the company's IND. However, the need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND or required amendment. In such a case, the FDA may authorize shipment of the test article in advance

of the IND submission.[28]

- **Treatment INDs.** A treatment IND may be granted only after sufficient data have been collected to show that the drug in question "may be effective" and does not pose unreasonable risks. In addition, the following criteria must be met: (i) the drug must be intended to treat a serious or immediately life-threatening disease; (ii) there is no satisfactory alternative treatment available; (iii) the drug is already under investigation, or trials have been completed; and (iv) the trial sponsor is actively pursuing marketing approval.

  An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow the FDA to obtain additional data on the safety and effectiveness of the drugs in question.

- **Parallel Track Studies.** The FDA has adopted a "Parallel Track" policy,[29] which facilitates access to promising new drugs for AIDS/HIV related diseases under a separate protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prior IRB review and approval and informed consent. The FDA is responsible for assuring that the availability of a drug under the parallel track program does not interfere with the drug sponsor's ability to carry out well-controlled studies on the drug and does not encourage patients with other approved treatment alternatives to resort to untested investigational drugs.

- **Open Label Protocols or Open Protocol INDs.** These are usually uncontrolled Phase 3 studies, carried out to obtain additional safety data. They typically are used when the controlled trial has ended and treatment is continued so that subjects and controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prior IRB review and approval, and informed consent.

- **Real World Evidence.** The FDA has begun paying closer attention to opportunities to generate valid scientific evidence, using electronic health records, registries, and administrative and claims data, which was originally collected for non-regulatory purposes, to support regulatory decision making.[30] This, together with other real world evidence as combined with patient preference data and other information, can be used for a variety of purposes in the context of biologics and devices including the support for the validity of a biomarker and support for a petition to reclassify certain medical devices or in the context of post approval studies.

Device Trials

The FDA has established a series of regulations designed to prevent unsafe or ineffective devices from being marketed or promoted in interstate commerce. These are referred to collectively as "device controls" and include requirements for registration of device manufacturing and other facilities, listing of devices manufactured or distributed by those facilities, compliance with "good manufacturing practice" standards, the FDA marketing approval or clearance requirements, reporting requirements, and more. An investigational device exemption, or IDE, permits the shipment of a device otherwise subject to these device controls for use in a clinical trial to assess its safety and effectiveness. Note, however, that many investigational devices are still subject to design controls under the FDA's Quality System Regulation ("QSR"). The FDA exempts from its IDE requirements investigations

of the following categories of devices:

- Many devices in commercial distribution before May 28, 1976, when used or investigated in accordance with the labeled indications in effect at that time
- Certain devices determined by the FDA to be substantially equivalent to other devices that are used or investigated under the indications for use reviewed by the FDA as part of the substantial equivalence determination
- Diagnostic devices that meet certain requirements specified by the FDA[31]
- Devices undergoing consumer preference testing, testing of modifications, or testing of a combination of two or more devices in commercial distribution if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- Devices intended solely for veterinary or animal research use
- Custom devices unless they are being used to determine safety or effectiveness for commercial distribution

1. Significant Risk and Non-Significant Risk Determinations

A significant risk (SR) device is an investigational device that (i) is intended as an implant and presents potential for serious risk to the health, safety or welfare of subjects; (ii) is intended to be used to support or sustain human life and presents a potential for serious risk to the health, safety or welfare of subjects; (iii) 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 subjects; or (iv) otherwise presents a potential for serious risk to the health, safety or welfare of subjects.[32] A non significant risk (NSR) device is one that does not meet the criteria listed above, is not a banned device and is not the subject of a notification from the FDA that an IDE application is required.[33]

2. IDE Applications

A sponsor must submit an IDE application to the FDA if:

- The sponsor intends to use an SR device in a clinical investigation
- The sponsor intends to conduct an investigation that involves an exception from informed consent under 21 C.F.R. § 50.24
- The FDA notifies the sponsor that an application is required for an investigation

A clinical investigation involving an SR device may not be initiated until the FDA has approved the IDE application. The FDA Center for Devices and Radiological Health, which oversees medical device investigations, has not developed a form similar to the 1571 used for studies of investigational new drugs. FDA regulations do, however, specify the required content of an IDE application:

- Name and address of the sponsor
- Detailed information about prior investigations and a summary of their outcomes
- Detailed information about the investigational plan

- Information about the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device in sufficient detail to appropriately evaluate quality control
- An example of the agreements to be entered into by all investigators to comply with investigator obligations under Part 812, and a list of the names and addresses of all investigators who have signed the agreement (similar to the content provided on a Form-1572 in investigational drug studies)
- A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.
- A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.
- The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with 21 C.F.R. § 812.20(b)(6) .
- If the device is to be sold, the amount to be charged and an explanation of why the price does not constitute commercialization of the device
- Environmental assessment information
- Copies of all labeling for the device
- Copies of all forms and informational materials to be provided to subjects to obtain informed consent
- Any other relevant information the FDA requests for review of the application.

Once the FDA has received a completed application, the agency may approve the application, approve it with modifications, disapprove it, or request additional information. An SR investigation may begin after the FDA and the relevant IRB have approved the application, or thirty days after the FDA receives the application, as long as IRB approval has been secured and the FDA has not notified the sponsor to delay initiation. An NSR study may begin after the IRB approves the protocol and consent documents.[34]

As with drug studies, the FDA generally requires advance approval of changes to investigational plans that are likely to have a significant effect on scientific soundness of trial design and/or validity of data resulting from the trial such as a change in indication, or a change in type or nature of the study control.[35] Approval must be granted by the FDA and the IRB in SR studies and by the IRB only in NSR studies. There are exceptions, however, including for emergency use, certain developmental changes to the device, and other minor changes to the clinical protocol. Notice of these types of changes must be provided to the FDA within five (5) working days.

FDA and IRB approval also is required for each site that will participate in a device investigation. The FDA will consider IDE applications that do not contain a certification of IRB approval for each site, but the sponsor must submit that certification in an IDE supplement when that approval is secured and to open any new study sites to enrollment.

A sponsor may report minor changes in the following areas as part of its annual progress report: study purpose, risk analysis, monitoring procedures, labeling, informed consent materials and IRB information. If, however, the changes affect the validity of the data, risk-benefit analysis, scientific soundness of the investigational plan, or the rights, safety, or welfare of subjects involved in the study, they must be approved in advance.

3. Documentation and Reporting Requirements

The IDE regulations require sponsors and investigators to prepare and submit specified reports in a complete, accurate, and timely manner. These include, but are not limited to, reports of:

- Study progress generally
- Significant risk device determinations
- Failure to secure informed consent for any reason[36]
- Certain adverse events and unanticipated problems affecting risks to subjects and others
- Deviations from the investigational plan for any reason
- Withdrawal of IRB or FDA approval
- Final report

A complete listing of all the required reports may be found at 21 C.F.R. § 812.150 .

4. Early and Expanded Access

The FDA has described four ways providers may access investigational devices prior to FDA approval and outside the scope of an approved clinical trial. These are: (i) emergency use for life-threatening or serious diseases or conditions; (ii) compassionate use for patients who do not meet the criteria for inclusion in a trial but may benefit from use of the device; (iii) treatment use, to expand the number of subjects who may be permitted to participate in a trial that shows promise; and (iv) continued access to investigational devices for subjects participating in a trial after the trial is complete but prior to FDA approval.[37]

- **Emergency Use.** To qualify for emergency use, the prospective patient must be suffering a life-threatening or serious disease or condition that requires immediate treatment; there must be no available, generally acceptable alternatives for treating the patient; and there must be no time to use existing procedures to obtain FDA approval. It is the treating physician's responsibility to determine whether these criteria have been met, to assess a patient's potential for benefits from the unapproved use, and to have substantial reason to believe that benefits will exist. Where emergencies are reasonably foreseeable, sponsors or physicians should obtain FDA approval through standard IDE procedures or through the compassionate, treatment or continued use procedures described below. The FDA considers an emergency reasonably foreseeable if the device could be used in an emergency.[38]

  In the event an unapproved investigational device is used in an emergency under this exception, the device developer must notify the FDA immediately after shipment. In addition, the physician employing the device should make every effort to protect subjects including, as applicable: (i) obtaining an independent assessment by an uninvolved physician; (ii) obtaining informed consent from the patient or legally authorized representative; (iii) notifying the appropriate IRB as soon as practicable; and (iv) obtaining authorization from the IDE holder, if an approved IDE for the device exists.

  After the emergency, the physician must: (i) report to the IRB within five days and otherwise comply with IRB requirements; (ii) evaluate the likelihood of a similar need occurring again and, if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for subsequent use; and (iii) if an IDE for the use already exists, notify the sponsor of the emergency use, or if an IDE does not exist, notify

the FDA of the emergency use, and provide the FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results. Subsequent emergency use may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If one has been filed and disapproved by the FDA, the device may not be used even in an emergency.

- **Compassionate Use.** The FDA allows patients who do not meet the requirements for participation in a clinical investigation but for whom the treating physician believes the device may provide a benefit in treating or diagnosing their disease or condition to access that device during the clinical trial. The patient's condition must be serious and there must be no available, generally acceptable alternatives for treatment. This provision is typically approved for single patients, but may be approved to treat a small group.

  Prior FDA approval is needed before compassionate use occurs. In order to obtain FDA approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation. The physician should not treat the patient (or patients) identified in the supplement until the FDA and the appropriate IRB both approve the use of the device under the proposed circumstances.[39]

- **Treatment Use.** Approved IDEs specify the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in a study. During the course of a clinical trial, if the data suggest that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. To qualify for a treatment use IDE, the disease or condition must be life threatening or serious, and patients must have no comparable or satisfactory alternatives to the investigational device. If the disease is life-threatening (i.e., there is a reasonable likelihood that death will occur within a matter of months or premature death is likely without early treatment), a device may be eligible for a treatment use IDE prior to completion of all clinical trials; if the disease is serious, a device ordinarily may be made available for treatment use only after all clinical trials have been completed.

  Thus, in summary, the FDA will consider the use of an investigational device under a treatment use IDE if all of the following criteria are met:[40] (i) the device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;

  (ii) there is no comparable or satisfactory alternative device or other therapy to treat or diagnose that stage of the disease or condition in the intended patient population; (iii) the device is under investigation in a controlled clinical trial for the same use under an approved IDE, or the clinical trials have been completed; and (iv) the sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

  Treatment use may begin 30 days after the FDA receives the treatment IDE submission, unless the FDA notifies the sponsor otherwise.

- **Continued Access.** The FDA may allow continued enrollment of subjects after a controlled clinical trial under an IDE has been completed to allow access to the investigational device, while a marketing application is being prepared by the sponsor or reviewed by the FDA, and to facilitate the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. This is referred to as an "extended investigation." The FDA will approve an extended investigation only if it identifies a public health need or preliminary evidence is submitted that the device will be effective and no significant safety concerns have been identified for the proposed indication.[41]

The difference between a treatment use IDE and use of an investigational device under the continued access policy is that a treatment use IDE can be submitted earlier in the IDE process (i.e., as soon as promising evidence of safety and effectiveness has been collected but while the clinical study is ongoing) but is intended only for patients with serious or immediately life-threatening diseases or conditions, whereas continued access generally is available only after completion of a clinical trial but for a broader range of patients.

- **Additional Exceptions.** The FDA from time to time approves additional exceptions to standard approval processes. For instance, guidance issued in June 2005 under the Project Bioshield Act of 2004 permits the FDA to allow the use of unapproved medical products or approved medical products for unapproved purposes during a declared emergency involving a heightened risk of attack on the public or U.S. military forces.

Additional Requirements

1. Labeling and Marketing

The FDA also regulates how investigational drugs and devices are labeled[42] and the circumstances under which a sponsor may promote or charge for their use[43] . The immediate package of an investigational new drug intended for human use must include the following statement: "Caution: New Drug—Limited by Federal (or United States) law to investigational use." The label of an investigational drug may not contain any statement that is false or misleading, and may not represent that the drug is safe or effective for the purposes for which it is being investigated. A similar ban applies to promotion, test marketing, or commercial distribution of the investigational drug by sponsors and individuals not independent of, or under the control of, a sponsor[44] , and investigators. Sponsors may not charge for investigational drugs in clinical trials proceeding under an IND without the FDA's prior written approval. Even then, sponsors are limited to the amount necessary to recover costs of manufacture, research, development, and handling. In addition, a sponsor may not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

An investigational device or its immediate package must include a label with the following information: (i) name and place of business of the manufacturer, packer, or distributor; (ii) quality of contents, if appropriate; (iii) quantity of contents, if appropriate; and (iv) the following statement: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." In the case of a device study, at a minimum, the label or other labeling also must describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

As with drugs, sponsors of investigational devices may not promote or profit from their products. The label of an investigational device may not bear any statement that is false or misleading, and may not represent that the device is safe or effective for the purposes for which it is being investigated. A similar ban applies to promotion, test marketing, or commercial distribution of the device by sponsors and investigators. Sponsors may not charge for investigational devices in clinical trials proceeding under an IDE other than the amount necessary to recover costs of manufacture, research, development, and handling and may not unduly prolong an investigation.

While marketing or promoting investigational drugs or devices is prohibited, the FDA recognizes the practical need to recruit clinical investigators and study subjects through dissemination of information on investigational products. An FDA guidance entitled "Guidance for Industry and FDA Staff: Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects" (March 19, 1999)[45] defines the

recommendations and restrictions regarding such information dissemination for devices. See also the "Recruiting Study Subjects—Information Sheet" which applies to both drugs and devices.[46]

2. Waiver of IND or IDE Requirements

A sponsor may request the FDA to waive any of the requirements found at 21 C.F.R. Part 312 .[47] A waiver request may be submitted either in an IND or in an IND information amendment. In an emergency, a request may be made by telephone or other rapid communication means. The request must contain at least one of the following:

- An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved
- A description of an alternative submission or course of action that satisfies the purpose of the requirement; or
- Other information justifying a waiver.

The FDA may grant the waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects and that one of the following is met: (i) the sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved; (ii) the sponsor's proposed alternative satisfies the requirement; or (iii) the applicant's submission otherwise justifies a waiver.

As with drugs, sponsors may request the FDA to waive any requirement of 21 C.F.R. Part 812 .[48] A waiver request, with supporting documentation, may be submitted separately or as part of an IDE application. The FDA may grant a waiver of any requirement it deems not required by the act, nor necessary to protect the rights, safety or welfare of the study subjects. It is important to understand, however, that each requirement applies unless and until the FDA expressly waives it.

In May 2018, President Trump signed the "Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017."[49] More commonly known as the "Right to Try Act," the Act aims to help terminally ill patients who have exhausted approved treatment options and are unable to participate in a relevant clinical trial. The Act potentially provides access to drugs that have completed a Phase 1 clinical trial but has not been approved or licensed by the FDA. The Act also limits the liability of the sponsor, the manufacturer, the prescriber, or the dispenser who provides or declines to provide the eligible investigational drug to the eligible patient. Additionally, the act also limits the use of clinical outcomes associated with the use of an eligible investigational product to delay or adversely affect the review or approval of the drug.