

FDA Medical Device Approval: Things You Didn't Learn in Medical School or Residency

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ABSTRACT

The Food and Drug Administration (FDA) does more than regulate food and drug products. Through its medical device evaluation process, FDA affects every orthopedic surgeon's practice and every orthopedic patient every day. FDA regulations affect the development of each orthopedic device in some way, from the product's inception to its senescence, but the regulatory process and what the FDA's stamp of approval means are not part of the curriculum in medical school or residency.

Each device follows a specific pathway from manufacture to physician use and patient care depending on the assessment of risk associated with the device or classes of devices. The evaluation of safety and effectiveness involves a complex process of biomechanical, engineering, preclinical, laboratory, clinical, and epidemiological assessment.

How different types of devices get to the patient are reviewed, and the basics of the regulatory process are explained in this paper. Common myths are set straight, and FDA's concerns with "off-label" use are discussed. The role of the orthopedic surgeon in the regulatory process is also introduced.

The Food and Drug Administration (FDA), a public health regulatory agency, has a wide purview over not only most food products and animal and human therapeutic drugs but also cosmetics, therapeutic products of biologic origin, animal drugs and feed, and a variety of medical devices, including orthopedic implants and devices for diagnostic and external therapeutic use. There are 6 centers and a variety of affiliated offices and organizations within the agency under the Department of Health and Human Services (HHS) umbrella; all strive to promote and protect the public health by assuring that only those products for the treatment of disease and conditions affecting the public's quality of life get to market that are reasonably safe and effective.

FDA has a number of different functions; they include marketing clearance or approval and proper labeling of

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medical products before they can be sold in the United States; alerting health care professionals and the public to problems with products; removing problem products from the market; monitoring imports; and protecting patient safety by regulating clinical trials involving investigational products and monitoring postmarket performance of devices through postmarket surveillance studies, inspections, manufacturing controls, and medical device reports to FDA.

Brief Legislative History of the FDA

The FDA has a long history dating back to its inception in 1862 and establishment of its official regulatory authority 101 years ago with the passage of the Federal Food and Drug Act.¹ Regulation of modern medical devices such as orthopedic implants began with the passage of the Medical Device Amendments in 1976, which established the definition of different classifications of devices by risk to health and regulatory pathways for medical devices coming to the public market. Over time, modifications have been made to update the regulations to keep up with medical progress and technology. Most recently, the Medical Device User Fee and Modernization Act of 2002 [(MDUFMA), P.L. 107-250,] amends the Federal Food, Drug, and Cosmetic Act² to include user fees (payments) for premarket reviews, the establishment of inspections conducted by accredited persons (third-parties), and new regulatory requirements for reprocessed single-use devices such as drills or sawblades.

Organizational Structure

The Center for Devices and Radiological Health (CDRH) in the FDA, one of FDA's 6 centers, is responsible for premarket and postmarket regulation of medical devices (Figure)³. In CDRH's Office of Device Evaluation, one of 8 offices in the Center, the 5 branches of the Division of General, Restorative and Neurologic Devices (DGRND) evaluate most devices used for the treatment and diagnosis of orthopedic musculoskeletal and neuromuscular diseases, a wide variety of devices used in plastic and reconstructive surgery, general surgery, and neurological surgery, and also diagnostic and manual surgical instruments and wheelchairs, for example. The CDRH is responsible for regulating the manufacture, repackaging, re-labeling, and/or import of medical devices sold in the United States. This is accomplished through several scientific activities, including

- reviewing requests to research or market medical devices;
- collecting, analyzing, and acting on information about

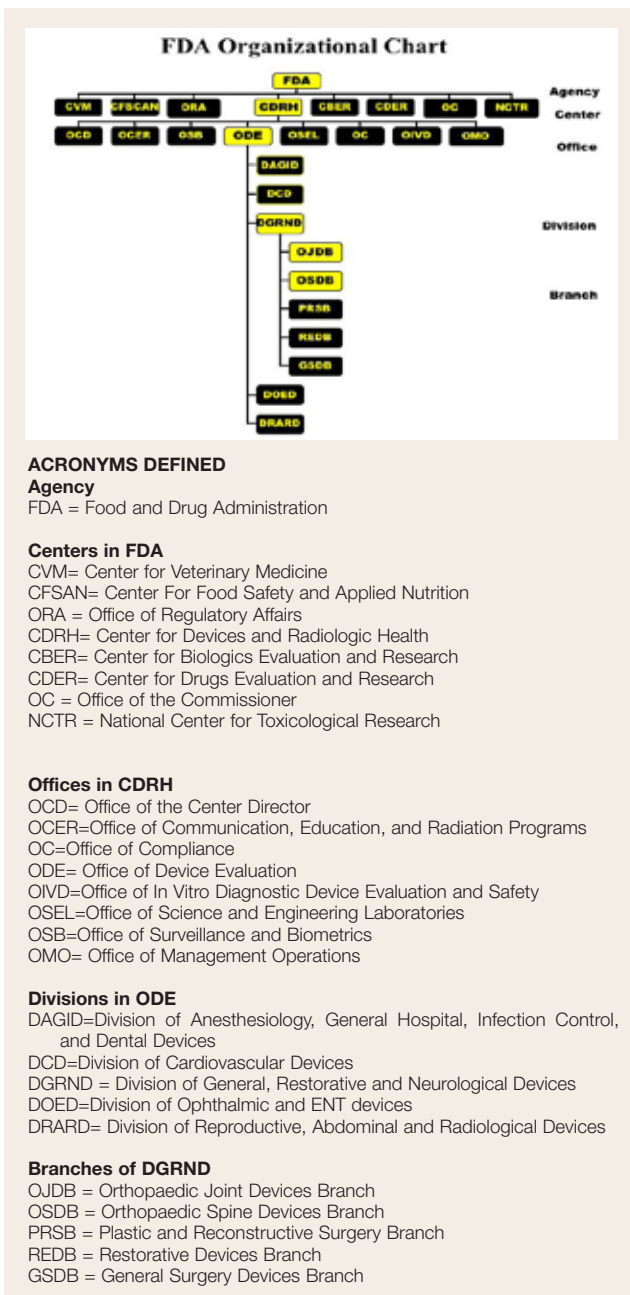


Figure. Organizational structure of the FDA.³

injuries and other adverse experiences in the use of medical devices and radiation-emitting electronic products;

- setting and enforcing good manufacturing practice regulations and performance standards for radiation-emitting electronic products and medical devices;
- monitoring compliance and postmarket surveillance programs for medical devices and radiation-emitting electronic products, and
- providing technical and other non-financial assistance to small manufacturers of medical devices.⁴

The level of regulation imposed upon any one medical device depends upon its classification.

3 CLASSES OF MEDICAL DEVICES

Cleared Versus Approved

The FDA has established 3 categories (classes) of medical devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness.⁴ These 3 classes are based on the risk to the patient and how the risks are mitigated. Evaluation of safety and effectiveness of devices is conducted under different levels of scrutiny based on the classification of risk and pathway to market.

From a regulatory perspective, the terms “cleared” and “approved” have different regulatory implications as well as implications of scientific scrutiny.

- In general, class II devices are compared with legally marketed devices or devices in use prior to 1976 with a previous clinical history and “cleared” as substantially equivalent through the premarket notification process to those legally marketed devices, also called “predicates” (in use previously).
- In general, novel class III devices, which most often require clinical data through a clinical trial to demonstrate safety and effectiveness, are “approved” as safe and effected through the premarket “approval” process.

Differing Pathways to Market

In order to fully understand what the terms “cleared” and approved connote, one has to understand the device classifications and the risk to health they signify. The pathways to market are paralleled by the scientific evidence and scrutiny each requires (Table).

Most **class I devices** are exempt from FDA notification. Class I devices are those for which only “general controls” are sufficient to provide reasonable assurance of their safety and effectiveness. “General controls” include basics like strategies for preventing mislabeling of the device; quality system regulations such as design controls, registration of manufacturing facilities, and good manufacturing practices; record keeping; and Medical Device Reporting (MDR) of adverse events as identified by the user, manufacturer, and/or distributor of the medical device. Examples of class I devices include manual surgical instruments such as scalpels, drills, saw blades, retractors, and general surgical instruments to aid in reconstruction and implantation of devices. As most class I devices are exempt from premarket review, the regulatory process for class I devices is simpler than that for class II or III devices, although a few class I devices such as surgeon’s gloves, removable skin staples, and removable skin clips do require Premarket Notification through the 510k process.

Most **class II devices** require Premarket Notification 510(k) clearance prior to marketing. For class II devices, “general controls” are not sufficient to address potential risks to health, and additional “special controls,” evalua-

Table. The 3 Classes of Medical Devices and the Evaluation Process for Each

Class and Controls for safe use	Premarket Submission	Postmarket Surveillance	Examples
I Low risk: General controls establish safety	Exempt rarely: 510k Notification	Medical Device Adverse Event Reporting (MDR) labeling	Scalpels, drills, saw blades, retractors, and general surgical instruments
II Moderate risk: Controlled by benchmarks and <ul style="list-style-type: none"> • Marketed prior to 1976 • Standardized bench testing • Labeling • Guidance documents • Occasionally clinical data 	510k—PreMarket Notification	Occasionally post market surveillance <ul style="list-style-type: none"> • Registries 	Intramedullary nails, plates, and screws, most joint replacement <i>components</i> , and most spinal fixation implants; vertebral body replacements, and some bone void fillers and graft extenders
III Unreasonable and significant risk: Controlled by all of above and clinical data review for safety and effectiveness	Rare: 510k with clinical studies Most: PMA- Premarket Approval after clinical trial under IDE or Outside USA study	Common : <ul style="list-style-type: none"> • Post Approval Clinical Studies • Registries 	Cervical pedicle screws; metal-on-metal total hip replacement systems clinical data Alternative bearing total hip replacement systems; total hip resurfacing systems; mobile bearing total knees and total ankles. Cartilage repair devices Total joint replacement systems for the spine: Total disc replacements, disc nucleus replacements, etc. Combination devices with biologics, drugs, or manipulated cells or proteins

tions specific to the device, are required. Special controls may include postmarket surveillance, patient registries, clinical data, labeling requirements, guidance documents, and accepted testing standards such as those described by the American Society for Testing and Materials (ASTM) or the International Organization of Standards (ISO). Most implanted orthopedic devices are class II, including intramedullary nails, plates and screws, most joint replacement components, and most spinal fixation implants, vertebral body replacements, and some bone void fillers and graft extenders.

If a device can be traced to similar devices in use before 1976, it is usually a class I or II device. Devices in use before 1976 and other legally marketed devices that have already been cleared for marketing as substantially equivalent to a device are called **predicates**.

An example of a predicate device might be a Charnley hip stem or a hip stem that is already cleared for marketing but to which a manufacturer wants to make a minor modification.

If the premarket notification for a class II device provides data characterizing the device that compare it with a predicate and shows that it has the same intended use and the same technological characteristics—or if the class II device has different technological characteristics but those characteristics are shown by evidence in the application to be as safe and effective as the predicates' characteristics—the device can be deemed substantially equivalent

and thus “cleared” for legal marketing. Devices not available before the 1976 Medical Device Amendments but with established safety and effectiveness may also fall into this class.

Thus, because of the incremental nature of device development, the majority of device applications cleared under the 510(k) require an intermediate level of regulatory evaluation with comparisons with existing devices using bench-top testing standards, and they do not generally require clinical studies. These preclinical testing methods may include product manufacturing; in vitro and in vivo testing (toxicity/genotoxicity, biomaterial biocompatibility, immunogenicity/inflammatory responses, and models of product effectiveness); and product intended-use labeling review. In some rare cases, such as for cervical pedicle screw systems, or in cases in which specific indications/populations are different from those of the legally marketed predicate devices, FDA requests clinical data to support equivalence.

The rest of medical devices are in class III. Most class III devices require Premarket Approval (PMA). Data in a PMA application must demonstrate a “reasonable assurance” of safety and effectiveness. Device types in this class were not marketed prior to the Medical Device Amendments (1976) or they are devices for which the initial classification panel determined that special controls could not be established. A product will be classified as class III if “general controls” are not adequate to provide reasonable assurance of safety and effectiveness and

FACTS VERSUS MYTHS

Myth 1: FDA tests medical devices using preclinical and clinical testing methods.

Fact: Contrary to popular belief, FDA does not design or test new medical products--manufacturers do. FDA evaluates the data about their products that are provided in the various premarket applications manufacturers submit to FDA. In most cases, FDA does not inspect testing facilities or verify reports or results for class I or class II devices.

Myth 2: FDA controls and regulates medical procedures and thus the practice of medicine.

Fact: In fact, FDA does not regulate medical procedures. FDA regulates the products, but not how the medical community chooses to use them. FDA does not regulate the practice of medicine. Professional societies, hospitals, and medical boards supervise and determine appropriate medical practice.

Myth 3: FDA reviews and clears advertising and promotional materials that manufacturers use.

Fact: FDA does not review and clear promotional materials for device marketing. However, it does assure that labeling and instructions for use are accurate, are without unsubstantiated promotional claims, and allow safe use of the device. FDA does have an enforcement arm, the Office of Compliance, that deals with anyone who violates the regulations under the law.

Myth 4: All device approvals require randomized concurrently controlled multicenter clinical trials.

Fact: Although approval of a device may require clinical data, it may not necessarily require a randomized concurrently controlled clinical trial. Depending on the type of device, the indications for device use, the known or

unknown risks to health, and the devices like it already on the market, a device approval may or may not require clinical data.

Myth 5: All devices that FDA approves can then be approved for reimbursement by state and federal insurance companies and vice-versa.

Fact: Insurance reimbursement determinations for procedures and new devices are not within the purview of the FDA. Medicare and Medicaid are regulated by a number of other agencies, including the Center for Medicare and Medicaid Services (CMS), the federal agency responsible for administering the Medicare, Medicaid, SCHIP (State Children's Health Insurance), HIPAA (Health Insurance Portability and Accountability Act), CLIA (Clinical Laboratory Improvement Amendments), and several other health-related programs.⁵ FDA approval does not automatically guarantee that a procedure using a new device will be approved for reimbursement by CMS.

Myth 6: A device that is in use in Europe or in other countries outside the United States can automatically be used in the United States.

Fact: Although the FDA does accept foreign data⁶ in support of a marketing application, a sponsor does have to actually submit a marketing application. If required to have a clinical study, the sponsor does have to comply with regulations as stated in the Code of Federal Regulations for conduct of clinical studies (21CFR 812) and meet the definition of valid scientific evidence (21CFR 860.7). In no cases can an orthopedic implant be cleared (generally class II) or approved (generally class III) without submission of a marketing application to the FDA.

there is not sufficient information to establish "special controls," as described previously, that would provide such assurance.

Class III devices tend to pose higher risk and/or raise new types of safety and effectiveness questions that must be answered prior to approval for marketing.

Class III devices usually support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to the patient or they may be transitional devices (devices that were regulated as drugs prior to 1976.) These devices typically require the highest level of scrutiny and a complete preclinical and clinical review through PMAs, with most requiring clinical studies.

Although the majority of PMA applications contain clinical data, study designs are not prescribed by any regulations.⁷ Clinical studies are conducted under the Investigational Device Exemptions (IDE) regulations, which allows for patient access to new devices for the purpose of research for the collection of safety and effectiveness information after a proof of concept and relative safety is established by preclinical studies. IDE protocols for significant-risk devices are reviewed by FDA to assure that patient safety is maintained throughout the period of research.

However, a hierarchy of "valid scientific evidence," much like the "levels of evidence"⁸ described for classification of journal review of clinical trials, is described in the regulations (21CFR860.7). Valid scientific evidence is required to establish the safety and effectiveness of the device for its intended use in the intended population. As described in the regulation, valid scientific evidence may range from

well-controlled investigations, partially controlled studies, and studies and objective trials without matched controls to well-documented case histories conducted by qualified experts and, in some cases, reports of significant human experience with a marketed device.

Orthopedic devices that require approval through the PMA pathway include total disc replacements, disc nucleus replacements, mobile bearing total knee and ankle replacements, and total ceramic-on-ceramic and total resurfacing hip replacement systems.

Labeling: On-Label Versus Off-Label Use

One of the ways that FDA assures the safe (and effective) use of the device is by proper labeling of the device. By regulation (21CFR PARTS 801, 809, 812, 814 AND 820), FDA assures that all labeling elements are clear and present according to this regulation. It also requires that patient labeling be clear and understandable for all patients. This includes appropriate warnings and precautions, indications, and contraindications.

The term labeling is defined as including all printed matter accompanying any product or device.

Legal use of the device as labeled for the indications and intended use for the populations described by the indications is termed "use as labeled or on-label use." All devices that are cleared or approved have specific labeling terminology that defines safe and effective use of the device. Off-label use is, according to FDA, use of a medical device outside of the approved indications and instructions for use on the product label.

Off-Label Use

FDA recognizes that off-label use of drugs and devices by physicians is often appropriate and may represent the standard of practice. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and educated, good medical judgment.

It is the responsibility of a physician using a product for an indication not in the approved labeling to be well informed about the product, to base its use on a firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product by a physician, without promotion by manufacturer, in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE), or review by an Institutional Review Board (IRB) (FDAMA § 906 (21 USC § 396))² These applications for research of an investigational product are needed when the data collected in these investigations would support the marketing or claims made on the labeling of the device (IDE), drug, or biologic (IND or orphan product [IRB]). Certain types of clinical studies do not require an FDA-approved IDE, including

those consistent with the practice of medicine, that involve basic physiological research or are investigating a physiological principle, are not intent on developing data on the device for supporting a marketing application, or are studying a cleared/approved device within the indications noted in the device's label to address the research question.⁹

On the other hand, the law prohibits medical device manufacturers from proactively discussing or promoting off-label uses or from distributing written materials that mention off-label uses. FDA does not restrict other parties from discussing off-label uses or distributing written materials concerning them. Physicians have the same responsibility that companies have when it comes to promoting off-label use of a device. Section 906 of the Federal Food Drug and Cosmetic Act [21 U.S.C. 396, PRACTICE OF MEDICINE]² draws a distinction between promotion and practice of medicine.

While FDA does not regulate how physicians use devices or the general practice of medicine, the agency does have several concerns about off-label use.

The most important concern that the FDA has about these off-label uses is that they are not subject to a rigorous premarket review process to identify adverse events, and therefore the safety of the device for human use is not known. For example, some cement restrictor devices, cleared for use to prevent cement migration in the femoral canal during total hip replacement, are being used off-label as fusion cages in the spine. In these cases, neither mechanical testing to address even the most basic mechanical strength requirement for the off-label use (intervertebral body fusion of the spine and/or maintaining disc height) nor potential adverse events have been assessed.

In addition to the safety concerns, off-label uses may diminish or eliminate the incentive to study or seek FDA approval for new indications. Moreover, the lack of clinical studies may impede reimbursements and payments by insurance companies, because evidence is lacking to demonstrate that the off-label use is reasonable and necessary for the Center for Medicare and Medicaid Services (CMS) coverage determinations.

WHAT PART DO ORTHOPEDIC SURGEONS AND PROFESSIONAL SOCIETIES PLAY?

In clinical practice, professional societies and their members can ensure safe use of medical devices by providing and participating in adequate training for new technologies prior to widespread use, understand the need for high-quality clinical trials, understand the regulatory process, and commit to and participate in postmarket surveillance studies.

Orthopedic surgeons are already involved with promoting the mission of the FDA in several ways. Practicing orthopedic surgeons, in various areas of expertise, serve on or consult for the Orthopaedic and Rehabilitation Devices Advisory Panel, which advises the FDA on the approval of

new devices, reclassification of devices, appropriate testing methods, and other issues related to the approval process. The American Academy of Orthopaedic Surgeons exhibits committee works with FDA at the annual meeting to ensure appropriate disclaimers for scientific presentations and vendor product displays. Finally, the FDA has orthopedic surgeons on staff; their functions include aiding in product and clinical study design reviews and in the development of guidance documents and education of review staff.

Adverse-Event/MDR Reporting

Part of the process of medical device use for the treatment of musculoskeletal disease should include a commitment to detailed, timely adverse event/MDR reporting, both to the manufacturer and to FDA. This is important because initial preclinical and clinical testing that helps to establish the safety of medical devices is typically conducted with small samples of the target population before FDA approves the products for sale. In some cases, problems can remain unknown in smaller trials, only to be discovered when a product is used by a large number of physicians and its use extends to populations not studied in the clinical trials.

When problems with FDA-regulated products occur, the agency wants to know about them and has several ways for the public to make reports. The agency evaluates each report to determine how serious the problem is before taking action.¹⁰

FDA MDR regulations have required firms who have received complaints of device malfunctions, serious injuries, or deaths associated with medical devices to notify FDA of the incidents. Additional postmarketing activities, such as Postmarket Surveillance monitoring after device clearance, postapproval studies as part of PMA approval, and Device Tracking for ensuring that certain devices can be traced to the user/patient, provide additional information about devices in general use. The MDR regulation provides a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner. Although the requirements of the regulation can be enforced through the Federal Food Drug & Cosmetic (FFD&C) Act,^{2,11} FDA relies on the goodwill and cooperation of all affected groups to accomplish the objectives of the regulation.¹²

RESOURCES

For more information on how you can get involved, please refer to the following links:

- Advisory Panels: <http://www.fda.gov/oc/advisory/academicianpractitioner.html>
 - Contact Dr. Ronald Jean at Ronald.jean@fda.hhs.gov
- Full-time or part-time employment with FDA:
 - Medical Device Fellowship program: <http://www.fda.gov/cdrh/mdfp/about.html>
 - Orthopaedic Devices Branch, contact: Pauline.fogarty@fda.hhs.gov

Hospitals and surgery centers are required to report suspected medical device-related deaths to both the FDA and the manufacturers. Reporting requirements and instructions may be found on the FDA website.^{10,13}

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