

Chapter 3

FDA Regulation of Medical Devices*

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§ 3:1 Introduction**Research References**

West's Key Number Digest, Patents ⇨220

The United States Food & Drug Administration (FDA) has extensive premarket and postmarket regulatory jurisdiction over medical devices that are entered into interstate commerce, and their manufacturers.¹ FDA's authority to regulate medical devices arises out of the Federal Food, Drug, and Cosmetic Act (FDCA).² As originally written, the FDCA only had very limited provisions addressing the regulation of medical devices. By the mid-1970s, it had become clear to Congress that, due to a combination of significant and rapid scientific advances and the occasional marketing of some unsafe, ineffective, and even fraudulent devices, an increase in FDA regulatory authority over medical devices was needed.

Congress's first and most comprehensive legislative effort was the 1976 Medical Device Amendments, enacted on May 28, 1976,³ which vastly expanded FDA's statutory authority by creating a comprehensive regulatory scheme for devices. Congress has subsequently promulgated multiple laws that have revised and expanded FDA's regulatory authority over medical devices.⁴

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¹The Center for Devices and Radiological Health (CDRH) also has regulatory jurisdiction over both medical and non-medical radiation emitting devices, including lasers, x-ray machines, microwave ovens, and televisions. CDRH regulates these products to avoid unnecessary exposure to the public to radiation. CDRH's jurisdiction over radiation-emitting products is beyond the scope of this chapter.

²21 U.S.C.A. §§ 301 passim.

³Medical Devices Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified at 15 U.S.C.A. § 55 (1994) and 21 U.S.C.A. passim (1994)).

⁴The Medical Device Amendments of 1976 have been subsequently amended by the: Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511 (1990) (codified at 21 U.S.C.A. § 301 passim and 42 U.S.C.A. §§ 263b-n (1994)); Medical Device Amendments of 1992, Pub. L. No. 102-300, 106 Stat. 238 (1992) (codified at 21 U.S.C.A. §§ 301 passim and 42 U.S.C.A. § 26); Food and Drug Administration Modernization Act of 1997, Pub. L. No 105-115, 111 Stat. 2296 (1997) (codified at 21 U.S.C.A. §§ 301

§ 3:2 Medical device definition**Research References**

West's Key Number Digest, Patents ¶220

FDA's definition of a medical device covers a wide variety of products. The Federal Food, Drug, and Cosmetic Act (FDCA)¹ defines the term "device" as:

an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is: 1) recognized in the official *National Formulary*, or the *United States Pharmacopoeia*, or any supplement to them, 2) 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 3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve 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 its primary intended purposes."²

Manufacturers are sometimes uncertain if their product will be regulated as a device or a drug because the product may incorporate aspects of both. To determine if a particular product is a "drug" or "device," FDA first considers the product's primary mode of action. If the product's primary mode of action is mechanical, FDA generally considers it to be a device, under the primary regulatory jurisdiction of the Center for Devices and Radiological Health (CDRH).³ If the primary intended use of the product is achieved through chemical action, or by being metabolized, the product is usually regulated either as a drug by the Center for Drug Evaluation and Research (CDER) or a biologic by the Center for Biologics Evaluation and Research (CBER). According to FDA, however, the fact that a product is not metabolized

passim and 42 U.S.C.A. passim); the Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 107-250, 116 Stat. 1588 (2002); and the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

[Section 3:2]

¹21 U.S.C.A. §§ 301 passim

²21 U.S.C.A. § 321(h).

³21 U.S.C.A. § 321(g),(h).

and does not achieve its principal purpose by chemical action does not automatically make it a device. For example, products such as laxatives that work by mechanical action still may be considered drugs because they are “drug-like” substances.

§ 3:3 Medical device definition—Combination products

Research References

West's Key Number Digest, Patents ¶220

Health-care products that include aspects of both a drug and a device are referred to as combination products. One example of a combination product is a drug-eluting coronary stent. The FDA center with primary regulatory jurisdiction over combination products is generally determined by whether the primary purpose of these products is performed by the drug or by the device portion of the combination product. Additionally, the greater the concern about the risks presented by the “drug-type” element of the combination product, the more likely it is that the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) will take lead responsibility in regulating the product.

To help manufacturers of combination products determine which FDA center has primary regulatory authority, FDA regulations¹ provide manufacturers a mechanism for obtaining an official agency determination on primary regulatory jurisdiction. Manufacturers can prepare a request for designation (RFD) for submission to FDA's Office of Combination Products.² In the RFD, the manufacturer can make an argument as to how the combination product should be regulated and, thus, which center should have primary regulatory jurisdiction.

[Section 3:3]

¹21 C.F.R. Part 3.

²OCP was created in 2002 as a result of the Medical Device User Fee and Modernization Act. Its main duties include assigning combination product reviews to a center and coordinating timely premarket reviews involving more than one center. It also must ensure the consistency and appropriateness of combination-product postmarket regulation.

§ 3:4 Medical device classification**Research References**

West's Key Number Digest, Patents ⇨220

FDA has assigned roughly 1,700 different generic types of devices to one of three classifications (class I, II, or III) based upon the level of control FDA feels is necessary to protect the public health.¹ Regardless of the classification, all devices are subject to *at least* compliance with general controls, which include: the adulteration and misbranding provisions of the Food, Drug, and Cosmetic Act (FDCA);² establishment registration and device listing; notification and repair; replacement or refund; records and reports; banned devices and Good Manufacturing Practices (unless exempt) as codified by CDRH as the Quality Systems Regulation (QSR).³

The three classes and the requirements which apply to them are:

Class I. Class I devices are those devices that FDA considers to pose the least risk to the public health. Most, but not all, class I products are exempt from the premarket notification requirements of Section 510(k).⁴ As noted above, class I devices are still subject to general controls. Examples of class I devices include surgical scalpels, tongue depressors, and examination gloves. Thus, most class I devices can be marketed in the U.S. without having to go through FDA's premarket clearance process.

Class II. Class II devices are those devices for which general controls alone are not sufficient to ensure safety and effectiveness. Most, but not all, class II devices require FDA clearance of a Section 510(k) premarket notification prior to marketing. Some class II devices are additionally subject to special controls, which can include special labeling requirements, mandatory performance standards, and postmarket surveillance. Examples of class II devices

[Section 3:4]

¹Center for Devices and Radiological Health, U.S. Food and Drug Administration, Device Advice, at <http://www.fda.gov/cdrh/devadvice/313.html>, last updated August 4, 2004 (hereinafter "Device Advice").

²21 U.S.C.A. §§ 301 passim.

³See section 3:17 *infra*.

⁴See section 3:17 *infra*.

include AC-powered patient beds, dental implants, and biliary stents. Endosseous dental implants and *in vitro* fertilization products are examples of class II devices subject to special controls.

Class III. Class III devices are those devices for which general and special controls alone are not sufficient to establish safety and efficacy. In general, these devices: (1) are used in supporting or sustaining human life; or (2) are for a use which is of substantial importance in preventing impairment of human health; or (3) present a potential unreasonable risk of illness or injury. Most class III devices require approval of an extensive marketing application called a Premarket Approval Application (PMA) before being marketed in the United States. Examples of class III devices include such devices as coronary artery stents, replacement heart valves, and silicone gel-filled breast implants. There are some exceptions to this rule which will not be discussed in this brief chapter.

Manufacturers wishing to determine a device's potential classification should first turn to the medical device portions (Chapter 21) of the Code of Federal Regulations (CFR).⁵ As mentioned above, FDA has classified over 1700 types of devices, with each device type codified and described in the CFR. Other methods that may help a manufacturer in determining the classification of its device are: to request a meeting with appropriate agency officials; to submit a Request for Designation (RFD) to FDA;⁶ informally contact staff at the Center for Devices and Radiologic Health's (CDRH's) Office of Device Evaluation (ODE) to ask for their non-binding opinion; conduct a search of FDA's databases for clearances or approvals for similar devices; examine the trade press for clearances or approvals of similar devices; or conduct a search of the informal guidance documents posted on CDRH's Web site. In some cases, companies may even file a 510(k) notification to learn whether FDA agrees with the company's classification determination. There are also a number of device-specific guidance documents that FDA

⁵21 C.F.R. § 807.81 et seq.

⁶See section 3:3, *supra*.

posts on its Web sites which can be helpful in determining a device's class.⁷

Importantly, the "intended use"⁸ of a device can be a significant factor in determining the device's classification. For example, lasers that are used for most dermatological and urological procedures are regulated as class II devices. However, lasers intended for LASIK, viewed by FDA as posing a higher risk to patients than lasers used for dermatology or urology, are regulated as class III devices.

§ 3:5 Medical device classification—Reclassification

Research References

West's Key Number Digest, Patents ⇨220

As experience and knowledge about a device increase, FDA can revise the original classification of a device via the reclassification process. FDA may, on its own or in response to a third-party petition, change a device's classification by regulation. A manufacturer who wishes to have a device reclassified to a lower class must convince FDA that the less stringent class requirements will be sufficient to provide sufficient reasonable assurance of safety and effectiveness.

If a determination is made to reclassify a device, FDA publishes a proposed rule to reclassify in the Federal Register, which includes the scientific justification for reclassification and includes a period for public review and comment. Subsequently, a final rule is published in the Federal Register and the device type is reclassified, if FDA does not change its position based on the public comments. This is a very long and arduous process.

§ 3:6 Premarket requirements

Research References

West's Key Number Digest, Patents ⇨220

⁷The Center for Devices and Radiological Health's Web site is available at <http://www.fda.gov/CDRH/>.

⁸21 C.F.R. §§ 801.4, 807.92. The intended use of a device refers to a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended." according to "the objective intent of the persons legally responsible for the labeling of devices."

Depending upon the device classification, FDA may require premarket clearance or approval prior to commercial marketing of the device in the United States. There are two primary types of premarket applications: premarket notifications under Section 510(k)¹ (510(k)); and PMA (Premarket Approval) applications. Broadly, under Section 510(k) of the FDCA,² manufacturers wishing to market certain class I, and most class II, devices require clearance of a 510(k). Manufacturers wishing to market most class III devices will require FDA approval of a PMA. As indicated above, FDA has exempted most class I devices and some class II devices from the 510(k) requirement, and a few class III devices from the PMA requirements.

The following chart summarizes some of the differences between the 510(k) and PMA requirements.

	<i>510(k) Premarket Notification</i>	<i>Premarket Approval (PMA)</i>
<i>Devices Subject to Requirement</i>	Some class I, and most class II devices.	Most class III devices.
<i>Clinical Data Requirements</i>	Most are not supported by clinical data; “Hybrid” 510(k) notifications include clinical data.	Clinical studies usually required to support submission.
<i>Evidence of Safety and Efficacy Required</i>	Information and data to support the “substantial equivalence” of the device to one or more legally marketed predicate devices.	Clinical data and/or scientific evidence demonstrating that the device is reasonably safe and effective for its intended use(s).

[Section 3:6]

¹21 U.S.C.A. § 360(k).

²21 U.S.C.A. §§ 301 passim.

	<i>510(k) Premarket Notification</i>	<i>Premarket Approval (PMA)</i>
<i>Marketing Rights</i>	No exclusivity. Competitors can cite to another manufacturer's cleared devices in their own 510(k) notices.	Like a Product License. Competitors cannot cite to another manufacturer's approved PMA to show safety and effectiveness.
<i>Average FDA Review Time From Receipt to Final Decision</i>	54 days (FY 06).	284 days (FY 06).
<i>Regulations on Device Changes</i>	Must file new 510(k) if the change "could significantly affect" the safety or efficacy of the device; or represents a major change to the intended use of the device.	Must file a new PMA, some form of PMA supplement, or annual report depending on the nature and effect of the change on the safety and effectiveness of the device.
<i>Advisory Panel Review</i>	No Advisory Panel ¹ Review for almost all 510(k) devices.	Advisory Panel Review for some but not all PMAs. Generally, no Advisory Panel Review for PMA Supplements.

¹ An Advisory Panel is a panel of outside experts that CDRH will convene to provide advice with respect to the device in question. 21 U.S.C. § 355(n).

§ 3:7 Premarket notification

Research References

West's Key Number Digest, Patents ⇨220

Section 510(k) of the the Federal Food, Drug, and Cosmetic Act (FDCA)¹ requires the filing of a 510(k) premarket notification by a manufacturer prior to: 1) initial marketing of a device; 2) making a change or modification to a cleared device that “could significantly affect the safety or effectiveness”² of the device; or 3) making a major change or modification to the intended use of a cleared device.³ FDA requires manufacturers to submit to FDA a 510(k) at least 90 days prior to the intended introduction of the device into the U.S. marketplace. However, a manufacturer who submits a 510(k) may not market its device in the U.S. until FDA grants clearance for the 510(k) through a formal letter or call an “order.”

Unlike in the patent process, where the applicant attempts to prove to the USPTO that their invention is novel, the goal of the 510(k) process is to demonstrate to FDA “substantial equivalence” to one or more legally marketed class I or class II devices, or class III devices for which a PMA (Premarket Approval) is not required. These devices which are called the “predicate device(s).” Establishing substantial equivalence requires the applicant to demonstrate that: (1) the new device has the same intended use as the predicate device; and (2) either (a) the same technological characteristics as the predicate device, or (b) different technological characteristics, but the change in technology does not raise any *new* questions of safety and effectiveness. FDA has developed a decision tree that facilitates making a substantial equivalence determination.⁴

Applicants can claim substantial equivalence to multiple predicate devices in the 510(k) submission, as certain features of the new device may be captured in one predicate, and other features may be captured in other predicate(s). For example, a company may use the intended use of one predicate and the technological features of another predicate to build its substantial equivalence argument.

Although 510(k) submissions will vary somewhat in format

[Section 3:7]

¹21 U.S.C.A. §§ 301 passim.

²21 C.F.R. § 807.81(a)(3)(i).

³21 C.F.R. § 807.81.

⁴Office of Device Evaluation, Guidance on the CDRH Premarket Notification Review Program (K86-3) (June 30, 1986).

depending upon the types of data that accompanies the submission, which can include preclinical data, software data, and clinical data, certain basic elements are found in all 510(k) applications as required by the Code of Federal Regulations.⁵ The required elements are:

Device Name. The device's name, including both the trade or proprietary name and the classification name, must be included in a 510(k) premarket notification.

Identification. The applicant's name and street address must be included in the 510(k) premarket notification.

Registration Number. If applicable, the FDA establishment registration number of the owner or operator submitting the premarket notification should be included.

Classification. The applicant should include the class of the device, (i.e., class I, II, or III).

Description. The 510(k) notification should include a physical description of the new device, together with an explanation of its intended use, principles of operation, power source, composition, and other information necessary to understand the device.

Substantial Equivalence Comparison. Applicants should attempt to make a comparison of the new device to its predicate as easy as possible for the FDA reviewer. The 510(k) notification should, therefore, include a discussion of the similarities and differences between the device and its predicate device(s), and should make use of comparative tables whenever possible. Differences should be explained, not ignored.

Software. Applications for devices that contain software must submit software data in accordance with the appropriate guidance document from the Center for Devices and Radiologic Health (CDRH).

Standards. The applicant should identify any standards met by the device, such as standards for electrical safety and electromagnetic interference.

Performance. Performance data are often needed to help demonstrate that the proposed device is as safe and effective as the predicate device. This often includes bench and/or animal testing.

Biocompatibility. Any material differences between

⁵21 C.F.R. §§ 807.87, 807.90, 807.92, and 807.93.

the device to be reviewed and the predicate device must be stated explicitly. Even if the materials are identical, the nature and duration of the contact of the materials must be the same, and the material must be processed in the same way, in order to rely on predicate biocompatibility information. If the predicate device biocompatibility data cannot be leveraged, the applicant will need to conduct testing based on the duration and nature of the device's contact with the human body.

Sterility. Submissions for devices that are labeled sterile must cite their sterilization method, the method used to validate the sterilization cycle, and the device's Sterility Assurance Level (SAL).

Labeling. Although applicants may submit drafts of their device labeling, the submission should be representative of the final version.

Class III Certification and Summary. As discussed above, a few class III devices are still subject to the 510(k) process. All 510(k) submissions for these devices must have a special added certification statement by which the applicant certifies that it has searched for all available information relative to that device's safety and effectiveness, and the 510(k) notification must include citations to any adverse safety and effectiveness data.

510(k) Summary or Statement. A premarket notification must include either a summary of the 510(k) safety and effectiveness information upon which the substantial equivalence determination is based, or a statement that the 510(k) applicant will make this information available to any person within 30 days of a written request. Most applicants choose to submit a 510(k) summary to avoid having to indefinitely fulfill such third-party requests post-clearance.

Truthful and Accuracy Statement. All 510(k) applicants must include a statement certifying that all information in the application is truthful and accurate and that no material fact has been omitted.

Premarket notification submissions that include clinical information in order to demonstrate substantial equivalence

are often referred to as “hybrid 510(k)s.”⁶ In 510(k)s that include clinical data, FDA requires the study sponsors to either disclose certain financial interests of the clinical investigators or certify that the clinical investigators do not hold any disclosable financial interests. Moreover, any 510(k) containing clinical data must be accompanied by a certification that the applicant has complied with the clinical trial registration requirements.

Finally, FDA also requires submitters of a 510(k) notice to pay a user fee to the agency. Congress authorized CDRH to collect the user fees to help defray the cost of the review of 510(k)s and to help the agency meet certain performance goals for making substantial equivalence determinations.

Although FDA’s response to applications under section 510(k) establishes, for all practical purposes, whether a particular device can be marketed without a PMA, FDA does not “approve” a premarket notification in the same way that it approves a PMA. FDA’s response to section 510(k) notifications, known as a “clearance,” makes clear that its findings extend only to whether a device is substantially equivalent to a predicate device and not whether it is safe and effective for its intended use(s). A company is prohibited from using the 510(k) clearance as an endorsement of the product by the agency.⁷

If CDRH finds the device not substantially equivalent (NSE), and thus a class III device, the manufacturer is left with four options. The manufacturer can: request reclassification as discussed above (a lengthy regulatory process); submit a PMA; resubmit the 510(k) after redefining the indications for use statement, or making changes to the device that address the issues that led FDA to determine that the original device was NSE; or request a de novo review.

§ 3:8 Premarket notification—De novo downclassification

Research References

West’s Key Number Digest, Patents ☞220

⁶If information concerning similarity to a predicate device must be obtained through a clinical trial, the trial is subject to the requirement of the IDE regulation, 21 C.F.R. § 812.2.

⁷21 C.F.R. § 807.97.

Under is become known as the de novo downclassification process, if a device manufacturer receives written notification from FDA that its device is not substantially equivalent to a legally marketed predicate and, therefore, is designated as a class III device, the manufacturer may, within 30 days of receiving that notification, submit a “de novo” request arguing that the device should be placed in class I or II based on its low level of risk.¹ In order to fulfill the requirements of Section 513(f)(2), the manufacturer has to prove two main elements: (1) that the device is novel; and (2) the device is low-risk. In essence, the manufacturer has to show that but-for the lack of a suitable predicate, the device would have been found substantially equivalent to a class I or II device. If FDA reclassifies the device as either class I or class II, then the device may be marketed and may serve as a predicate for future 510(k) submissions for devices in that device type.

§ 3:9 Premarket notification—Modifications to existing cleared devices

Research References

West’s Key Number Digest, Patents ☞220

One of the more challenging decisions for a holder of a FDA cleared premarket notification (510(k)) is when to submit a new 510(k) for a change the 510(k) holder intends to make to the legally marketed device. FDA’s regulations require that a new 510(k) notification be cleared by FDA before the 510(k) holder makes any change or modification to the device that “could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process”; or makes a major

[Section 3:8]

¹21 U.S.C.A. § 360c(f). Congress included this section to limit unnecessary expenditure of CDRH and manufacturer resources that could occur if low risk devices were subject to premarket approval (PMA) under section 515. The section was not intended to significantly increase the number of not substantially equivalent determinations or to otherwise alter the 510(k) provisions of the Act or CDRH’s approach to the 510(k) classification process.

change or modification in the intended use of the device.¹ Typically, 510(k) sponsors place emphasis on the word “significantly” and try to argue that the proposed modification could not significantly affect the device’s safety or effectiveness, whereas FDA typically places emphasis on the word “could.”

Although the 510(k) holder is responsible for making the initial determination if a change or modification could significantly affect safety or effectiveness, FDA always retains the right to evaluate the company’s decision. If FDA disagrees with the company’s decision not to file a new 510(k) notification for a device modification or change, the agency may make the company file a retrospective 510(k), and discontinue marketing the device during the pendency of the 510(k)’s review. The agency may also take enforcement action against the company. As a practical matter, however, if the company has made a good faith effort to document the reasons that it did not submit a new 510(k) for the device change, if the reasons appear genuine, and there are no demonstrated safety problems with the modified device, FDA may allow the company to continue marketing the device while the new 510(k) notification is pending.

§ 3:10 Premarket approval applications

Research References

West’s Key Number Digest, Patents ¶220

The Premarket Approval (PMA) process is the most stringent premarket process. Unlike the 510(k) process, which only requires a demonstration of substantial equivalence, the PMA process requires that the applicant demonstrate that its product is reasonably safe and effective for its intended use(s). In order to meet that standard, a company must often conduct clinical trials requiring a significant expenditure of both time and money. As an alternative to the full PMA process, certain class III devices may be approved

[Section 3:9]

¹21 C.F.R. § 807.81(a)(3)(i).

through a product development protocol (PDP).¹ The PDP combines the clinical evaluation of a device with the marketing approval. In practice, the PDP is rarely used, and will not be addressed further in this chapter.²

A PMA is required for three types of class III products, categorized based upon their status at the time of the passage of the 1976 Medical Device Amendments. Class III preamendment devices which were devices commercially distributed before passage of the 1976 Act, only require a PMA if explicitly called for by FDA through a published regulation. FDA has been quite slow in calling for these submissions. Class III transitional devices, those devices that were regulated as drugs before 1976 but are now regulated as devices, require a PMA. Likewise, all class III devices that were first made commercially available after 1976 must obtain a PMA.

A PMA submission must contain the information required under 21 C.F.R. § 814.20. This material includes the information described below:

The applicant's name and address;

A table of contents for the submission;

A description of the device and its functional components;

A description of the principles of the device's operation;

A description of the methods used to manufacture the device—methods should be described in sufficient detail that a person familiar with good manufacturing practices can understand the processes involved in manufacture of the device;

References to all performance standards with which the device complies—this includes any testing standards. The company should explain any deviations from the standards;

A comprehensive review of all preclinical studies, including those related to performance, sterility and biocompatibility—the company should describe both the *in vitro* and *in vivo* experiments;

[Section 3:10]

¹21 U.S.C.A. § 360e(f).

²For more information on the PDP, please see the Food & Drug Law Institute's David G. Adams, et al., *Food and Drug Law Regulation* 511 (2d., 2008).

A comprehensive review of all clinical studies, including information on clinical site selection and subject recruitment, data accrual processes and methods, device failures, safety and efficacy data, comprehensive patient records, records of investigator compliance with financial disclosure and informed consent, and documentation of institutional review board approval for the study;

A bibliography of all reports related to the products including any data that may affect the agency's evaluation of the safety and efficacy of the device whether derived from company sponsored or independent studies, and copies of any published or unpublished information in the sponsor's possession;

An environmental impact assessment of the device, if applicable;

A financial certification or disclosure statement;

A copy of any proposed product labeling;

A summary of the device characteristics, indications for use, marketing history, studies completed to investigate the product and conclusions from these studies; and

Any additional information that FDA may request.

§ 3:11 FDA review of premarket approval applications

Research References

West's Key Number Digest, Patents ¶220

The Premarket Approval (PMA) application review process is a lengthy and exhaustive one, including a comprehensive review of not only the preclinical and clinical data submitted, but often an inspection of the clinical sites and the facilities where the device is designed and manufactured. Multiple offices and personnel of the Center for Devices and Radiological Health (CDRH) are engaged in the review of a PMA, including scientists, clinicians, biocompatibility specialists, and software specialists, in addition to the staff at the Office of Compliance (OC). Review of the PMA may also involve the use of Advisory Panels to assist FDA with assessment of the product.

Given the extensive data requirements for a PMA, the review process often extends beyond the statutory review period of 180 days nominally required for FDA to review an original PMA. The review process often requires multiple

requests for additional information by both the Office of Device Evaluation (ODE) and OC before final approval, if approval is obtained at all.

§ 3:12 FDA review of premarket approval applications—Premarket approval supplements

Research References

West's Key Number Digest, Patents ⇌220

If a company wishes to modify a device that is subject of an approved Premarket Approval (PMA) in a way that affects the safety and efficacy of the device, the company must submit a PMA supplement. The scope of material required to support this supplement is limited to the data needed to demonstrate that the modified device is safe and effective for its indicated use(s). The type and scope of the proposed change to the design, manufacturing process, or labeling dictates the form the supplement must take.

FDA regulations state that a PMA Supplement is required for the following changes that affect the safety or efficacy of a PMA-approved device: (1) new indications for use of the device; (2) labeling changes; (3) the use of a different facility or establishment to manufacture, process, or package the device; (4) changes in sterilization procedures; (5) changes in packaging; (6) changes in the performance or design specifications of the device; (7) extension of the device's expiration date (if the device has an expiration date).¹ Some changes are deemed automatically to affect the safety and effectiveness of the device, such as changes in the manufacturing location.

Any change which does not require a PMA supplement should be submitted in the device's PMA Annual Report.²

[Section 3:12]

¹21 C.F.R. § 814.39(a).

²21 C.F.R. § 814(e).

§ 3:13 FDA review of premarket approval applications—Investigational device exemptions**Research References**

West's Key Number Digest, Patents ⇌220

An Investigational Device Exemption (IDE) allows manufacturers to ship an unapproved device in interstate commerce for the purposes of conducting clinical research in support of a premarket notification (510(k)) or Premarket Approval (PMA) submission. Without such an exemption, shipment of an unapproved device in interstate commerce violates the Federal Food, Drug, and Cosmetic Act (FDCA).¹

The IDE regulations² apply to most clinical investigations involving new products or new uses for existing products. Device studies are separated into two categories: significant risk and nonsignificant risk studies. A significant risk (SR) device study is a study of an investigational device that: is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or otherwise presents a potential for serious risk to the health, safety or welfare of a subject.

Conversely, a nonsignificant risk (NSR) device study is one that does not pose a significant risk to patients. Significant risk studies must meet all of the regulatory requirements set forth in 21 C.F.R. Part 812, including the requirements that the sponsor obtain FDA approval of the IDE, as well as approval of the investigational plan and informed consent form from each participating Institutional Review Board (IRB) before commencing the study. In the case of a NSR study, the sponsor may begin the study without obtain-

[Section 3:13]¹21 U.S.C.A. §§ 301 passim.²21 C.F.R. Part 812.

ing FDA approval of the study provided that each reviewing IRB approves the study and agrees it is a NSR study. Informed consent must be obtained from each subject regardless of whether it is a significant or nonsignificant risk study.

As stated above, a sponsor of a proposed human clinical investigation that meets the definition of a significant risk study must submit an IDE application to FDA. Such application must include the following information:

Name and address of sponsor;

Report of prior investigations, including biocompatibility, in vitro, and in vivo testing, as well as published and unpublished adverse information;

Investigational plan, including a description of the intended use of the device, objectives and duration of the study, analysis of risk, justification, patient population, monitoring procedures, and the protocol;

Device description and description of manufacturing;

Example of investigator agreement;

Certification that all investigators who will participate in the study have signed the investigator agreement;

Names, addresses and chairpersons of IRBs;

Participating institutions;

Statement of noncommercialization;

Claim of categorical exclusion from environmental assessment;

Labeling; and

Informed consent materials.³

Sponsors and investigators each have responsibilities under the IDE regulations, including recordkeeping and reporting obligations. Those responsibilities vary somewhat depending on whether the study is an Significant Risk (SR) or a Nonsignificant Risk (NSR) study.

§ 3:14 Investigational device exemptions— Investigational device exemption supplements

Research References

West's Key Number Digest, Patents ¶220

Typically an Investigational Device Exemption (IDE) supplement is required for any change to the investigational

³21 C.F.R. § 812.20

plan; however, study sponsors may make certain modifications without submitting an IDE supplement to FDA. Such modifications include: 1) developmental changes in the device that do not constitute a significant change in design or basic principles of operation that are made in response to information gathered during the course of investigation; and 2) changes or modifications to clinical protocols that do not affect a) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol, b) the scientific soundness of an investigational plan submitted in the IDE, or c) the rights, safety or welfare of the human subjects involved in the investigation.¹ To make such a change, the study sponsor need only submit a notice of the change or modification to FDA within five days after the change or modification is made. Of course, FDA may disagree with the sponsor's determination and has discretion to require an IDE supplement.

§ 3:15 Investigational device exemptions—Pre-IDE meetings

Research References

West's Key Number Digest, Patents ¶220

FDA allows sponsors who intend to conduct clinical studies in the United States the opportunity to meet with FDA to discuss their investigational plan in a "pre-IDE meeting."¹ Such a meeting can be obtained by submitting a written request setting forth a description of the device; the proposed conditions of use; a proposed investigational plan; and the expected performance of the device, if available.² The agency has 30 days in which to review the request and schedule a meeting with the sponsor.³ These types of pre-IDE meetings are also often used to meet with the agency about the company's proposed regulatory pathways for its new device

[Section 3:14]

¹21 C.F.R. § 812.35.

[Section 3:15]

¹21 U.S.C.A. § 360j(g).

²21 U.S.C.A. § 360j(g).

³21 U.S.C.A. § 360j(g).

and the proposed content of the company's marketing submission. Although the company may receive valuable feedback from the agency, the outcomes of the meetings are not binding on FDA. There are certain other, more formal meetings, afforded to sponsors under the Federal Food, Drug, and Cosmetic Act (FDCA)⁴ which are generally more binding on the agency if agreements can be reached between FDA and the applicant.

§ 3:16 Investigational device exemptions—Clinical trial registration

Research References

West's Key Number Digest, Patents ⇨220

Recently, FDA established registration requirements for “applicable clinical trials.” An applicable device clinical trial is defined as: (1) “a prospective clinical study of health outcomes comparing an intervention with a device subject to [premarket notification (510(k)) applications, Premarket Approval (PMA) applications and Humanitarian Device Exemptions premarket requirements] against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes)”; and (2) “a pediatric postmarket surveillance [requirement].”¹ Thus, it may be the case that a study being conducted under an IDE (Investigational Device Exemption) must be registered with the ClinicalTrials.gov data bank.

§ 3:17 Postmarket requirements¹

Research References

West's Key Number Digest, Patents ⇨220

Once a manufacturer obtains clearance or approval to mar-

⁴21 U.S.C.A. §§ 301 passim.

[Section 3:16]

¹42 U.S.C.A. § 282.

[Section 3:17]

¹This chapter only highlights the basic requirements FDA's postmarket jurisdiction.

ket a device in the U.S., they are subject to a myriad of post-market obligations. Some of the requirements even begin before the products are marketed, such as ensuring that the devices are designed and manufactured in accordance with the Quality Systems Regulation. Under FDA's postmarket jurisdiction, manufacturers of medical devices are subject to continued and comprehensive postmarket regulatory review, oversight, and periodic inspections by FDA. Failure to comply with the regulations administered by the FDA, or failing to timely and adequately respond to any adverse inspectional observations or product safety issues, could result in FDA enforcement action, which can include Warning Letters, fines and civil penalties, product recall or seizure, injunctions, refusal to grant export approval, import detentions, invocation of FDA's Application Integrity Policy,² and even criminal prosecution.

One area of particular sensitivity for FDA in the enforcement arena is product labeling and product promotion. By law, companies are required to promote their products only for those uses that FDA has cleared or approved. Moreover, such labeling must not be false or misleading. If FDA determines that manufacturer's promotional materials, labeling, training or other marketing or educational activities constitute promotion of an unapproved use, FDA could subject the manufacturer to regulatory enforcement actions. There are other federal statutes in addition to the Federal Food, Drug, and Cosmetic Act (FDCA)³ under which the government may take legal action and seek penalties.

§ 3:18 Postmarket requirements—Quality system regulation

Research References

West's Key Number Digest, Patents ⇨220

²FDA may invoke an Application Integrity Policy (AIP) in instances when it suspects that the information submitted in support of a premarket submission is false or fraudulent. Under the AIP program, FDA will thoroughly evaluate all data submitted and compare it to the raw data from the company's original records. FDA has a myriad of additional enforcement options, including placing all of the company's pending submissions on hold until the data integrity questions are resolved, requesting the company to recall any related marketed products, and civil and criminal prosecution.

³21 U.S.C.A. §§ 301 passim.

FDA has codified Good Manufacturing Practices for medical devices as the Quality System Regulation (QSR). The QSR requires that domestic and foreign manufacturers have a quality system in place for numerous activities, from the design and development of a device, to the production and processing of the device, to recordkeeping and servicing of devices in the field.¹ Specifically, the QSR requires medical device manufacturers of finished devices to implement and comply with procedures covering the following activities:

- Management Responsibility;²
- Quality Audits;³
- Personnel (and Training);⁴
- Design Controls;⁵
- Document Controls;⁶
- Purchasing Controls;⁷
- Device Identification and Traceability;⁸
- Production and Process Controls;⁹
- Inspection, Measuring and Test Equipment;¹⁰
- Process Validation;¹¹
- Receiving, In-Process, and Finished Device Acceptance;¹²
- Nonconforming Product;¹³
- Corrective and Preventive Action (CAPA);¹⁴
- Device Labeling and Packaging;¹⁵

[Section 3:18]

¹21 C.F.R. Part 820.

²21 C.F.R. § 820.20.

³21 C.F.R. § 820.22.

⁴21 C.F.R. § 820.25.

⁵21 C.F.R. § 820.30. The design control requirements do not apply to most class I devices.

⁶21 C.F.R. § 820.40.

⁷21 C.F.R. § 820.50.

⁸21 C.F.R. §§ 820.60, 820.65.

⁹21 C.F.R. § 820.70.

¹⁰21 C.F.R. § 820.72.

¹¹21 C.F.R. § 820.75.

¹²21 C.F.R. § 820.80.

¹³21 C.F.R. § 820.90.

¹⁴21 C.F.R. § 820.100.

¹⁵21 C.F.R. §§ 820.120, 820.130.

Device Handling, Storage, Distribution, and Installation;¹⁶
 Device Recordkeeping;¹⁷
 Complaint Handling;¹⁸
 Servicing;¹⁹ and
 Statistical Techniques.²⁰

Though comprehensive with respect to the scope of the activities covered, the QSR also provides flexibility to medical device manufacturers as to what provisions may apply to a particular medical device or company. For example, the regulation states that, “[i]f a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged.”²¹

§ 3:19 Postmarket requirements—Registration and listing

Research References

West’s Key Number Digest, Patents ☞220

FDA requires manufacturers, repackagers, relabelers, certain types of specification developers and initiators, and distributors of medical devices or components in commercial distribution to register their establishment and submit device listing information.¹ All establishment registration and device listing information must be submitted to FDA electronically using FDA’s Unified Registration and Listing System (FURLS), along with an annual registration fee.²

¹⁶21 C.F.R. §§ 820.140; 820.150; 820.160; 820.170.

¹⁷21 C.F.R. §§ 820.180; 820.181; 820.184; 820.186.

¹⁸21 C.F.R. § 820.198.

¹⁹21 C.F.R. § 820.200.

²⁰21 C.F.R. § 820.250.

²¹21 C.F.R. § 820.1(a).

[Section 3:19]

¹21 C.F.R. § 807.20.

²The Food and Drug Administration Amendments Act of 2007, PL 110-85 § 224, 121 Stat 823 (2007).

§ 3:20 Postmarket requirements—Inspections**Research References**

West's Key Number Digest, Patents ☞220

FDA uses the establishment registration and device listing information to maintain a database of companies subject to FDA inspection, as well as the types of products manufactured or distributed by each firm. FDA periodically conducts inspections of registered facilities to determine if the establishment is in compliance with various FDA regulations. The frequency of inspection is generally based on a number of factors including the level of risk of the devices manufactured by the firm; the date of the company's last inspection; whether major Quality System Regulation (QSR) violations were observed during previous inspections; whether the firm conducted a recent recall, whether the company has filed any adverse event reports that may be of concern to the agency, and whether FDA has received complaints alleging non-compliance of the company. In addition, to ensure compliance with the IDE (Investigational Device Exemption) and related regulations, FDA regularly inspects sponsors, clinical investigators, and institutional review boards, as part of the Bioresearch Monitoring (BIMO) program. Based on the results of these inspections, FDA can take a number of actions, including the enforcement actions discussed above.

§ 3:21 Postmarket requirements—Medical device reporting and adverse events**Research References**

West's Key Number Digest, Patents ☞220

FDA requires manufacturers, importers, and user facilities to report certain adverse events involving marketed devices in order to ensure that the agency is promptly informed of all serious problems or potentially serious problems associated with marketed devices. The Medical Device Reporting (MDR) requirements are found in 21 C.F.R. Part 803. Under the MDR regulation, medical device manufacturers are required to report to FDA any information that indicates that one of their marketed devices has or may have caused or contributed to a death or serious injury or has malfunc-

tioned in a way which would likely cause or contribute to death or serious injury if the malfunction of the device or one of its similar devices were to recur. The MDR regulation requires the report to be filed within 30 days of whenever a company employee becomes aware of the information, and the manufacturer must provide all information to FDA that “is reasonably known to them.”¹ However, the manufacturer must submit to FDA a report in 5 days, if the manufacturer becomes aware of a reportable event if: (1) the event necessitates remedial action by the manufacturer to prevent an unreasonable risk of substantial harm to public health; or (2) FDA requests the manufacturer file a 5-day report.

§ 3:22 Postmarket requirements—Product removals and corrections

Research References

West’s Key Number Digest, Patents ¶220

FDA has the legal authority to order device manufacturers to cease distribution of devices regulated by the agency and notify health professionals and user facilities to cease using such devices, where it makes a finding that there is “a reasonable probability that a device intended for human use would cause serious, adverse health consequences or death.” More commonly, device manufacturers undertake voluntary product recalls. FDA’s corrections and removals regulations require manufacturers to submit a written report to FDA of any non-exempt product removal or correction initiated either: (1) to reduce a risk to health posed by the device; or (2) to remedy a violation of the Act caused by the device which may present a risk to health, unless that information has previously been reported to FDA under the Medical Device Reporting (MDR) regulation.¹ Reports must be made within ten working days of the initiation of the removal or correction and must describe, among other things, the event giving rise to the information reported and the corrective or removal actions that have been, and are expected to be

[Section 3:21]

¹21 C.F.R. § 803.50.

[Section 3:22]

¹See 21 C.F.R. Part 806; see also 21 C.F.R. Part 7.

taken, and any illness or injuries that have occurred with the use of the device (including, if applicable, the MDR numbers).

§ 3:23 Conclusion

Research References

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Prior to distributing a medical device in the United States, in most cases, a company must obtain premarket clearance or approval from the FDA, and then must comply with FDA's substantial postmarket requirements. The above discussion only presents a very brief overview of FDA's extensive regulatory authority over the medical device industry to give the reader a flavor for the complex nature of FDA's jurisdiction over the medical device industry. There are many more regulatory requirements than those addressed in this chapter and understanding FDA's interpretation of those requirements is crucial to successfully managing the premarket clearance and approval process and in avoiding enforcement actions which can be extremely damaging to companies and individuals. Consultation with a subject matter expert is strongly advised when a company attempts to obtain market clearance and to achieve compliance with FDA's complex postmarket requirements.