RESEARCH REGULATORY COMPLIANCE

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CHAPTER

2

Investigational New Drug and Device Exemption Process

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1. INTRODUCTION

The US Food and Drug Administration (FDA) oversees the clinical translation and final approval, for commercial marketing, of investigational drug (including biological) products and medical devices intended for human or animal use. As defined in the Federal Food, Drug and Cosmetic Act:

- A drug is any article intended for use in the diagnosis, cure, mitigation, prevention, or treatment of a disease in man or animals, including articles (other than food) intended to affect the structure or function of the body of man or animals.
- A device is an instrument, apparatus, implement, machine, in vitro reagent, or similar article intended for use in the diagnosis, cure, mitigation, prevention, or treatment of a disease in man or animals. A device must not achieve its principle intended purpose through chemical action within the body or by being metabolized.

The jurisdiction of the FDA also includes the oversight of food products (except meats and poultry) for human consumption, animal feeds and drugs, radiation-emitting products for consumer or occupational use, and cosmetics.

2. HISTORICAL PERSPECTIVES [1]

The FDA's oversight of drug products and medical devices has evolved and expanded over many years, primarily as a result of identified or reported hazards and safety concerns. The following discussion focuses on major congressional actions and events that have led to the FDA's current regulatory jurisdiction over drugs, biologics, and medical devices.

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Prior to the early 1900s, the states predominantly assumed control over domestically produced food and drugs, with federal oversight being limited to respective imported products. As might be anticipated, such state-by-state oversight was inconsistent, and the adulteration and misbranding of foods and drugs were prevalent. In recognition of such, Congress passed the Food and Drugs Act in 1906. This act, which was initially administered by the Bureau of Chemistry, prohibited the interstate transport of adulterated or misbranded foods and drugs. For drug products, the act focused primarily on the regulation of appropriate drug standards and product labeling. Drug products were required to meet standards of identity, strength, quality, and purity as defined in the *United States Pharmacopeia* and *National Formulary*, unless variations from these standards were clearly stated on the product label. In 1912, the Food and Drugs Act was amended (Sherley Amendment) to prohibit the labeling of drug products with false therapeutic claims intended to defraud the consumer; however, federal oversight of this standard was difficult to enforce. There was no requirement, under this act, for federal approval of a drug product prior to its distribution in the commercial market. In 1927, the Bureau of Chemistry was reorganized into two separate entities, with regulatory functions being assumed by the Food, Drug and Insecticide Administration, which three years later became known as simply the Food and Drug Administration.

As a result of continuing false therapeutic claims and safety issues, Congress approved, in 1938, a new bill entitled the Food, Drug and Cosmetic Act (FD&C Act). A primary impetus for the passage of this new act was the death of more than 100 people, many of whom were children, from a marketed sulfanilamide "elixir" that contained an untested, highly toxic solvent similar to ethylene glycol (antifreeze). A key feature of this new law was a requirement for premarket approval of all new drugs by the FDA, based on data submitted by the manufacturer proving that the drug was safe. While the FD&C Act did not initially require, as a condition for premarket approval, the submission of data demonstrating effectiveness of the drug product, it did strengthen the FDA's oversight of false therapeutic claims by removing the requirement to prove "intent to defraud" in misbranding cases. The FD&C Act also required that drugs be labeled with adequate directions for safe use. In addition, it brought medical devices and cosmetics under the control of the FDA, authorized inspections of factories involved in the manufacture of drug products, and added court injunctions to the other processes (e.g., seizures, prosecutions) available for FDA's enforcement of the act.

In 1951, the FD&C Act was amended (Durham–Humphrey Amendment) to define drug products that could or could not be safely used in the absence of medical supervision, thereby creating two classes of drug products, prescription drugs and over-the-counter drugs. Following the 1962 thalidomide tragedy in Europe, during which thousands of children were born with birth defects associated with their mother's use of this new sedative, Congress amended (Kefauver–Harris Amendment) the FD&C Act to require that drug manufacturers prove both the safety and effectiveness of drug products as a condition for their approval for commercial marketing. This amendment also required the agency to assess the effectiveness of all drug products introduced into the commercial market since 1938. The amendment established good manufacturing practice standards for the drug industry and granted the FDA greater access to company production and control records to verify compliance with these standards. In addition, the amendment mandated the informed consent of individuals who participate in clinical trials of investigational drug products.

In 1972, the regulation of biologics, including serums, vaccines, and blood products, was transferred from the National Institutes of Health to the FDA. In 1976, the FD&C Act was once again amended (Medical Device Amendments) to provide assurance that medical devices introduced into the commercial market were also both safe and effective. Medical device manufacturers were now required to register with the FDA and comply with device-specific good manufacturing practice standards. Depending on the risk of the medical device, it must be either prior approved by the FDA for commercial marketing (i.e., for higher-risk devices) or must meet certain general performance standards (i.e., for lower-risk devices). In 1994, Congress passed the Dietary Supplement Health and Education Act, which defined "dietary supplements" and classified them as a "food." This act also established labeling requirements for dietary supplements and authorized the FDA to affect good manufacturing practice standards for such products.

3. RELEVANT REGULATORY/OVERSIGHT AGENCIES, REGULATIONS, AND GUIDANCE DOCUMENTS

The FDA oversees the clinical translation and final approval, for commercial marketing, of investigational drug (including biological) products and medical devices intended for human use. FDA regulations governing these processes are published under Title 21 of the Code of Federal Regulations (i.e., 21 CFR). These regulations and related FDA guidance documents may be accessed via the FDA's website at www.fda.gov.

3.1 Drugs and Biologics

3.1.1 Responsible Food and Drug Administration Entities

Within the FDA, the clinical investigation and the approval, for commercial marketing, of drugs and biologics are overseen by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), respectively. Each of these centers incorporates various offices (Tables 1 and 2) for the initial and ongoing review of investigational drug products involved in various stages of clinical translation and also offices that address compliance with applicable FDA regulations and IND commitments.

3.1.2 Requirements for the Submission of an Investigational New Drug Application

The use or the evaluation (for safety and/or effectiveness) of a non-FDA-approved drug or biologic in a clinical (human) research study generally requires the prior submission and FDA-acceptance of an investigational new drug (IND) application. FDA procedures and requirements governing the use of INDs, including procedures and requirements associated with the submission and FDA review of IND applications and the responsibilities of IND sponsors and investigators are addressed under 21 CFR part 312, *Investigational New Drug Application*.

As addressed within these FDA regulations, there are exceptions to the requirement for the submission of an IND application for human research studies involving certain types of products that meet, or would seem to meet, the definition of a "drug" product.

TABLE 1 Review Offices–Center for Drug Evaluation and Research [2]

Office of antimicrobial drug products
OFFICE OF DRUG EVALUATION I
Division of Cardiovascular and Renal Products
Division of Neurology Products
Division of Psychiatry Products
OFFICE OF DRUG EVALUATION II
Division of Anesthetic, Analgesic and Addiction Products
Division of Metabolism and Endocrinology Products
Division of Pulmonary, Allergy and Rheumatology Products
OFFICE OF DRUG EVALUATION III
Division of Dermatology and Dental Products
Division of Gastroenterology and Inborn Errors Products
Division of Bone, Reproductive and Urologic Products
OFFICE OF DRUG EVALUATION IV
Division of Medical Imaging Products
Office of Hematology/Oncology Drug Products

TABLE 2 Review Offices–Center for Biologics Evaluation and Research [3]

Office of Vaccines Research and Review
Office of Blood Research and Review
Office of Cellular, Tissue and Gene Therapy

- In accordance with the IND regulations at 21 CFR 312.2(b), clinical studies directed at the evaluation or use of an FDA-approved drug for an "off-label" indication (i.e., a clinical indication that is not currently specified in the FDA-approved product labeling) are exempt from the requirement for the submission of an IND application if the study meets each of the following criteria:
  - It is not intended to support FDA approval of a new indication or a significant change in the product labeling.
  - It is not intended to support a significant change in the advertising for the drug product.
  - It does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

- It is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in 21 CFR parts 50 and 56 (more information about the IRB approval process is provided in Chapter 1, Human Subjects).
- It is conducted in compliance with 21 CFR 312.7, which addresses promotion and charging for investigational drugs.

Other products that are listed under this section of the FDA regulations as being exempt from the submission of an IND application include in vitro diagnostic biologic products (blood grouping serum, reagent red blood cells, antihuman globulin) that are intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; drugs intended solely for tests in vitro or in laboratory animals; and placebos.

- Subject to the provisions of the Dietary Supplement Health and Information Act of 1994, dietary supplements are regulated as "foods" and are therefore exempt from the regulations governing a "drug" product, provided that they are labeled or being investigated for intended use in affecting the structure or function of the body (i.e., a structure or function claim). However, the labeling or the evaluation, in a human research study, of a dietary supplement for the diagnosis, prevention, mitigation, treatment, or cure of a certain disease (i.e., a disease claim) causes the supplement to fall under the definition of a "drug" and requires the submission and FDA-acceptance of a corresponding IND application.
- Certain human cells, tissues, and cellular- and tissue-based products (HCT/Ps) are regulated solely under section 361 of the Public Health Service Act. As such, they are not regulated as "drug" products, and therefore their evaluation or use in a human research study does not require the submission of an IND application. To qualify for this exemption, the HCT/P must meet each of the following criteria [4]:
  - Minimal manipulation of the HCT/P is required for its clinical use or clinical research use or evaluation.
  - The HCT/P is intended for homologous use (i.e., a use that is the same as its natural use).
  - The HCT/P is not combined with another article, except water, crystalloids, or a sterilizing, storage, or preserving agent that does not, in itself, raise safety concerns.
  - Either the HCT/P (1) does not have a systemic effect and is not dependent on metabolic activity; or (2) the HCT/P is for autologous use, for allogeneic use in a first- or second-degree blood relative, or for reproductive use.

Entities involved in the clinical use or investigation of HCT/Ps are required to register with the FDA and provide a listing of the respective products.

- Clinical investigations involving nonapproved radioactive drugs for certain, basic research uses do not require the submission of an IND application provided that:
  - The research study is intended to obtain basic information regarding the metabolism or kinetics of the radioactive drug or regarding human physiology, pathophysiology, or biochemistry, but *not* intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and/or effectiveness of the radioactive drug for such purposes.

- The radioactive drug/clinical investigation is prospectively approved by an institutional Radioactive Drug Research Committee (RDRC) that functions in accordance with the corresponding FDA regulations at 21 CFR 361.1. For an RDRC to approve a research study under these regulations, it must meet the following, fundamental requirements (and also several, additional specific requirements): (1) the mass of the radioactive drug to be administered must be known to not cause any clinically detectable pharmacological effect in humans based on data available from published literature or other valid human studies; (2) the total radiation dose that an individual will receive from participation in the study is the smallest radiation dose practical to perform the study and within the limits specified in the regulation; and (3) the study is approved by an IRB and is compliant with the requirements for informed consent. More information about the IRB approval process is provided in Chapter 1, Human Subjects. The RDRC approval process is discussed in more detail in Chapter 5, Radiological Hazards and Lasers.

Although substances labeled with "cold" (i.e., nonradioactive) isotopes are not technically covered by these regulations, the FDA has issued guidance specifying that the submission of an IND application is not required for basic research studies involving the use of such substances if they meet the same general regulatory requirements (i.e., with obviously the exception of the radiation dose limits) [5].

Sponsors of IND applications are required to wait for 30 days following the FDA's receipt of the application before commencing the incorporated clinical trial(s). Typically, the agency will respond to the sponsor within this 30-day interval; however if no FDA response is received, the sponsor may proceed to initiate the clinical trial (i.e., provided it has been approved by an acceptable IRB). Should the FDA identify significant concerns during its review of the IND application, it will issue a "clinical hold" notification, which, as the name implies, requires the sponsor to delay (or terminate) clinical trial initiation until the agency's concerns are adequately addressed.

3.1.3 Components of an IND Application [6]

The major components of an IND application include:

- Cover sheet (i.e., completed and signed Form FDA 1571, *Investigational New Drug*)
- Introductory statement and general investigational plan
  - The introductory statement should address the name of investigational drug (and, if applicable, other active drugs in the drug product) and its pharmacological class and structural formula (if known), the dosage form of the drug product, and the proposed route of administration of the drug product. The introductory statement should also summarize any prior human experience (i.e., in any country) with the investigational drug and address if it has previously been withdrawn from investigation or marketing.
  - The general investigational plan should briefly describe the rationale for the investigational drug or proposed human study, the clinical indication(s) that will be evaluated, the kinds of clinical trials that are planned for the first year, the number of research subjects that will be enrolled into these clinical trials, and anticipated risks.
- Investigator's brochure, to contain the following information:
  - A brief description of the drug substance and the formulation, including the structural formula, if known.
  - A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

  - A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
  - A summary of information relating to the safety and efficacy of the drug in humans obtained from prior clinical studies.
  - A description of possible risks and side effects to be anticipated based on prior experience with the drug under investigation or related drugs and of precautions or special monitoring to be done as part of the investigational use of the drug.
- Clinical trial protocol
  - Phase 1: Initial introduction of an investigational drug into humans. May involve patients or normal volunteers. Designed to determine the pharmacokinetics and pharmacologic actions of the drug, the side effects associated with increasing doses, and (if possible) gain early evidence on effectiveness. Also include human studies of drug metabolism, structure–activity relationships, and mechanism of action as well as studies in which unapproved drugs are used as research tools to explore biological phenomena or disease processes.
  - Phase 2: Controlled studies to evaluate the effectiveness of the drug for a particular indication or indications in patients with the respective disease or condition and to determine the common short-term side effects and risks of the drug.
  - Phase 3: Expanded controlled and uncontrolled evaluations of the drug to obtain additional information about its safety and effectiveness, so as to permit an overall evaluation of the benefit-to-risk relationship of the drug and to provide an adequate basis for product labeling.
  - Phase 4: Human studies conducted following FDA approval to market the drug commercially. May include additional surveillance studies mandated by the FDA as a condition of approval or, for example, studies involving pediatric or elderly patients or new clinical indications.
- Chemistry, manufacturing and (quality) control information
- Labeling
- Pharmacology and toxicology information
- Previous human experience with the investigational drug
- Additional information
  - To include, if applicable, information related to special topics such as drug dependence and abuse potential, radioactive drugs, and pediatric studies.
- FDA requested information
  - To include, if applicable, information requested by the FDA subsequent to a pre-IND meeting.

3.1.4 Manufacturing and Labeling Requirements

Investigational drugs and biologics being used or evaluated in phase 2 or 3 clinical trials are required to be manufactured and labeled in compliance with the FDA's current good manufacturing practice (cGMP) regulations at 21 CFR parts 210 and 211. For phase 1 (including phase 0) clinical trials, FDA regulations specify that the investigational drug or biologic must be manufactured in accordance with the principles of cGMP; however strict compliance with the FDA's cGMP regulations at 21 CFR part 211 is not required [7]. Rather, under this scenario, the FDA will oversee the manufacture and labeling of the investigational drug or biologic in accordance with respective procedures and statements contained within the submitted IND application [8].

3.1.5 Good Clinical Laboratory Practice Requirements for Supporting Nonclinical Safety Data

Nonclinical (i.e., laboratory or animal) safety studies, performed in support of the submission of an IND application, are required to be conducted in compliance with the FDA's current good laboratory practice (GLP) regulations at 21 CFR part 58. Note that nonclinical studies directed at evaluating the effectiveness of the investigational drug or biologic are *not* required to be conducted in compliance with these GLP regulations. Investigational drugs and biologics used for GLP-compliant safety studies must be well characterized with regard to their identity, strength, quality, and purity; however, they are not required to be manufactured in strict compliance with the previously discussed cGMP regulations. The FDA's cGLP regulations incorporate extensive validation requirements and laboratory controls, and as a result, nonclinical studies subject to these regulations are typically conducted at contract facilities that specialize in their performance. The costs associated with the conduct of cGLP-compliant, nonclinical safety studies typically represent the greatest expense associated with the initial submission of an IND application. It is thus recommended that, in the absence of an applicable (i.e., related to the class of drug under development) FDA guidance document, the nature and scope of the preclinical safety studies required for FDA acceptance of an IND application be prior discussed with the agency via the pre-IND process to include, if applicable, a discussion of the potential acceptability of existing nonclinical safety data that were not collected in strict compliance with the GLP regulations.

3.1.6 Good Clinical Practice Requirements

IND sponsors and study site investigators, who are involved in the performance of clinical trials being conducted under an FDA-accepted IND application, are required to comply with the good clinical practice (GCP) guidelines of the International Commission on Harmonization (ICH) [9]. These GCP guidelines represent an international ethical and scientific quality standard for designing, conducting, recording, and reporting investigations that involve the participation of human subjects. Compliance with these guidelines provides public assurance that the rights, safety, and well-being of research participants are protected and that the resulting clinical trial data are credible. Adherence to the GCP guidelines, which have been adopted by the FDA, is subject to audit by the agency. Prior to initiation of a clinical trial, study site investigators are also required to obtain the approval of an IRB that operates in compliance with the FDA's regulations at 21 CFR part 56. Informed consent of the study participants must be obtained in compliance with the FDA regulations at 21 CFR part 50.

3.1.7 Food and Drug Administration Guidance Documents

CDER and CBER have published numerous guidance documents (Table 3) related to the IND submission process, many of which are related to IND requirements associated with specific diseases or conditions or with specific classes of drug or biological products. FDA guidance documents may be readily searched and accessed via the FDA website at www.fda.gov.

3.1.8 Food and Drug Administration Approval for Commercial Marketing

FDA approves drug and biologic products for commercial marketing based on data, collected under an FDA-accepted IND application, which demonstrate that the drug is safe and effective at the recommended dosage and for the clinical indication(s) specified in the proposed product

TABLE 3 Pertinent Investigational Drug and Biologic Guidance Documents

- *Guidance for Clinical Investigators, Sponsors and IRBs: Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND*, September, 2013.
- *Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*, January, 2004.
- *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic Biotechnology Derived Products*, November, 1995
- *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions—Statement of Investigator*, May, 2010
- *Guidance for Industry: Exploratory IND Studies*, January, 2006
- *Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use—Qs & As*, May, 2013
- *Guidance for Industry: CGMP for Phase 1 Investigational Drugs*, July, 2008
- *Guidance for Industry: INDs for Phase 2 and Phase 3 Studies—Chemistry, Manufacturing and Controls Information*, May, 2003
- *Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, January, 2010
- *Guidance for Industry: Good Laboratory Practices—Questions and Answers*, July, 2007
- *Guidance for Industry: E6 Good Clinical Practice—Consolidated Guidance*, April, 1996
- *Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects*, October, 2009
- *Draft Guidance for Industry: Charging for Investigational Drugs Under an IND—Qs & As*, May, 2013
- *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*, February, 2000
- *Guidance for Industry: IND Meetings for Human Drugs and Biologics—Chemistry, Manufacturing and Controls Information*, May, 2001
- *Claims That Can Be Made for Conventional Foods and Dietary Supplements—Office Nutritional Products, Labeling, and Dietary Supplements*, March, 2007.
- *Guidance for Industry: Structure/Function Claims (dietary supplements)—Small Entity Compliance Guide*, March, 2007.
- *Guidance for Industry: Botanical Drug Products*, June, 2004.
- *Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue (i.e., human cells, tissues and cellular and tissue-based products)—Jurisdictional Update, August*, 2008.
- *Guidance for Industry and Researchers: The Radioactive Drug Research Committee—Human Research Without an Investigational New Drug Application*, August, 2010.
- *Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects*, October, 2009.

labeling. In the case of drug products, these data are submitted to the agency in the form of a new drug application (NDA). For biologic products, the data are submitted in the form of a biologic licensing application (BLA). Following the expiration of patent and/or market exclusivity rights, an abbreviated new drug application (ANDA) may be submitted to the FDA to obtain approval to commercially market a generic version of a currently marketed drug product. FDA approval of an ANDA is based primarily on the sponsor demonstrating bioequivalence to the innovator drug. An abbreviated BLA pathway has been established for the approval of generic biologic products, although there have been no generic biological products approved via this pathway to date.

3.2 Medical Devices

3.2.1 Responsible Food and Drug Administration Entity

The FDA entity responsible for the oversight of medical devices and their approval for commercial marketing is the Center for Devices and Radiological Health (CDRH).

TABLE 4 Review Offices—Center for Devices and Radiological Health [10]

Office of Device Evaluation
Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
Division of Cardiovascular Devices
Division of Ophthalmic and Ear, Nose, and Throat Devices
Division of Neurological and Physical Medicine Devices
Division of Orthopedic Devices
Division of Surgical Devices
Division of Reproductive, Gastro–Renal, and Urological Devices
Office of In Vitro Diagnostics and Radiological Health
Division of Chemistry and Toxicology Devices
Division of Immunology and Hematology Devices
Division of Microbiology Devices
Division of Radiological Health
Division of Mammography Quality Standards

CDRH incorporates two offices for the initial and ongoing review of investigational drug products (Table 4). It also has offices that oversee compliance with applicable FDA regulations and IDE commitments.

3.2.2 Investigational Device Exemption Applications

Notably, the FDA regulations that govern the submission of investigational device exemption (IDE) applications are not applicable to human research studies that involve only the use of a non-FDA-approved medical device [11]. However the evaluation, for safety and/or effectiveness, of a nonapproved medical device in a clinical research study may require the submission and FDA acceptance of an IDE application if the reviewing IRB determines that the investigational device, or how it is being used in the study, constitutes a "significant risk device" study. The FDA's *Investigational Device Exemption* regulations at 21 CFR part 812 define a significant risk device as:

> 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 ($) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The submission and FDA-acceptance of an IDE application is not required for clinical research studies that have been determined by the reviewing IRB to be a nonsignificant risk device study (i.e., the study of a device that does not meet the definition of a significant risk

device study). As per statements included in the FDA regulations at 21 CFR Sec. 812.2(b)(1), a nonsignificant risk device study is considered to already have an approved application for an IDE provided that the sponsor:

- labels the device in accordance with the IDE regulations (21 CFR Sec. 812.5);
- obtains approval of the study by an IRB that operates in compliance with the FDA's regulations at 21 CFR part 56 and that has reviewed the sponsor's justification as to why the device is not felt to be a significant risk device;
- obtains the informed consent of the study participants in compliance with the FDA regulations at 21 CFR part 50;
- monitors the research study in accordance with the FDA regulations at 21 CFR Sec. 812.46;
- maintains and ensures that study-site investigators maintain the records required at 21 CFR Sec 812.140 and Sec. 812.150;
- complies with the prohibitions against product promotion and other practices as addressed under 21 CFR Sec. 812.7.

The FDA regulations at 21 CFR 812.2(b) and (c) address certain categories of medical device studies that are exempt from the submission of an IDE application. Included in this category are clinical studies or comparisons of FDA-approved medical devices in which the devices are being studied for the indications specified in their FDA-approved product labeling. Clinical evaluations of the safety and effectiveness of an FDA-approved medical device for a new clinical indication (i.e., not specified in the current FDA-approved product labeling) are, however, subject to the IDE regulations and may require the submission of an IDE application based on the IRB's determination of their significant risk status. Clinical studies of in vitro diagnostic devices (IVDs) are exempt from the requirement for the submission of an IDE application provided that the IVD and its proposed evaluation meet all of the following criteria [12]:

- the IVD is labeled in accordance with the regulations at 21 CFR 809.10(c);
- the procedures associated with the use of IVD are noninvasive (with the exception of simple venipuncture);
- use of the IVD does not require an invasive sampling procedure (e.g., biopsy, use of general anesthesia, or placement of an arterial, femoral, subclavian, or iliac line or catheter) that presents significant risk;
- the IVD does not by design or intention introduce energy into a subject;
- the IVD is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Other types of devices that are listed under Section 812.2(c) of the FDA regulations as being exempt from the submission of an IDE application include a device:

- undergoing commercial testing, testing of a modification, or testing of a combination or two or more devices in commercial distribution, if the testing does not put subjects at risk;
- intended solely for veterinary use or solely for research on or with laboratory animals and labeled in accordance with 21 CFR Sec 812.5(c); or

- that is a "custom device." A custom device is a device that deviates from an FDA-approved or approvable device to comply with the prescription order of an individual physician or dentist and is intended for use in an individual patient identified in this order. Custom devices are not generally available in finished form for purchase or for prescription use, and they cannot be offered for commercial distribution through labeling or advertising.

Sponsors of IDE applications are required to wait for 30 days following the FDA's receipt of the application before commencing the incorporated clinical investigation. Typically, the agency will respond to the sponsor within this 30-day interval; however, if no FDA response is received, the sponsor may proceed to initiate the clinical investigation (i.e., provided it has been approved by an acceptable IRB). Should the FDA identify significant concerns during its review of the IDE application, it will issue a "clinical hold" notification, which, as the name implies, requires the sponsor to delay (or terminate) the clinical investigation until the agency's concerns are adequately addressed.

3.2.3 *Components of an IDE Application [13]*

The major components of an IDE application include:

- Cover sheet, to include the name, address, and dated signature of the sponsor of the IDE application
- Overall clinical plan
  - The overall clinical plan should provide the descriptive title for each currently planned study of the investigational device and a summary of the study design, sample size, primary outcome measures, and expected principle results.
- Report of prior investigations of the device
  - This section of the IDE application should include reports of all prior laboratory, animal, and, if applicable, human testing of the investigational device. Each study should be summarized to include an adequate description of the study methods, outcome data, and relevant (i.e., safety and/or effectiveness) conclusions of the study.
- Investigational plan
  - Feasibility study: Directed at, or involving, an initial evaluation of the investigational device in humans, an evaluation of potential safety issues associated with the use of the device, an assessment of device design and/or certain human factors associated with the use of the device, or an evaluation of other device or device application characteristics.
  - Pilot study: Directed at obtaining preliminary data on which to base a subsequent pivotal study of the investigational device.
  - Pivotal study: The results of treatment or diagnosis with the investigational device are compared with a placebo, active treatment, or historical control in such a manner so as to permit a quantitative evaluation.
- Example: Investigator's agreement and certification of investigator agreements
  - All study site investigators are required to execute a written agreement specifying that they will comply with the investigator responsibilities incorporated under the IDE regulations (i.e., similar to a form FDA 1572 for investigators participating in IND studies). The IDE sponsor must certify that such a signed agreement will be obtained

from all investigators who are currently participating, or will participate, in clinical investigations of the device.
- Reviewing IRBs and other involved institutions
- Device charges
  - If applicable, the IDE sponsor must specify the amount that will be charged for the investigational device and provide an explanation of why such charges do not constitute commercialization of the device.
- Device labeling
- Consent materials
- Other relevant information
  - To include, if applicable, information requested by the FDA subsequent to a pre-IDE meeting.

3.2.4 *Manufacturing Requirements*

The manufacture and labeling of medical devices for human use must, with certain limited exceptions, be compliant with the FDA's cGMP regulations at 21 CFR part 820, titled *Quality System Regulation*. Of note, the manufacture of medical devices being evaluated under an IDE application is subject to compliance with only subpart C, Sec. 820.30 *Design Controls*, of these quality system regulations [14].

3.2.5 *Good Clinical Laboratory Practice Requirements for Supporting Nonclinical Data*

As with investigational drugs and biologics, nonclinical (i.e., laboratory or animal) safety studies conducted in support of an IDE application are subject to compliance with the FDA's current GLP regulations at 21 CFR part 58. Investigational devices used for GLP-compliant safety studies should be well characterized with regard to their design specifications.

3.2.6 *Good Clinical Practice Requirements*

There is no requirement, per se, for IDE sponsors and investigators involved in the conduct of medical device clinical trials to be compliant with the previously discussed ICH guidelines for good clinical practice. Rather, for medical device research, "good clinical practice" is interpreted as meaning compliance with the primary regulations addressed in the previous paragraphs and the FDA's conflict-of-interest regulations at 21 CFR part 54, *Financial Disclosure by Clinical Investigators* [15]. Also, as with investigational drugs, investigators involved in the conduct of medical device clinical trials are required to obtain the prospective approval of an IRB that operates in compliance with the FDA's regulations at 21 CFR part 56. Informed consent of the study participants must be obtained in compliance with the FDA regulations at 21 CFR part 50.

3.2.7 *Food and Drug Administration Guidance Documents*

CDRH has also published numerous guidance documents (Table 5) related to the clinical investigation and approval, for commercial marketing, of medical devices, and these guidance documents may be readily searched and accessed via the FDA website (www.fda.gov).

TABLE 5 Pertinent Investigational Medical Device Guidance Documents

- *Device Advice: Comprehensive Regulatory Assistance, http://www.fda.gov/medicaldevices/deviceregulationandguidance/default.htm*
- *Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies, January, 2006*
- *Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Frequently Asked Questions About Medical Devices, January, 2006*
- *Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff: Design Considerations for Pivotal Clinical Investigations for Medical Devices, November, 2013*
- *Guidance for Industry and FDA Staff: in Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions, June, 2010*
- *Guidance for Industry and Food and Drug Administration Staff: Mobile Medical Applications, September, 2013.*
- *Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects, October, 2009.*
- *Guidance for Industry and Food and Drug Administration Staff: The 510k Program: Evaluating Substantial Equivalence in Premarket Notifications, July, 2014*

3.2.8 Food and Drug Administration Approval for Commercial Marketing [15]

The FDA approves medical devices for commercial marketing based on the sponsor's submission of a premarket notification (also known as a "510k") or a premarket approval (PMA) application. The regulatory "class" to which the medical device is assigned determines the type of application (i.e., 510k or PMA) that must be submitted to the agency. Class I medical devices have the lowest risk to the patient and/or user associated with their intended use and also with their labeled indications for use; whereas class III medical devices have the greatest, respective risks. If the medical device-of-interest (new device) is determined to be a class I or class II device, the submission and FDA acceptance of a 510k application is generally required to permit its commercial marketing (i.e., unless the medical device is also classified as being "exempt" from this submission and approval process). The submission and FDA-acceptance of a PMA is generally required to permit the commercial marketing of medical devices that are determined to fall under class III. FDA has established risk-based classifications for more than 17,000 medical devices and has grouped them into 16 medical specialties, referred to as "medical device classification panels," which are published in the FDA regulations at 21 CFR Parts 862–892. Within these panels are listings of applicable devices to include a general description of the device and its intended use, the risk classification (i.e., class I, class II, or class III) that has been assigned to device, and information about marketing requirements, including, if applicable, the conditions under which a class I or class II device may be considered exempt from the requirement to submit a 510k application. The information submitted to the FDA with a 510k application must demonstrate that the new device is "substantially equivalent" to a legally marketed device (i.e., a "predicate" device) that did not require the submission of a PMA for its approval (or that initially required the submission of a PMA, but was subsequently reclassified from class III to class II). A new device is considered to be substantially equivalent to a predicate device if it has the same intended use and technological characteristics as the predicate or if it has the same intended use as the predicate and different technological characteristics, and the information submitted to the FDA with the 510k application does not raise new questions of safety and effectiveness and demonstrates that the new device is at least as safe and effective as the predicate device. Thus, it is not necessary for the

new device to be identical to the predicate device to obtain FDA approval of a 510k application; however, IRB-approved, clinical studies may be required to prove equivalent safety and effectiveness if they are not identical. Class III medical devices are those that support or sustain human life, are of substantial importance in preventing the impairment of human health, or which present a potential, unreasonable risk of illness or injury. For class III medical devices, the FDA has determined that the general controls (premarket notification, manufacturer registration and device listing) applied to class I and II medical devices are insufficient to assure their safety and effectiveness. Thus, FDA approval to commercially market a class III medical device is subject to the agency's review and acceptance of a PMA application, which must incorporate valid scientific data (typically collected under an IDE application) that demonstrate that the new device is safe and effective for its intended human use.

4. REGULATORY MANDATES

The FDA regulations that govern IND [16] and IDE [17] applications define the sponsor of the application as the individual or entity (e.g., company, governmental agency, academic organization, or other organization) who takes responsibility for and initiates the respective clinical investigation of the investigational drug or device. The sponsor does not actually conduct the investigation unless it is a sponsor–investigator application. An investigator is the individual who actually conducts the clinical investigation (i.e., under whose immediate direction the investigational drug or device is administered or dispensed to a subject) at a certain study site. In the event that a clinical investigation is conducted by a team of individuals, the investigator is the responsible leader of the team, with the other members being subinvestigators. A sponsor–investigator is an individual who both initiates and conducts a clinical investigation, and under whose immediate direction the investigational drug or device is administered or dispensed. Only an individual may be the sponsor–investigator of an IND or IDE application.

In addition to the previously addressed regulations that govern or are associated with submission of IND and IDE applications, sponsors and investigators are required to comply with certain, respective responsibilities that are defined within the IND [18] and IDE [19] regulations. Sponsor–investigators are required to comply with both of these sets of responsibilities.

4.1 Sponsor Responsibilities

Sponsors of IND or IDE applications are responsible for:

- Selecting appropriately qualified investigators and providing them with the information necessary to conduct the clinical investigation properly.
  - Before permitting an investigator to participate in a clinical investigation, the sponsor must obtain from the investigator a signed investigator's statement (form FDA 1572 for IND applications) or investigator's agreement (for IDE applications), curriculum vitae or other statement of qualifications, and financial disclosure information. Regarding the latter, the FDA regulations at 21 CFR part 54, *Financial Disclosure by Clinical Investigators*, require the IND or IDE sponsor to identify any substantially involved clinical investigator or subinvestigator who (or whose immediate family member) has, as defined within

these regulations, an equity interest, proprietary interest, or financial interest in the investigational drug or device or the company that owns the investigational drug or device being evaluated under the IND or IDE application. The sponsor is required to describe, in writing, any steps taken to minimize the potential for bias resulting from any of these disclosed financial conflicts-of-interest and to retain these documents on file subject to FDA review at the time of submission of an NDA, BLA, PMA, or 510k application to obtain approval to commercially market the drug or device.
    - Before the clinical investigation commences, the IND or IDE sponsor is required to provide each study site investigator with a copy of the investigator's brochure (IND studies) or, at a minimum, the IRB-approved clinical protocol (for IND and IDE studies). An investigator's brochure is not required for single-site clinical investigations being conducted under a sponsor-investigator IND or IDE application [20].
    - The IND or IDE sponsor must promptly inform investigators of serious and unexpected adverse events and/or other newly identified, significant risks felt to be related (or possibly related) to the investigational drug or device.
- Ensuring proper monitoring of the progress and conduct of the clinical investigation at each of the involved study sites.
    - The sponsor is responsible for selecting an individual, qualified by training and experience, to monitor the clinical investigations being conducted under the FDA-accepted IND or IDE application.
    - Sponsors are responsible for ensuring that the clinical investigation is being conducted in accordance with the clinical protocol contained within the FDA-accepted IND or IDE application. If it is discovered, through monitoring or other processes, that an investigator is not complying with the clinical protocol or applicable FDA or IRB requirements, the sponsor must promptly either secure compliance or terminate the investigator's participation in the investigation.
- Maintaining an up-to-date IND or IDE with regard to information concerning the pharmacology and safety of the investigational drug or device, the manufacture of the drug or device, and current or planned clinical investigations being conducted under the IND or IDE.
    - The IND or IDE sponsor is required to review and evaluate evidence relating to the safety and effectiveness of the investigational drug or device as it is being obtained from the study site investigators. The sponsor is required to promptly report, to the FDA, serious and unexpected adverse events felt to be related to the investigational drug or device in accordance with the criteria and timelines specified in the IND and IDE regulations. Should it be determined that the investigational drug or device presents an unreasonable risk-to-benefit ratio for the clinical indication for which it is being evaluated, the sponsor must discontinue the respective clinical investigation(s), so notify the FDA, and so notify all involved IRBs and current and previously involved investigators.
    - The IND or IDE sponsor is required to submit annual reports to the FDA summarizing the safety and efficacy data that have been accrued from ongoing clinical investigations of the investigational drug or device.
    - The IND or IDE sponsor is required to submit clinical protocol modifications or new clinical protocols involving the investigational drug or device to the respective FDA-accepted IND or IDE application. As outlined in the IND and IDE regulations,

certain types of protocol modifications (e.g., modifications that affect the safety of the study participants) may require FDA notification (i.e., via the submission of a protocol amendment or supplemental IDE application) prior to implementing the modifications, whereas other types of modifications may be addressed in the annual report. New clinical protocols must be submitted to the IND or IDE application prior to their implementation. Sponsors must also update, in a timely manner, the FDA-accepted IND or IDE application with any new information related to the manufacture of the investigational drug or device or with pertinent safety or effectiveness information obtained from nonclinical studies.

- Ensuring accountability of the investigational drug or device.
  - The IND or IDE sponsor is required to maintain adequate records of the sponsor's receipt, shipment, or other disposition of the investigational drug or device.
  - The IND or IDE sponsor shall ensure that study site investigators have in place adequate records for investigational drug or device accountability and that supplies of the investigational drug or device are being stored in a secure manner in accordance with the sponsor's established storage conditions.
  - The IND or IDE sponsor shall ensure the return or other authorized disposition of remaining supplies of the investigational drug or device from each investigator whose participation in the respective clinical investigation has been completed or otherwise discontinued.
- Maintaining sponsor records and reports required under the regulations governing IND and IDE applications for the period specified in these regulations.
- Registering phase 2 and phase 3 clinical trials on the ClinicalTrials.gov database and submitting certification (form FDA 3671) of this registration to the FDA-accepted IND or IDE application [21].

4.2 Investigator Responsibilities

Investigators involved in the conduct of a clinical investigation under an FDA-accepted IND or IDE application are responsible for:

- Protecting the rights, safety, and welfare of research subjects.
  - The investigator must involve an IRB that complies with the FDA's regulations at 21 CFR Part 56 in the initial and continuing review and approval of the conduct of the clinical investigation at the investigator's study site.
  - The investigator must, in accordance with the FDA regulations at 21 CFR part 50, obtain the written informed consent of each human subject prior to his/her participation in any procedures being conducted for the purpose of the clinical investigation, unless the reviewing IRB approves a waiver or an exception from the requirement for written informed consent in accordance with the provisions of these regulations. The investigator is required to document the informed consent process (including the date and time that consent was obtained) in the case histories of the research subjects.
  - The investigator must promptly report unexpected adverse events that are related, or potentially related, to the investigational drug or device to the responsible IRB in accordance with IRB policies.

- Ensuring that the clinical investigation is being conducted in accordance with statements contained within the signed statement of investigator (form FDA 1572) or investigator's agreement.
  - Investigators are not permitted, in the absence of prior IRB approval, to deviate from the FDA-accepted and corresponding IRB-approved clinical protocol except when necessary to eliminate an apparent immediate hazard to the research subject(s).
  - Investigators are required to promptly report all changes in research activity (e.g., protocol deviations) and all unanticipated problems involving risks to human subjects or others to the responsible IRB.
- Ensuring control and accountability of the investigational drug or device.
  - The investigator must ensure that the investigational drug or device will be administered only to research subjects who are under the direct supervision of the investigator or under the supervision of a subinvestigator who is responsible to the investigator. The investigator must not supply the investigational drug or device to any person who is not authorized to receive it.
  - The investigator must maintain adequate records of investigational drug or device accountability, and must store supplies of the drug or device in a secure manner in accordance with the sponsor's established storage conditions. Upon completion or termination of the investigator's participation in the clinical investigation, unused supplies of the investigational drug or device must be returned to the sponsor or disposed of in accordance with the instructions of the sponsor.
- Submitting requested and required reports to the sponsor.
  - The investigator must prepare and maintain (i.e., for each research subject) adequate and accurate case histories that document all observations and other data pertinent to the evaluation of the investigational drug or device. Case histories include case report forms and respective supporting documents, such as signed and dated copies of source medical records.
  - The investigator must promptly report identified serious adverse events to the sponsor in accordance with the criteria specified by the sponsor.
  - The investigator must provide, in a timely manner, reports requested by the sponsor (e.g., progress reports, final report), including initial and routinely updated certifications and disclosures of the investigator's and subinvestigators' financial interest related to the drug or device under investigation.
- Maintaining investigator records and reports required under the regulations governing IND and IDE applications for the period specified in these regulations.

5. KEY PERSONNEL AND UNIVERSITY COMMITTEES DESIGNATED TO IMPLEMENT REGULATORY MANDATES

At most academic institutions, the entity responsible for ensuring compliance with the IND and IDE submission requirements will be the institution's responsible IRB. Some institutions have established specific offices to provide IND and IDE support to their faculty who are involved in this process. An example is the University of Pittsburgh's Office for Investigator-Sponsored IND and IDE Support (www.o3is.pitt.edu). Such support may also be provided by the institution's clinical and translational science institute or equivalent.

Depending on institutional policies, it may be a requirement that the institution be named as the sponsor of the IND or IDE application, on which the institution assumes the regulatory responsibilities of the sponsor. Alternately, the institution may require that the involved faculty member be designated as the sponsor-investigator or sponsor of the application.

6. COMMON COMPLIANCE CHALLENGES

Based on the author's experience, the most common compliance challenge for the sponsor of an IND or IDE application is in addressing the routine submission of the various reports and amendments (e.g., annual reports, safety reports, protocol amendments, information amendments, supplemental IDE applications) necessary to ensure an up-to-date application. The most common compliance challenge facing investigators are unauthorized deviations from the IRB-approved and FDA-accepted clinical protocol. The latter also becomes a compliance challenge for the IND or IDE sponsor, because it is a sponsor responsibility to routinely monitor the conduct of the clinical investigation at each study site and to take appropriate action when noncompliance with the clinical protocol is identified [22,23].

A protocol deviation refers to any unplanned instances of protocol noncompliance [24]. For example, situations in which the investigator failed to perform tests or examinations required by the protocol or failures on the part of the study subjects to complete scheduled visits as required by the protocol would be considered protocol deviations. In accordance with FDA [25] and IRB [26] regulations and statements contained within the investigator-signed form FDA 1572 or investigator's agreement [27], investigators are not permitted to deviate from the IRB-approved and FDA-accepted clinical protocol unless they have obtained prior authorization to do so from the reviewing IRB or the deviation is necessary to eliminate apparent immediate hazards to the human subject(s). As previously stated, investigators are required to promptly report to the responsible IRB all changes in research activity and all unanticipated problems involving risk to human subjects or others. Notably, the responsible IRB is subsequently required to submit all reports of unanticipated problems involving risks to human subjects or others to the responsible institutional official and to the FDA [28]. This would include reports of protocol deviations wherein the deviation (e.g., failure to perform a safety evaluation in accordance with approved clinical protocol) involves a risk to the study participant.

7. ADDRESSING NONCOMPLIANCE

Failure to submit the reports and protocol amendments required to maintain an up-to-date IND or IDE application should be corrected by the sponsor as soon as identified. For investigator noncompliance identified through investigator quality assurance efforts or sponsor monitoring, the investigator should ensure prompt reporting of such to the responsible IRB and to the sponsor (i.e., if not already involved). For sponsor or investigator noncompliance identified during an FDA audit, the involved agency inspector will issue a form FDA 483 with the identified items of noncompliance listed. The sponsor or investigator is instructed to respond to the form FDA 483 within a specific period (i.e. 15 days), and then the FDA's Office of Scientific Investigations will subsequently review the form FDA 483 observations, the sponsor's or investigator's response

to these observations, and the inspector's establishment inspection report to determine whether additional action (e.g., issuance of an FDA warning letter) is warranted.

In responding to identified noncompliance, it should always be recognized that the IND or IDE sponsor or investigator is personally responsible for complying with applicable FDA regulations and responsibilities. It is not appropriate for the sponsor or investigator to place the blame for noncompliance on a subinvestigator, research coordinator, or other individual who is involved in the clinical investigation. For each identified item of noncompliance, the sponsor's or investigator's response should routinely include a summary of the sponsor's or investigator's conclusion, based on investigation, as to why the problem occurred and the steps or processes that have been subsequently put in place in an effort to prevent a recurrence of the problem.

References

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[16] 21 C.F.R. Part 312, investigational new drug application, sec. 312.3(b).
[17] 21 C.F.R. Part 812, investigational device exemptions, sec. 812.3.
[18] 21 C.F.R. Part 312, investigational new drug application, subpart D—responsibilities of sponsors and investigators.
[19] 21 C.F.R. Part 812, investigational device exemptions, subpart c—responsibilities of sponsors; subpart e—responsibilities of investigators.
[20] 21 C.F.R. Part 312, investigational new drug application, sec. 312.55(a).
[21] http://clinicaltrials.gov/.
[22] 21 C.F.R. Part 312, investigational new drug application, sec. 312.50.
[23] 21 C.F.R. Part 312, investigational new drug application, sec. 312.56(b); 21 CFR Part 812, investigational device exemptions, sec. 812.46(a).
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[25] 21 C.F.R. Part 312, investigational new drug application, sec. 312.66; sec. 312.50; sec. 312.60.
[26] 21 C.F.R. Part 56, institutional review boards, sec. 56.108(a).
[27] 21 C.F.R. part 812, investigational device exemptions, sec. 812.43(4).
[28] 21 C.F.R. Part 56, institutional review boards, sec. 56.108(b).