

# Devices and Biologics

The Food and Drug Administration (FDA) is responsible for protecting public health by assuring the safety and effectiveness of a variety of medical products including drugs, devices and biological products. It also has responsibility for advancing public health by helping to speed innovations that make treatments more effective, safer and more affordable. Although much of the information in this book is geared toward the study of drugs, many CRCs also will be involved in clinical trials of devices and biological products. The precepts of conducting good research (GCPs, etc.) are the same in any clinical trial, but there are some differences in the regulations when the potential product is a device. In this section, we will discuss some of these differences.

The Center for Devices and Radiological Health (CDRH) within the FDA is responsible for both the pre-market and post-market regulation of medical devices. The CDRH page can be found on the FDA web site ([www.fda.gov](http://www.fda.gov)). A medical device is a product used for diagnosis, therapy or surgery purposes in patients, and that acts by physical, mechanical or physico-chemical (drug-device combination) means. Medical devices include a wide range of products that vary in complexity from tongue depressors to artificial hearts and x-ray machines.

There are different types of marketing applications a medical device manufacturer may submit to CDRH. Most medical devices reach the market through either the pre-market approval (PMA) process or the pre-market notification process (510(k)). The great majority are approved through the 510(k) process.

The FDA recognizes different classes of medical devices based on their design complexity, their use characteristics and their potential for harm if misused. “Class” refers to the level of regulatory control attached to the device. The definitions pertaining to the classification of devices are found in 21 CFR 860 (Medical Device Classification Procedures).

Class I devices are subject only to the general controls authorized by or under sections 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and

reports) and 520 (general provisions) of 21 CFR 860. A device is in class I if these general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, or if the device is not life-supporting or life-sustaining or for a use that is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury. Examples of Class I devices are examination gloves and elastic bandages.

Class II devices are subject to special controls because general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness. Special controls can include the need for performance standards, post-market surveillance, patient registries, the development and dissemination of guidance documents and other appropriate actions the FDA deems necessary to provide this assurance. Examples of Class II devices are powered wheelchairs and infusion pumps.

Class III devices, which are usually novel devices, require the submission of PMAs (pre-market approvals). These devices tend to have a higher risk or raise new safety and effectiveness questions that must be answered before being approved for marketing. Data in a PMA application must demonstrate a “reasonable assurance” of safety and effectiveness. Examples of Class III devices include implantable pacemakers and automated external defibrillators.

Manufacturers submit 510(k)s for devices similar to those already on the market. Data in a 510(k) submission must demonstrate that the new device is substantially equivalent in safety and effectiveness to a Class II device already on the market. Most device applications cleared under the 510(k) program are based on non-clinical testing with no clinical data, while the majority of PMA applications do contain clinical data.

Many devices are designed and developed as tools to accomplish a specific task that is already an established practice, so the intended patient population and anticipated effects of the device are known before testing begins. This is different than the drug development process, in which a new molecular entity may be identified before determining any potential clinical applications.

Another major difference between device and drug development is the interpretation of safety events seen in a clinical trial. A control group is almost always necessary to interpret safety information from a drug trial, while a control group may not be needed to identify adverse events related to the use of a device.

Pre-market trials tend to be simpler than drug trials when demonstrating safety with regard to intended use, and compliance is usually easier to measure in device trials. There are a number of other differences between device and drug trials. For example, it may not be possible to “blind” the device, so many device trials are conducted with the investigator and subject both aware of the device being used. It also may not be possible for a direct comparison with a competitor device, either because there is no comparable device or because of the logistics involved.

When studying a drug, the dose may be an issue; with a device, the size of the device may be an issue, especially in implantable devices. Implanting a

device may carry a greater risk than prescribing a drug, especially in later-phase trials when more is known about a drug. Depending on the device, there may be more precise endpoint determination (especially when there is electronic information storage on the device). Many endpoints in drug trials, on the other hand, are quite subjective (think of a depression rating scale vs. a “hard” measurement such as blood pressure).

Some differences also exist in the collection and reporting of medical events between device and drug trials. (These are discussed in more detail in Chapter 14.)

If you will be monitoring device trials, it is recommended that you read the device regulations found in CFR 21 Part 812 (Investigational Device Exemptions) and CFR 21 Part 814 (Pre-market Approval of Medical Devices). 21 CFR Part 860 (Medical Device Classification Procedures) and 21 CFR Part 803 (Medical Device Reporting), which covers adverse event reporting, will also be helpful.

## Biologics and Vaccines

The Center for Biologics Evaluation and Research (CBER) is the organization within the Food and Drug Administration that is responsible for ensuring the safety and efficacy of vaccines, blood and blood products, and cells, tissues and gene therapies designed for the prevention, diagnosis and treatment of human diseases, conditions or injury. The CBER page can be found on the FDA web site ([www.fda.gov](http://www.fda.gov)).

The Biologics License Application (BLA) is a request for permission to introduce a biologic product into interstate commerce (21 CFR 601.2). (This means approval for marketing.) The BLA is regulated under 21 CFR 600-680. The application, which shows the clinical efficacy and safety of a biologic product in humans and requests marketing approval in the U.S., usually is submitted to the FDA after completion of phase III trials.

The regulations that apply to drugs also apply to biologics. In addition to these, the regulations in the preceding paragraph regulate the BLA.

Vaccine clinical development follows the same general pathway as drugs and other biologics. A sponsor who wishes to begin clinical trials with a vaccine must submit an Investigational New Drug application (IND) to the FDA. The IND describes the vaccine, its method of manufacture and quality control tests for release. Also included are information about the vaccine’s safety and ability to elicit a protective immune response (immunogenicity) in animal testing, as well as the proposed clinical protocol for studies in humans.

Clinical trials for vaccines are typically conducted in three phases, just like drugs and biologics. Initial human studies, referred to as phase I, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase II studies are dose-ranging studies and may enroll hundreds of subjects. Finally, phase III trials typically enroll thousands of individuals and provide the proof of effectiveness and safety required for licensing.