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Preface

Until relatively recently, research institutions and investigators had not been named as defendants in lawsuits involving clinical trials. However, the death of Jesse Gelsinger in a clinical trial, which took place now more than a decade ago, proved to be a defining moment for the clinical research enterprise and opened the floodgates to litigation as well as to new legislation and regulations governing clinical research.

Yet, many of the resources needed to support clinical research in the midst of these changes are missing. This is certainly the case with health professionals’ and administrators’ need for readily available information about clinical trial law. The literature on American law and clinical trials is severely limited for most topical areas and completely absent for others. Experts acknowledge the need to understand how the law affects medical practice and research, yet there is no current, comprehensive source for those associated with clinical trials to consult concerning the various legal aspects and potential pitfalls these trials embrace. Because clinical trial litigation is of such recent vintage, it is particularly difficult for the non-lawyer to find and interpret the relevant information, further underscoring the need for such a resource.

This book is intended to begin to fill this gap as a resource containing information and reference material to help identify and understand the legal issues, many of which are quite complex, that are associated with clinical trials. This book is limited to American law, and it is beyond its scope to


Preface

discuss the legal aspects of international clinical trials, which is a topic deserving of a book unto itself.³

On many occasions the author of this book has needed to consult a comprehensive review of clinical trial law but could find only one book that came close—Clinical Research Law and Compliance Handbook.⁴ It provides an excellent and practical overview of regulatory and compliance requirements in structuring a clinical trial, but does not deal with clinical issues raised during the conduct of such trials to the extent this book does. The current book, on the other hand, provides an overview of relevant regulatory schemes and emphasizes and integrates into the reading cases involving the clinical aspects of trials. As such, the work will be a resource/research aid handbook designed more for clinical investigators, their institution administrators, and counsel.

When reading the cases discussed in this book, it is important to remember that because a court has ruled one way in one jurisdiction it does not necessarily mean that courts in other jurisdictions will rule the same. After all, only the US Supreme Court renders decisions that become the law of the land. However, given the limited number of published court opinions in this area of the law, it is likely that courts from different jurisdictions will consider how other courts have ruled and may give some weight to these earlier decisions.

Finally, a word about what this book is not. It is not intended to be an academic or philosophical treatise on the law. It is meant to be an easy to read, practical resource for, primarily, non-lawyers who need this information but who do not want to undertake in-depth reading on the policy and analysis behind the law in each area, as would be expected of a legal resource for law students or attorneys. In addition, the references provided in each chapter are intended to offer health professionals a comprehensive resource of materials that they may consult for further reading on each topical area covered.

Patricia M. Tereskerz

Chapter 1 Research malpractice and negligence

As clinical trials continually undergo increased examination, commentators note that law suits involving these trials will likely continue to increase in the face of relatively recent high-profile litigation, which has garnered considerable media attention.1,2 Before moving on to a discussion of the specific legal aspects of clinical trials and research malpractice, it is first important to establish baseline definitions and gain an understanding of what is being discussed. The first part of this chapter is dedicated to explaining what is meant by terms frequently used throughout the book and to providing a brief overview and history of the research enterprise. Terms used throughout will follow the federal definitions as set out in the Code of Federal Regulations. This is followed by a discussion of the basic elements required to prove negligence.

1.1 Background

Federal regulations concerning clinical trials can trace their origins to international guidelines or codes. In particular, the Nuremberg Code3 was adopted after World War II, following the horrendous Nazi medical experiments. The Code, which requires voluntary consent of human subjects, sets

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forth the following ten ethical principles for research involving human subjects.4

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

The Nuremberg code was followed by the Declaration of Helsinki, which provides international guidance for biomedical research undertaken by physicians. This Declaration was first adopted in 1964 and has been amended six times since, most recently in October 2008, and replaces all previous versions.

The United States Congress enacted the National Research Act of 1974, following several highly visible American research abuses which occurred in the mid-1970s, including the notorious Tuskegee syphilis experiments in which African-American men with syphilis were left untreated for many years so that researchers could study the clinical progression of syphilis.

In 1979, the Belmont Report, which was written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral

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Research, was codified. The Department of Health, Education and Welfare, now the Department of Health and Human Services (DHHS), adopted the principles described in the Belmont report—respect for persons, beneficence, and justice—to assure a uniform system of human subject protection throughout relevant federal agencies and departments. These regulations are referred to as “The Common Rule” which provides the basic elements of informed consent. The Common Rule will be discussed in more detail in Chapter 4 on informed consent.

The Office for Protection of Research Risk (later named the Office of Human Research Protections (OHRP)) was established to oversee development and implementation of policies and procedures to protect research participants participating in DHHS-sponsored research, and is under the purview of the DHHS. The National Human Research Protections Advisory Committee (now called the Secretary’s Advisory Committee on Human Research Protections) was also put into place to provide broad scientific and ethical guidance to OHRP. While OHRP is charged with oversight, management, and guidance for clinical trials and other research studies in humans, the Food and Drug Administration (FDA) is responsible specifically for approving clinical trials to test a new drug, biological product, or medical device.

1.2 Drugs: brief description of definitions

Clinical investigation and research subject

The appendix to this chapter includes selected reprinted portions of relevant definition sections of the Code of Federal Regulations. Briefly, for the testing of new drugs, federal regulations state a “clinical investigation means any experiment that involves a test article and one or more human subjects.” Everyone participating in a clinical investigation is a subject, which is defined as a “human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.”

7 Codified at 45 CFR Section 46 (1981).
10 21 CFR Section 2c107(e); 45 CFR Section 46.109(e).
11 21 CFR Section 312.3(b). See also CFR 56.102(c)—limited to planned FDA submissions—from the IRB regs, as opposed to the IND regs.
12 Id. [NOW 21 CFR Section 312.3(b)] Id.
Definition of an institutional review board

Institutional Review Boards (IRB) protect the rights and welfare of human subjects and are the groups formally designated to review, approve, and conduct periodic review of research involving human subjects.\(^\text{13}\)

Definition of sponsor

The sponsor is the person or organization “who takes responsibility for and initiates a clinical investigation.” “[A] sponsor may be an individual or pharmaceutical company, government agency, academic institution, private organization, or other organization.”\(^\text{14}\) A sponsor may retain a “contract research organization” which “assumes as an independent contractor with the sponsor, one or more obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.”\(^\text{15}\)

1.3 Brief overview: conduct of clinical trials

Human clinical trials are undertaken in four phases, known as Phases I to IV. The Office of Human Protections describes the objectives of the four phases as follows:\(^\text{16}\)

*Phase I drug trial.* Phase I trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase I trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase I trials is to obtain sufficient information about the drug’s pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase II studies. Other examples of Phase I studies include studies of drug metabolism, structure–activity relationships, and mechanisms of actions in humans, as well as studies in

\(^{13}\) 21 CFR Section 56.201(g).

\(^{14}\) 21 CFR Section 312.3 (b).

\(^{15}\) Id.

which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase I investigations is generally in the range of 20 to 80.

**Phase II drug trial.** Phase II drug trials include controlled clinical studies conducted to evaluate the drug’s effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

**Phase III drug trial.** Phase III trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit–risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase III studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to FDA for approval to market the drug. Phase III trials usually involve several hundred to several thousand patient-subjects.

**Phase IV drug trial.** Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase IV) studies to delineate additional information about the drug’s risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.\(^\text{18}\)

### 1.4 Medical devices

Medical devices entering the market must also comply with the Food and Drug Cosmetic Act. However, the approval process for medical devices is less

\(^{17}\) Definitions of Phase II drug trials and Phase II vaccine trials are different. See: [http://www.avac.org/ht/d/sp/i/323/pid/323](http://www.avac.org/ht/d/sp/i/323/pid/323) for definitions.

\(^{18}\) 21 CFR 312.85.
arduous than that for drugs and often does not require “true” clinical trials for safety and efficacy.\(^1^9\) However, beginning in 1990, the FDA has required more rigorous device evaluations concerning their risks and benefits. Nevertheless, few new device evaluations involve randomized controlled clinical trials.\(^2^0\)

Given that there are so many different types of devices ranging from those that present little to no risk to other much more complicated devices such as implants, the Medical Device Amendment Act of 1976 acknowledges this variation and classifies devices into three categories based on the level of risk. An explanation of how devices are classified is available on the FDA website and is included in the appendix to this chapter.

### 1.5 Research malpractice: the basics

Most lawsuits dealing with research malpractice are grounded in the legal theory of negligence. To prove negligence, a plaintiff must prove each of the following elements: (1) the existence of a duty, recognized by law, to adhere to a standard to protect others against unreasonable risks; (2) a breach of this duty; (3) a causal connection, often referred to as “proximate cause,” between this breach; and (4) a resulting injury—damages.\(^2^1\) If a breach in duty does not result in any injury, then negligence cannot be established. Duty of care and standard of care are the two elements that have been treated somewhat differently within the research malpractice setting as opposed to medical malpractice. Therefore, Chapters 2 and 3 of this text will discuss the application of these elements in great detail with an eye as to how courts have treated these when it comes to clinical research.

To preface this discussion, it is important to distinguish medical research from medical practice and to consider some basic concepts of each. One noted scholar has emphasized the need for a well-founded approach to research-related injuries by the courts because it is necessary to consider what research is and how it is different from medical treatment.\(^2^2\)

Morreim notes that the primary difference between research and ordinary medical practice are the goals of each. The goal of research is to “advance

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\(^1^9\)Sweet BV, Schemm AK, Parsons DM. Review of the processes for FDA oversight of drugs, medical devices, and combination products. *J Managed Care Pharm.* 2011; 17: 40–50.

\(^2^0\)Id.


Clinical research and the law

Research may use techniques such as randomization, double-blinding, and inclusion of placebos as controls, which means a research participant’s personal interests may be secondary to the goal of the research. Further, Morreim points out that while those participating in clinical research may receive benefits from the study, it is not the goal of the research to benefit the individual research participant. In research, participants may be exposed to unanticipated risks of experimental treatments or receive only a placebo. This stands in contrast to medical practice, where the goal is to benefit the patient and, as embraced by the Hippocratic Oath, to “do no harm” to the patient. Although the risks are less known in research, investigators must still minimize known and unknown risks to the extent possible.

Despite these differences, courts have relied on the medical malpractice framework to guide their judgment in considering research malpractice cases. In some of the early court cases, courts were not willing to allow practices in research that were not consistent with accepted medical practice, and in fact it was not until the 1930s that courts accepted clinical research as a necessary enterprise where a court acknowledged that “[w]e recognize the fact that, if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation. . . .”

1.6 Negligence actions and research: interesting aspects of medical research negligence cases

One of the interesting aspects of negligence cases involving medical research is how a wide net has been cast in naming defendants in these cases and how traditional legal theories are being expanded to reach research malpractice lawsuits, illustrating how this is a relatively new and evolving area of the law. For example, defendants have been named in lawsuits involving clinical research who heretofore would not have been considered targets, including

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23 Id.
25 Carpenter v. Blake, 60 Barb NY 488, 523–24, rev’d 50 NY 696 (NY Gen Term 1871) (finding negligence in treatment deviating from standard practice.)
bioethicists and members of boards such as IRBs. The *Gelsinger* case, which will be discussed in detail later in this book, was one of the first instances in which the plaintiff’s attorney named defendants who had previously never been targets of malpractice claims, including a clinical ethicist and members of the IRB. In addition, lawsuits involving clinical trials have also attempted to apply novel legal theories, which will also be discussed in greater detail later in this book.

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Appendix to Chapter 1 Relevant portions of the code of federal regulations

Protection of human subjects


21—FOOD AND DRUGS
CHAPTER I—FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL

PART 50—PROTECTION OF HUMAN SUBJECTS

Subpart A—General Provisions

Sec.50.3 Definitions.

As used in this part:


(b) Application for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An Application for an Investigational Device Exemption, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.
(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, or for a health claim, described in 101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.

(c) **Clinical investigation** means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) **Investigator** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) **Sponsor** means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to
conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor–investigator), and the employees are considered to be investigators.

(f) **Sponsor–investigator** means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) **Institution** means any public or private entity or agency (including Federal, State, and other agencies). The word *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(i) **Institutional review board (IRB)** means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(j) **Test article** means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act (42 U.S.C. 262 and 263b–263n).

(k) **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l) **Legally authorized representative** means 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.

(m) **Family member** means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.
Clinical research and the law

(n) Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o) Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

(p) Parent means a child's biological or adoptive parent.

(q) Ward means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in 50.25.

(s) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.


Investigational new drug application


TITLE 21—FOOD AND DRUGS
CHAPTER I—FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D—DRUGS FOR HUMAN USE
PART 312—INVESTIGATIONAL NEW DRUG APPLICATION
Subpart A—General Provisions
Sec.312.3 Definitions and Interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:


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

*Contract research organization* means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

*FDA* means the Food and Drug Administration.

*IND* means an investigational new drug application. For purposes of this part, “IND” is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.”

*Independent ethics committee (IEC)* means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in 56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

*Investigational new drug* means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.

*Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team.
Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

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

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor–investigator under this part include both those applicable to an investigator and a sponsor.

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

Overview: FDA regulation of medical devices

From: http://www.qrasupport.com/FDA_MED_DEVICE.html. 05/06/2003. Many of the regulations enforced by the Food and Drug Administration (FDA) with regard to medical devices can be found in Title 21 Code of Federal Regulations (CFR) Part 800 to Part 1299. This reference is abbreviated to 21 CFR 800 to 1299.

Medical Device Definition

A medical device is defined within the Food Drug & Cosmetic Act as “... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation,
treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

Medical devices distributed in the United States are subject to General Controls, pre-marketing and post marketing regulatory controls, as outlined below.

General Controls include:

1. Establishment Registration by manufacturers, distributors, repackagees and re-labelers,
2. Medical Device Listing with FDA of devices to be marketed,
3. Manufacturing the devices in accordance with Good Manufacturing Practices,
4. Labeling medical devices in accordance with the labeling regulations, 21 CFR 801 or 21 CFR 809,
5. Medical Device Reporting of adverse events as identified by the user, manufacturer and/or distributor of the medical device.

Pre-marketing controls are device and device classification specific. Pre-marketing controls for a medical device may include: clearance to market by 510(k) or approval to market by Pre-Market Approval (PMA). Post marketing controls include Device Listing, Medical Device Reporting (MDR), Establishment Registration and Quality System Compliance Inspection.

**Device Classification**

There are 3 FDA regulatory classifications of medical devices: Class I, Class II and Class III. The classifications are assigned by the risk the medical device presents to the patient and the level of regulatory control the FDA determines is needed to legally market the device. As the classification level increases, the risk to the patient and FDA regulatory control increase. Accessories to medical devices, devices used with a medical device to support use of the device, are considered the same classification as the medical device.

The FDA classification of medical devices is based upon classifications for devices currently legally marketed in the United States. The FDA determines the device classification by the device intended use and risk the device presents to the patient. New medical devices are compared to legally