FDA-Regulated Research

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Introduction

The U.S. Food and Drug Administration (FDA) regulates drugs, biologics, and devices used in the diagnosis, mitigation, treatment, or prevention of diseases. This module addresses FDA-regulated clinical research and the responsibilities of researchers, Institutional Review Boards (IRBs), and sponsors when they participate in a study of an FDA-regulated product.

Learning Objectives

By the end of this module, you should be able to:

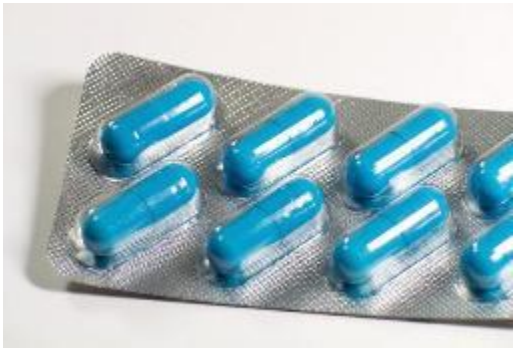
- Recognize when an Investigational New Drug (IND) application is and is not necessary.
- Describe the role of Form FDA 1572.
- Define what constitutes a medical device.
- Identify the responsibilities of sponsors and researchers as they relate to FDA-regulated research.

FDA Review

The FDA conducts a thorough review of drugs, biologics, and medical devices for safety and effectiveness before granting approval for marketing. Before a product is marketed, the sponsor submits an application for approval to the FDA. This application contains a proposed "package insert" that may also be referred to as "labeling." This insert summarizes what the FDA has determined to be a safe and effective use of the product. The FDA bases its approval decision upon bioresearch data generated and reported to the FDA by the sponsor to support the product's marketing approval. These data are collected by the sponsor during clinical research conducted under an IND application or an Investigational Device Exemption (IDE).

Drugs and Biologics

Investigational New Drug (IND)



Research involving a drug or biologic that has not yet reached the marketplace or that studies a new use of the marketed product requires an IND per 21 CFR 312 (Investigational New Drug Application 2014). A sponsor develops a research plan, which is then evaluated by the FDA. A sponsor can be a drug company, cooperative group, or even an individual physician. After careful review, the FDA will allow human studies to proceed if it determines that the risk of exposure to the drug is reasonable. This determination is based upon:

- Data from prior animal or human testing
- Methods of manufacturing
- Plans for testing and reporting significant toxicities
- A well-developed clinical research plan that minimizes risks to the subjects

Investigational Use of a Marketed Drug

Researchers may want to use an approved product in the context of clinical studies. When the principal intent of the product's investigational use is to develop information about safety or efficacy, an IND may be required. However, the clinical investigation of a marketed drug does not require an IND if the following conditions are met:

- The data will not be used to support a new indication, new labeling, or change in advertising.
- The research does not involve a route of administration/dosage level or subject population that significantly increases the drug product's risks of harm.
- The research is conducted in compliance with Institutional Review Board (IRB) review and informed consent requirements.
- The research is conducted in compliance with requirements for promotion and sale (21 CFR 312.2[b] [Investigational New Drug Application 2014]).

Exemption from IND submission requirements does not mean exemption from IRB review and approval, or from subjects' informed consent. The FDA should be consulted if there are any changes.

Form FDA 1572

The Form FDA 1572 (Statement of Investigator) is the agreement between the researcher and FDA. The Form FDA 1572 is also the document that notifies FDA of relevant changes in researchers conducting clinical trials under the IND.

- Researchers participating in drug and biologic studies subject to the IND regulations must sign Form FDA 1572.
- Form FDA 1572 outlines the commitments that must be made by the researcher(s) regarding the conduct of the study.
- Form FDA 1572 must list co-researchers who will be administering the drug or separate forms need to be submitted for these individuals.
- Form FDA 1572 must list the IRB of record for that study site (Investigational New Drug Application 2014).

"Off Label" Use of Drugs, Devices, and Biologics

Good medical practice and the patient's best interests require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If physicians use products for an indication not listed in the approved labeling, they have the responsibility to be well informed and to base the proposed use on scientific rationale and medical evidence.

Use of a marketed product in this manner, when the intent is the practice of medicine, does not require the submission of an IND or IDE per 21 CFR 312.2(d) (Investigational New Drug Application 2014). However, an individual organization may under its authority require oversight for this practice (such as, review by a Medical Practice or Pharmaceutics and Therapeutics Committee).

Devices

The Definition of a Medical Device

A medical device is any healthcare product that does not achieve its primary intended purpose by a chemical interaction or by being metabolized. Medical device examples include:

- Surgical lasers
- Sutures
- Pacemakers
- Diagnostic aids such as reagents and test kits for *in vitro* diagnosis

The Medical Device Amendments of 1976

The Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990 provide the regulatory framework for medical device development, testing, approval, and marketing. Manufacturers who wish to market a new medical device may need to submit a pre-market notification to the FDA. Some medical devices are exempt from the pre-market approval process. If the device is not exempt, FDA at 21 CFR 807.81(a)(1) (Establishment Registration 2014) determines whether the device is substantially equivalent to similar devices marketed before the 1976 amendment. These devices are often referred to as 510k devices (see 21 CFR

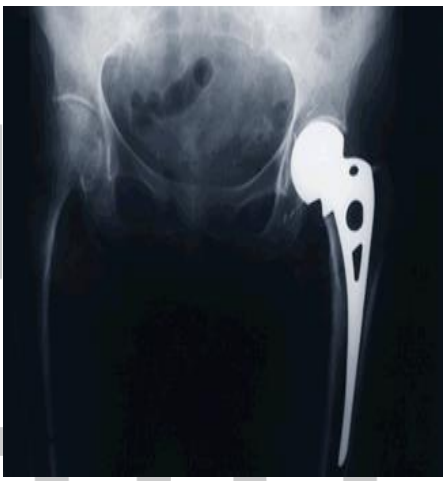
807.92). If the new device is not substantially equivalent, the company may need to demonstrate safety and efficacy in a pre-market approval application, which could include clinical trials.

Investigational Device Exemption (IDE)

An investigational device is a medical device that is undergoing clinical trials to evaluate safety and effectiveness. The IDE regulations at 21 CFR 812.2 (Investigational Device Exemptions 2014) specify how to conduct these clinical trials. The regulations require that devices be classified as significant risk (SR) or non-significant risk (NSR) devices. The sponsor often first makes this classification, but the IRB must agree with the determination. The risk determination should be based on the proposed use of the device and not on the device alone.

Significant Risk (SR) Devices

A SR device presents a potential for serious risk to the health, safety, or welfare of the subject and it:



- Is intended to be implanted into a human;
- Is used in supporting or sustaining human life;
- Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or
- Otherwise presents serious risk to health, safety, and welfare of a subject (21 CFR 812.3[m] [Investigational Device Exemptions 2014]).

The sponsor must submit an IDE application to the FDA per 21 CFR 812.20 (Investigational Device Exemptions 2014). There is no specific form for this purpose, but the regulations list elements required in the application. The trial cannot begin until FDA grants an IDE and the IRB grants approval for the study. By definition, a study with a SR device poses more than minimal risk to the human subjects and requires full IRB review.

Non-Significant Risk (NSR) Devices

A NSR device, by default, does not meet the criteria of significant risk. It is considered to have an approved IDE application (that is, no application is filed with the FDA), and is studied without FDA oversight if the sponsor complies with certain FDA requirements such as monitoring, record keeping, and properly labeling the investigational device. The IRB must agree that the study meets the criteria for non-significant risk. The clinical trial of a NSR device requires IRB approval, informed consent, and proper study monitoring and it must meet all other regulatory compliance requirements.

Informed Consent

Elements of Informed Consent

Elements of informed consent, as required by the FDA, are found in the regulations at 21 CFR 50.25.

The FDA also issued a new requirement to the elements of informed consent, which went into effect in March 2012. Beginning on that date, studies governed by the FDA must include the following statement in the informed consent form:

- "A description of this clinical trial will be available on **http://www.ClinicalTrials.gov**, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time" (Protection of Human Subjects 2014).
- In February 2012, the FDA also issued ***Guidance for Sponsors, Investigators, and Institutional Review Boards - Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)***.

Informed Consent Waiver

FDA at 21 CFR 50.23 and 50.24 (Protection of Human Subjects 2014) provides exceptions to the requirement for informed consent under certain circumstances. These circumstances are described below and will be discussed in more detail later in this module. **Note:** FDA distinguishes between the unplanned emergency use of a test article for one individual (21 CFR 50.23) and planned emergency research (21 CFR 50.24). The IRB must be notified within a maximum of five days if a test article was used in an emergency situation for one individual.

- In life-threatening conditions involving an individual person where requirements for an exception from informed consent are met. More specifically, FDA regulations (21 CFR 50.23) permit exception from informed consent in life-threatening situations where:
    1. The researcher, with the concurrence of another physician not participating in the clinical investigation, believes and certifies in writing that the situation for the human subject is life-threatening and necessitates the use of a test article (that is, an investigational drug, device, or biologic).
    2. The subject and/or legally authorized representative (LAR) is unable to communicate consent. The FDA (Protection of Human Subjects 2014) indicates that a LAR is:

> "An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."

3. There is insufficient time to obtain consent.
4. No alternative exists that will provide an equal or better chance of saving the subject's life.

- The FDA permits exception from informed consent requirements for planned emergency research (21 CFR 50.24). Unlike the exception noted in 21 CFR 50.23, the activities described in 21 CFR 50.24 are associated with an IRB-approved research study that involves research in emergencies. According to the FDA (Protection of Human Subjects 2014), emergency research are:

  > Investigations [that] involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury) cannot provide consent.

  The research must:

  1. Have the prospect of direct benefit to the patient.
  2. Must involve an investigational product.
  3. The product, in order to be effective, must be administered before informed consent from the subject or the subject's LAR can be obtained.
  4. There is no reasonable way to identify prospectively individuals likely to become eligible for participation.

FDA has issued the final guidance on ***Exception from Informed Consent Requirements for Emergency Research***.

Note: Unlike the use of a test article in an emergency situation for one individual (21 CFR 50.23), IRB prospective review of the full research plan is required for emergency research (21 CFR 50.24).

FDA Guidance on Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

On 24 July 2017, the FDA issued guidance that they will not object if an IRB approves a waiver or alteration of consent for a no more than minimal risk clinical investigation if the IRB determines that (FDA 2017):

- The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3[k] or 56.102[i]) to subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Is Verbal Consent Appropriate?

The FDA allows waiver of written documentation of informed consent (that is, consent of the subject is obtained, but the subject does not have to sign a consent document):

- When study participation presents minimal risk of harm to the subject; and
- When the research involves no procedures requiring written documentation of consent outside the context of participation in a research study.

With a waiver of written documentation of consent, the consent of the subject or the subject's LAR is still required. The IRB may require the researcher to provide the subject with written materials about the research per 21 CFR 56.109 (Institutional Review Boards 2014).

Emergency Use of an Investigational Biologic, Drug, or Device

Researchers and IRBs may be confronted with the need to use an unapproved investigational drug or device on a human subject in an emergency situation. In these circumstances, review by a convened IRB may not be feasible because of the problem's emergent nature. When this happens attention must be given to the IND/IDE requirements, informed consent, and IRB procedures. Please note:

- Regulations at 21 CFR 50.23 cover unplanned emergency use
- Regulations at 21 CFR 50.24 cover planned emergency research

The Definition of Emergency Use

Emergency use is the use of an investigational drug or device with a human subject in a life-threatening situation, or in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval. Life-threatening means that the likelihood of death is high unless an intervention interrupts the process. It also applies to a condition that is immediately and severely debilitating and that causes irreversible morbidity (such as, blindness or paralysis) per 21 CFR 56.102(d) (Institutional Review Boards 2014).

IND/IDE Requirements for Emergency Use

If an individual subject does not meet the criteria for an existing research plan, or an approved research plan does not exist, the usual procedure is for the physician to contact the manufacturer and determine if the drug can be made available for an "emergency use" under the company's IND. If there is no IND, the FDA per 21 CFR 312.36 (Investigational New Drug Application 2014), may authorize the manufacturer to allow the drug to be used in advance of an IND submission. In addition, if the company agrees to provide the product, the physician can contact FDA, explain the situation, and obtain an emergency IND to permit the drug's shipment. If there is no IDE, the physician may use the device and notify FDA of its use after the fact. The

physician should obtain both an independent assessment from another physician and informed consent from the subject, before emergency use of the device occurs.

IRB Review Requirements for Emergency Use

In an emergency use situation, the FDA at 21 CFR 56.104(c) (Institutional Review Boards 2014) permits an exemption from prior review and approval by an IRB. For emergency use of devices, concurrence of the IRB chair is required before the use takes place. However, individual organizations may have a variety of policies to handle this situation. For example, the researcher may be required to notify the IRB office when emergency use is being considered. HHS regulations do not prohibit a researcher from using any investigational or approved drug or device in an emergency situation for the subject's clinical care, but they do not consider information collected to be research data. FDA does consider this to be a research use and wants the data reported to them. IRB review and approval is required in all circumstances if the researcher wishes to use the data for research purposes.

After an Investigational Drug or Device Has Been Used In an Emergency

Subsequent use of the investigational product at the organization should have prospective IRB review and approval. If the IRB was not notified before the investigational drug or device was used in an emergency situation, the IRB should be notified per organizational policy or within five working days (Protection of Human Subjects 2014). The FDA and sponsor should be notified as necessary.

Further information on emergency use of investigational devices can be found at the FDA's ***Guidance on IDE Policies and Procedures***.

Responsibilities

Sponsor Responsibilities

A sponsor may be an individual, a private company, or other organization that is responsible for the initiation and conduct of a study involving a drug, device, or biologic. Researchers who design and conduct their own studies assume this responsibility in addition to their role as researcher. Often these are called "investigator-initiated" studies. The sponsor's responsibilities include:

- Selecting clinical researchers qualified by training and experience.
- Informing and qualifying researchers by obtaining their commitment to supervise the study, follow the research plan, and obtain consent.
- Monitoring the study's conduct by auditing documentation and conducting site visits.
- Completing regulatory filings related to the IND or IDE, adverse events, amendments or revisions, progress reports, withdrawal of IRB approval, and final reports.

- Controlling the distribution, tracking, and dispensation of the regulated products.

Researcher Responsibilities

- Ensuring IRB approval for the study is obtained before any subjects are enrolled.
- Ensuring that informed consent is obtained in accordance with FDA regulations.
- Ensuring that the investigation is conducted according to the investigational plan and applicable regulations.
- Administering the drug or using the device only in subjects under the researcher's supervision or under the supervision of a recognized sub-researcher.
- Maintaining adequate records of the dispensation of the drug or device.
- Returning unused materials at the end of trial.
- Preparing and maintaining adequate case histories and signed informed consent documents.
- Maintaining correspondence with the IRB and the sponsor to make sure that both have reviewed research plan amendments, recruitment materials, and Investigator's Brochures.
- Retaining records in accordance with regulations.
- Providing progress, safety, final, and financial disclosure reports.
- Notifying the sponsor if IRB approval is withdrawn.
- Comply with International Council for Harmonisation (ICH) guidelines, if applicable.

Inspections and Audits

The FDA's Bioresearch Monitoring Program conducts "not for cause" and "for cause" audits of IRBs, clinical researchers, and sponsors. The purpose of this monitoring is to ensure the quality and integrity of data submitted to FDA for regulatory decisions and to protect human subjects. The FDA may conduct on-site reviews of IRBs, research sites, pharmacies, manufacturing sites, etc. The FDA may also inspect, review, and copy records associated with the research.

21 CFR 11 – Electronic Records; Electronic Signatures

21 CFR 11 is often referred to as Part 11, and is intended to enable the use of electronic documents in the regulatory process for drugs and devices. Part 11 specifies processes that must be in place assuring that electronic documents and signatures are equivalent to paper documents and handwritten signatures.

For systems to comply with Part 11, a number of requirements must be met. For example:

- Computer systems utilizing electronic records and signatures must ensure accuracy, reliability, and consistent performance. Standard operating procedures (SOPs), audits, testing, and training are required.
- Computer systems must use and maintain secure, computer-generated, time-stamped audit trails independently recording the date and time of entries and actions that create, modify, or delete electronic records.
- Computer systems must use system checks ensuring that only those individuals authorized to use the system are allowed access to the system (and access only those parts of the system they have authorization to use), alter records, and perform operations.
- Procedures must be established to ensure that records are retained for a duration of time, in an appropriate format, and to meet FDA requirements at a minimum (Institutional Review Boards 2014; Investigational New Drug Application 2014; Investigational Device Exemptions 2014).

In 2003, FDA clarified the application of Part 11 and limited the scope of its enforcement. Under this narrower interpretation, FDA generally would not consider Part 11 to apply when computer systems are used to generate paper printouts of electronic records, and those paper records meet all the FDA requirements.

The FDA plans to publish a revised rule updating and clarifying the Part 11 requirements and the FDA's scope of enforcement. Until then, researchers and IRBs should check with their information technology support personnel (and as appropriate, sponsors) to ensure that either Part 11 compliance is maintained or that Part 11 does not apply.

FDA-Regulated Research

Dr. Welby is a pediatrician at University Medical Center, where one of his patients, Bobby, came to him with continuing “vasovagal fainting.” Vasovagal fainting occurs when standing up, whereby blood pools in the lower part of the body setting off a sequence of events resulting in a profound slowing of heart rate and drop in blood pressure ultimately causing fainting. This condition tends to occur in children who are relatively dehydrated.

Dr. Welby treated Bobby in the past by telling him and his parents to significantly increase his fluid and salt intake. Despite this, Bobby continued to have fainting episodes.

As luck would have it, Dr. Welby had recently reviewed the medical literature on Fludrocortisone, a steroid that is approved for use in children with adrenal insufficiency. He noted that the drug makes the body hold on to water and salt, so he decided to treat Bobby with Fludrocortisone to see if it would help decrease his fainting episodes. After taking the medication for several weeks, Bobby reported he had no fainting episodes since beginning this medication. Six months later, Bobby reported no fainting episodes.

Dr. Welby was so intrigued by Bobby's results that he wondered if Fludrocortisone should be given when vasovagal fainting is first diagnosed. He decides to treat all subsequent patients with increased fluid and salt intake and to randomly assign them to receive either Fludrocortisone at the dose and route of administration approved for use in children, or a placebo. Dr. Welby determines that he would need at least 30 patients in each group to draw any real conclusions about Fludrocortisone's affect on vasovagal fainting.

- Did Dr. Welby need to seek an IND from the FDA, along with IRB approval, before administering the drug to Bobby?

  Dr. Welby's intention in using the FDA-approved drug "off-label" was to specifically treat Bobby's medical condition. No IND application was needed. However, the medical center may have policies about using drugs off-label. If a doctor is intending to treat a patient, he or she may do so, consistent with good medical practice. This activity would not constitute research, and therefore not require IRB approval.

- Does Dr. Welby need to seek an IND from the FDA, along with IRB approval, before administering the drug, as described, to subsequent patients?

  Dr. Welby plans to systematically collect data to answer a hypothesis that would be relevant to patients with vasovagal fainting; this is a clinical investigation or research. Dr. Welby must obtain IRB approval before beginning this research. To conduct research without an IND, several conditions must be met to qualify for an IND exemption. It seems unlikely, at this stage, that Dr. Welby's intention is to use his data to "support a new indication, new labeling, or change in labeling" of the drug. The IRB would want to pay careful attention to any future research and also if Dr. Welby partners with the manufacturer of the drug. As Fludrocortisone is already approved for use in children for another indication at the dose and route of administration that Dr.

> Welby intends to use for his research, another condition is met for an exemption from an IND (See FDA regulations at 21 CFR 312.2[b]). As long as the research is conducted under IRB approval and in compliance with "requirements for promotion and sale," an IND will not be needed for this research. However, many IRBs would require concurrence from the FDA regarding this determination.

Summary

It is important for researchers and IRBs to understand and appreciate the FDA regulations so that they may fulfill their regulatory roles and responsibilities. There are many resources available (for example, guidance documents from the FDA) that could assist in interpreting and understanding the regulations.

References

- Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices, 21 CFR § 807 (2014).
- Institutional Review Boards, 21 CFR § 56 (2014).
- Investigational Device Exemptions, 21 CFR § 812 (2014).
- Investigational New Drug Application, 21 CFR § 312 (2014).
- Protection of Human Subjects, 21 CFR § 50 (2014).
- U.S. Food and Drug Administration (FDA). 2003. "Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application." Accessed March 2, 2016.
- U.S. Food and Drug Administration (FDA). 2017. "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects." July.

Additional Resources

- Electronic Records; Electronic Signatures, 21 CFR § 11 (2014).
- U.S. Food and Drug Administration (FDA). 2013. "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research." Accessed March 17, 2016.
- U.S. Food and Drug Administration (FDA). 2015. "Guidance on IDE Policies and Procedures." Last updated July 22.

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