

CODES AND REGULATIONS: MEDICAL DEVICES

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INTRODUCTION

The U.S. Food and Drug Administration (FDA or agency) regulates medical devices according to specific definitions, classifications, requirements, codes, and standards. The FDA's authority and framework for medical device regulation are specified in the Federal Food, Drug, and Cosmetic Act of 1938, as amended (FDCA). The FDCA is codified at Title 21, Chapter 9, United States Code (21 USC) (1). For purposes of medical device regulation, several acts of Congress amending the FDCA are especially significant: the Medical Device Amendments of 1976, the Safe Medical Devices Act of 1990, the Food and Drug Administration Modernization Act of 1997, and the Medical Device and User Fee and Modernization Act of 2002. The FDA has promulgated regulations for the efficient enforcement of the FDCA. These regulations, which generally have the force of law, are codified in Title 21 of the Code of Federal Regulations (21 CFR or the regulations) (2). The agency also has issued guidances and guidelines to assist in the regulation of medical devices (3).

Pursuant to the FDCA, the FDA determines the entities subject to regulation (e.g., manufacturers, specifications developers), evaluates whether products and regulated entities are in compliance, and initiates appropriate regulatory and enforcement actions to impose penalties for violations. The FDA's requirements affect each stage of a medical device's lifecycle. Some FDA requirements apply to particular periods of a medical device's lifecycle. Others apply more broadly. Design, technical development, pre-clinical testing, clinical study, market authorization, market approval, postmarket assessment, modification, obsolescence, redesign, and labeling requirements are part of this regulatory framework for medical devices. The FDA's Center for Devices and Radiological Health (CDRH) is the FDA component with primary responsibility for medical device regulation.

WHAT IS A MEDICAL DEVICE?

The FDCA contains definitions for the various product areas the FDA regulates, including medical devices. Under the FDCA, a "device" must be

- "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory"
- which is either "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 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" [21 USC § 321(h)].

To be a medical device, a product must achieve its "primary intended purpose" without chemical or metabolic action within or on the body. This characteristic distinguishes "devices" from "drugs". For example, perfluorocarbon gas is injected into the human eye to hold a detached retina in place. The gas has no metabolic reaction with the body and thus is regulated as a medical device. But determining whether the FDA would consider a product, a "device", or a "drug" can be difficult. Products can be medical devices even if there is some chemical or metabolic reactions within or on the body. For example, the body often reacts metabolically to hip and other implants. Because these reactions are side effects rather than the primary intended purpose of these implants, the products are medical devices.

The FDCA's definition of medical device includes a concept that is a key part of the FDA's regulatory framework: A medical device is both the physical product and its intended use or uses. "Intended use" is sometimes described as the express and implied claims made for a product. This concept means, for example, that a manufacturer (and his representatives) cannot, without penalty, label, or promote a laser for refractive correction eye surgery if it is legally marketed only for cardiac surgery. The manufacturer must apply to the FDA for authorization or approval to use the laser for a new indication. Changes in indications or uses can create regulatory hurdles for a manufacturer.

MEDICAL DEVICE CLASSIFICATION

Prior to 1976, the FDCA did not contain any specific provisions for medical device regulation. The Medical Device Amendments (MDA) of 1976 greatly expanded the FDA's statutory authority over medical devices and established a comprehensive regulatory scheme for medical devices. The MDA established three classes of medical devices based on the potential risk of the device to patients

or users. Devices with greater potential risks are subject to more regulatory controls.

Since 1976, the FDA has established classification regulations for > 1700 different generic types of devices, and grouped them into 16 medical specialties, such as cardiovascular, respiratory, general hospital, infection control, and restorative (4). Each of these generic types of devices is assigned to one of three regulatory classes depending on the level of controls needed to provide a reasonable assurance of the devices' safety and effectiveness. Unclassified devices and new devices are automatically Class III medical devices. But not all medical devices that a layperson likely would understand to be new remain "new" for purposes of the FDCA. If a manufacturer can show that its device is "substantially equivalent" to a device that was legally marketed in 1976, often referred to as a "predicate device", then the device becomes subject to the classification and requirements that apply to that predicate device.

Class I devices are those posing the least amount of risk. Examples include elastic bandages, examination gloves, and hand-held surgical instruments. Class I devices do not require FDA review prior to marketing. However, Class I devices are subject to the FDCA's general controls for all medical devices. These general controls are the regulatory common denominator for all medical devices, and include do not distribute adulterated or misbranded devices; register the commercial establishment with the FDA; list the marketed devices with the agency; label the devices in accordance with applicable labeling regulations; manufacture the devices in accordance with the quality system and good manufacturing practices regulations (many Class I devices, however, are exempt from this requirement); permit FDA inspection. The FDA has the authority to ban medical devices under appropriate circumstances; restrict the sale, distribution, or use of some devices; and require the submission of records and reports.

Class II medical devices have an intermediate level of risk. General controls alone are not sufficient to address the risks of Class II devices. Examples include powered wheelchairs, infusion pumps, and surgical drapes. Class II devices are subject to special controls that are developed to control risks specific to particular devices. Examples of the types of special controls used by FDA include performance standards, guidelines, postmarket surveillance, and patient registries. Most Class II devices require 510(k) premarket notification. The "510(k)" refers to FDCA section 510(k), codified at 21 USC § 360(k). A 510(k) submission contains information and data to show that the device is "substantially equivalent" to a legally marketed predicate device. Clinical data is usually not required for the FDA to clear a 510(k) submission for marketing. Some Class II devices are exempt from 510(k) clearance.

Class III medical devices are those presenting the greatest risks. Examples include replacement heart valves, silicone gel-filled breast implants, and implanted brain stimulators. In general, Class III devices are subject to premarket approval prior to marketing. General and special controls alone are insufficient to provide a reasonable assurance of the devices' safety and effectiveness. Class III devices are usually devices that are life sustaining, life supporting, or implantable, or have the potential for ser-

ious injury (e.g., sight threatening). New devices that are not substantially equivalent to a legally marketed device also are usually subject to premarket approval. A premarket approval application (PMA) contains extensive scientific and technical evidence that demonstrates that a reasonable assurance of safety and effectiveness exists for the device. Clinical studies are usually required to support FDA approval of a PMA.

Under the 1997 amendments to the FDCA, manufacturers of certain devices that have been found to be not substantially equivalent can request immediate reclassification into Class I or II based on the device's low risk level. This process is called *de novo* classification. If the FDA agrees, then the device becomes subject to the requirements of either Class I or II, and a PMA is not required.

FDA-REGULATED ENTITIES

The FDA regulates manufacturers, specification developers, distributors, contract manufacturers, sterilization facilities, importers, exporters, contract research organizations, and clinical researchers of medical devices. In addition, the FDA regulates, and otherwise influences, the use and nonuse of voluntary standards by these organizations and individuals to support their regulatory activities and submissions to the agency. The manner in which parties are regulated depends on their role in the distribution of the device and on the stage of the device's lifecycle. For example, the FDA requires preapproval of medical device clinical trials that present significant risks to patients. On the other hand, establishments must register with the FDA only after the FDA authorizes marketing of the device.

USE OF STANDARDS

The FDA recognizes that a device's conformance with recognized consensus standards can be used to support a PMA, 510(k), or other submissions to the agency (5). The FDA maintains a list of officially recognized standards (6). Some domestic and international standards focus on specific medical devices (e.g., respirators). Others characterize an important aspect of many medical devices, (e.g., electrical safety). The former is sometimes called a "vertical" standard. The latter is called a "horizontal" standard. The agency also issues guidance documents for specific devices that refer to the FDA-recognized standards or to other standards. Standards should be used consistent with FDA's guidances because there can be a considerable delay between the development of consensus standards and the agency's recognition of them.

ENFORCEMENT AND PENALTIES

The FDCA authorizes civil and criminal penalties for violations (21 U.S.C. §§ 331-337). The statute, for example, prohibits the adulteration or misbranding of medical devices as well as the introduction or delivery for introduction into interstate commerce, or the receipt in interstate commerce, of any adulterated or misbranded device. The

FDCA also prohibits the submission of false or misleading information to the agency, including the withholding of material or relevant information. For example, a failure to report to the FDA all device failures that occurred during the clinical trial of a Class III medical device is a violation. Such actions can lead to not only disapproval or withdrawal of the PMA for the device, but also civil and criminal penalties on manufacturer.

The FDCA authorizes the FDA to pursue some remedies administratively, including clinical investigator disqualifications, temporary detention of medical devices, and certain civil money penalties. Other remedies, including product seizures, injunctions, criminal charges, and some civil money penalties, require judicial proceedings in federal court. The FDA refers judicial enforcement actions to the U.S. Department of Justice, and works closely with the Justice Department to prosecute these actions. The FDCA is a strict liability statute, which means that a company's management may be prosecuted for a failure to detect, prevent, or correct violations. Knowing and following the rules is important.

REQUIREMENTS GENERALLY

Marketing safe and effective medical devices in the United States requires an understanding of FDA requirements that govern the entire life cycle of the device. These include requirements for conducting nonclinical laboratory studies and clinical trials, bringing a product to market, manufacturing practices, labeling, reporting device problems and patient injuries, carrying out recalls and corrective actions, and making modifications to the device.

NONCLINICAL LABORATORY STUDIES

Manufacturers and other entities must comply with the FDA's Good Laboratory Practices (GLP) regulations when conducting nonclinical laboratory studies that are going to be used to support any regulatory submission to the FDA (21 CFR Part 58). Good Laboratory Practices regulate the organization and personnel of the laboratory as well as the facilities, equipment, test operations and study protocols, and records and reporting. Failure to comply with these regulations may invalidate data submitted to the agency. Contract research organizations used to obtain data for regulatory submissions must comply with GLP regulations.

In addition, the study should conform to FDA-recognized standards that are relevant to particular aspects of the studies, for example, laser safety, toxicity, and biocompatibility. Also, the study's documentation should specifically identify and conform to those parts of FDA performance standards and guidance documents relevant to the device rather than simply state overall compliance with the standard or guidance. Whenever particular laboratory study practices will not conform to relevant guidance, the manufacturer or study sponsor should, prior to conducting the studies, discuss the discrepancies with knowledgeable FDA staff, obtain a variance from the GLP regulations if necessary, and document the reasons for the discrepancies.

CLINICAL TRIALS

The FDA regulates clinical trials of medical devices under its investigational device provisions [21 USC § 360j(g), 21 CFR Part 812]. Also important are the regulations for institutional review boards [21 CFR Part 56] and the protection of human subjects [21 CFR Part 50], and the consolidated guidance for good clinical practice [ICH E6]. Different Part 812 procedures apply depending on whether the device study presents "significant risk" or "nonsignificant risk" (7). A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices can include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease, or in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Nonsignificant risk devices are devices that do not pose a significant risk to human subjects. Examples include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and urological catheters. Although these latter devices generally are nonsignificant risk devices, the FDA could consider a particular clinical trial using these devices to be a significant risk study and regulate the trial accordingly.

An institutional review board (IRB) may approve a nonsignificant risk device study, and the study may proceed without FDA approval. But clinical studies involving significant risks must receive FDA approval prior to IRB approval. Sponsors, usually investigators or manufacturers, apply for this FDA approval through submission of an Investigational Device Exemption (IDE) application. Although IRBs are to evaluate whether a study is a nonsignificant risk, the FDA has final authority and does determine, from time to time, that an FDA-approved IDE is needed even though an IRB approved a clinical trial protocol as being a nonsignificant risk study.

The FDA's IDE regulations set forth the requirements for submitting IDEs and conducting device clinical trials. These regulations are first and foremost designed to protect human subjects from unnecessary risk. In addition, the IDE regulations are designed to guide the development and documentation of evidence needed to evaluate a device's safety and effectiveness in a PMA application, or a device's substantial equivalence in a 510(k) submission. An IDE is a request for an exemption from the restriction that only legally marketed medical devices can be distributed.

The FDA has a pre-IDE meeting program that can be extremely valuable (8). These meetings usually include FDA review of some portions of a planned IDE submission. Pre-IDE meetings can be requested in a variety of circumstances, and are intended to provide the sponsor with preliminary FDA input related to the device. For example, the pre-IDE meeting should help clarify whether any additional preclinical or technical data are needed, what concerns FDA reviewers may have, whether the proposed protocols are adequate from the FDA's perspective, and the appropriate regulatory path to market for the device. Sponsors planning to conduct nonsignificant risk studies

sometimes request a pre-IDE meeting to whether deficiencies exist in the protocols that might preclude marketing approval. Other sponsors find it useful to discuss issues related to ongoing preclinical testing.

An IDE sponsor must submit a detailed description of the device, including its intended use and indication for use, that is, what does the device do and in what kind of patients or user. The sponsor must submit an investigational plan and a detailed protocol for the proposed clinical trial, including proposed informed consent documents. An IDE application also requires other documentation, including results from all laboratory and animal studies conducted with the medical device proposed for the clinical study. These laboratory and animal studies must be conducted in conformity with GLPs. The sponsor must report all relevant published studies, both nonclinical and clinical, regarding the device. Information on all medical uses of the device, and on any clinical trials conducted outside the United States may also be required. If consensus standards exist for the device, the sponsor must identify them and explain whether the device conforms with them. If previous clinical trials were conducted under IRB-only approval, then that data must be submitted in the IDE.

The IDE regulations include an IDE application template (21 CFR 812.20). The FDA also has issued a number of guidance documents on IDE processes and specific types of medical devices (3). Prior to submitting an IDE application to FDA, agency guidance documents relevant to the medical device at issue should be reviewed, and relevant aspects of those guidances implemented. These guidances often recommend specific preclinical tests for categories of devices and can include template investigational plans. But these recommendations and templates are not always suitable for particular devices. Also, guidances are not binding on the FDA and may not fully reflect current agency thinking. Consultation with the FDA may be appropriate where a sponsor believes that modifications are needed for its device.

Once a sponsor submits a complete IDE, FDA must make a decision regarding the IDE submission no later than 30 calendar days from the stamped date of arrival of the IDE application at CDRH headquarters. The FDA's initial decision letter usually lists deficiencies in the IDE, even when FDA approves the IDE. A disapproval letter is rare, especially if the sponsor had a pre-IDE meeting with the FDA. Sponsors receiving a disapproval letter may find it useful to seek assistance from an experience regulatory affairs professional to help evaluate and resolve these deficiencies. If the FDA conditionally approves the IDE, but with deficiencies that have major impact on the clinical trial or the device's indications, these deficiencies should be resolved with the FDA before the clinical trial is started. The FDA usually "conditionally" approves an IDE application, meaning that the applicant may start the clinical trial immediately, but that the applicant must answer the deficiencies satisfactorily within a short time period (e.g., 30–45 days). When the FDA perceives a high risk to human subjects, it will initially approve the IDE for a limited number of subjects and study sites, and then approve expansion of the study after the preliminary data demonstrates reasonable safety. The FDA also typically

provides a list of deficiencies that do not have to be answered to conduct the clinical trial, but must be responded to in the marketing application [e.g., 510(k) or PMA]. If any aspect of the FDA's response letter is unclear, clarification should be sought from the FDA or an experienced regulatory affairs professional, or both.

Responsibilities of a clinical trial sponsor, include, but are not limited to, obtaining IRB approval, providing adequate informed consent, and ensuring that the investigators are trained and follow the approved protocol. Adequate record keeping, especially of adverse events, and study site monitoring are critical to success. Annual reports of the clinical study must be submitted to the FDA on the anniversary of the FDA's initial approval of the IDE. Also, serious adverse events must be reported to the FDA within five working days of their occurrence. All adverse events must be reported to the FDA even if the sponsor does not believe the event is related to use of the medical device being studied. Sponsors should also consult medical practice specialty standards and international standards that may be relevant to the study.

Although IDE sponsors (and their agents) may conduct limited advertising for subjects, they must not claim or suggest that the device is safe and effective for the uses it is being studied for. When discussing the device with potential investors, issuing reports on the company, and conducting similar activities, sponsors must carefully avoid making any conclusory statements regarding the device's safety and effectiveness. These restrictions continue until the FDA authorizes or approves the device for marketing. Sponsors also may not charge subjects, investigators, hospitals, or other entities a price for the device that is larger than that necessary to recover costs for manufacture, research, development, and handling. These costs should be documented in the event of an FDA inspection or audit.

Although clinical investigations of medical devices generally must comply with IDE requirements, some limited exemptions exist. For example, a diagnostic device that is noninvasive, does not require an invasive sampling procedure that poses significant risk to the subject, does not introduce energy into a subject, is not used as a diagnostic procedure without confirmation by another medically established diagnostic device, and meets certain other requirements, is exempt from IDE requirements. But the study must still comply with IRB and informed consent requirements.

REGULATORY PATHWAYS TO MARKET

Some medical devices require clearance through premarket "510(k)" notification, some medical devices require premarket approval, and others are exempt from premarket notification and premarket review. The majority of devices—more than 75%—have entered the market through 510(k) premarket notification.

Premarket notification is a process under which the FDA decides whether the evidence demonstrates substantial equivalence between a new device and a legally marketed (predicate) device. If the FDA decides that the device is substantially equivalent to the predicate device, then the

device is “cleared” for market. If the FDA decides that the device is not substantially equivalent, it is sometimes appropriate for a manufacturer to request *de novo* classification into Class I or II based on the device’s low potential risks. But if the FDA denies that request, the only pathway to market is the PMA approval process. Typically, the FDA will determine, in discussions with a manufacturer or sponsor, which of the three pathways to market is required: (1) 510(k) → substantial equivalence; (2) 510(k) → nonequivalence → *de novo*; (3) PMA. But, as noted, some medical devices are exempt from even 510(k) requirements.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) authorizes user fees for premarket reviews of PMAs, PDPs, certain supplements, 510(k)s, and certain other submissions (21 USC §§ 379i-379j). The MDUFMA also set agency performance goals for many types of premarket reviews. These goals become more demanding on the FDA over time. User fees must be paid at the time a submission is sent to the agency or the agency will not file or review it. The MDUFMA includes some fee exemption, waiver, and reduction provisions, including a fee waiver for the first premarket application by a small business.

PREMARKET NOTIFICATION EXEMPTIONS

Class I medical devices are exempt from 510(k) notification unless the FDA has by regulation stated that a particular medical device type is not exempt, or has specified conditions under which it is exempt. But the exemption applies only where the device is intended and indicated for the use or uses specified in the applicable regulation. If the device is to be marketed for a different use or medical condition, then the device is not exempt from 510(k) notification. If the new use presents extremely high risks or involves particularly vulnerable patients, a PMA may be required instead of a 510(k).

The same basic exemption rules apply to Class II devices, except that few Class II devices are exempt from premarket review. For devices exempt from premarket review by regulation, some changes in uses or indications do not require premarket review of the device because certain uses or indications are sufficiently similar to legally marketed intended uses. But in other instances, the FDA decides that an otherwise exempt device must receive premarket notification even though the uses or indications seem very similar. Although the FDCA provides a means for manufacturers to obtain a formal opinion from the FDA where uncertainty exists about the regulatory status of a device, an informal opinion may be sufficient, and preferable, in some situations. Manufacturers should consult an experienced regulatory affairs professional to evaluate how best to proceed in these circumstances.

PREMARKET “510(K)” NOTIFICATION

A 510(k) submission → substantial equivalence decision requires a determination by the FDA that

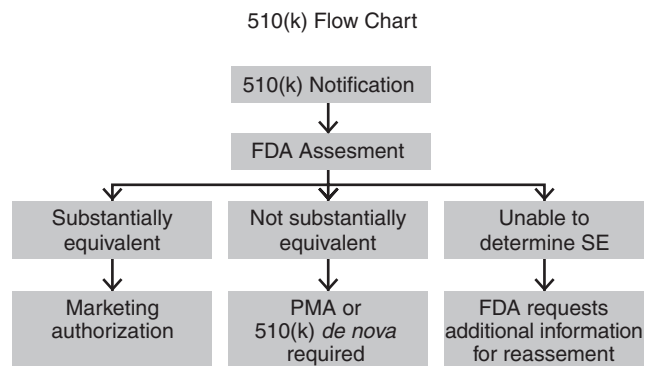
1. The intended use of the sponsor’s device is the same as that of the predicate device(s). Predicate devices

may be any Class I or II device with the same intended use. (A limited number of Class III devices marketed before 1976 also can be predicate devices if the FDA has not yet called for a PMA.)

2. The technological characteristics of the sponsor’s device must be either
 - (a) The same as the predicate device.
 - (b) Have performance characteristics that demonstrate that it is as safe and effective as the predicate device.

A substantially equivalent device is not “approved” for market. Instead, a 510(k) “clearance” decision is based on the FDA’s evaluation of whether the device is substantially equivalent to a legally marketed device for which a reasonable assurance of safety and effectiveness exists. “Substantial equivalence” is a term of art, and does not require that a sponsor’s device look or even operate the same as a predicate device. Two devices that visually appear dissimilar can be substantially equivalent under the FDCA. For example, the FDA cleared laser-light and water-jet microkeratomes as equivalent to vibrating steel blades to cut the cornea even though the former products use completely different cutting mechanisms than the latter.

The FDA has issued many guidance documents on various medical device types requiring premarket notification (3). The agency also has issued guidance documents for the 510(k) notification process. The FDA will provide prenotification consultation in telephone or in-person conferences to discuss a sponsor’s medical device and answer questions regarding written guidance documents and applicable standards. The FDCA requires the FDA to consider, in consultation with a sponsor, the “least burdensome”, appropriate means of evaluating a device (9). To maximize this requirement, a sponsor should understand, as much as possible, the requirements, guidances, and standards that apply to its medical device before meeting with FDA staff. As noted, guidances do not “bind” the FDA. But they can provide valuable information on the agency’s thinking on particular topics. Also, a sponsor should try to understand how similar devices have been regulated by the FDA.



The 510(k) submission → nonequivalence → *de novo* process use the same 510(k) processes to try to establish that substantial equivalence exists and obtain FDA

clearance for marketing. But when the sponsor is unable to do so, despite thorough efforts to do so, then the objective becomes convincing the FDA that a PMA is not necessary for regulatory control of the device. This requires a showing that the risks from the device are minimal, that the device is effective for its intended use, and that general controls and, in some cases, special controls will be sufficient to mitigate the product's risks. A request for *de novo* classification must be made within 30 days of receiving a not substantially equivalent determination, describe the device in detail, and provide a detailed recommendation for classification. The FDA then has 60 days to respond to that request with a written order classifying the device and identifying any special controls that may be needed if the device is in Class II. The device is then considered cleared and may be marketed. If the FDA keeps the device in Class III, PMA approval will be required before marketing.

MARKETING APPROVAL

Class III medical devices generally are high risk devices that cannot be regulated adequately by general and special controls alone. In other words, the FDA must review the safety and effectiveness data for these devices to determine if they should be approved for the treatment or diagnosis of diseases or other conditions in humans, and under what conditions. Class III devices may be approved for marketing under the humanitarian use device exemption (HDE), product development protocol (PDP), or premarket approval application (PMA) requirements.

HUMANITARIAN USE DEVICES

The FDCA's humanitarian use device exemption provision is narrow in that the objective is to provide rapid access to new therapeutic or diagnostic devices for patients with rare diseases or conditions, that is, so-called "orphan" devices (21 USC § 360j(m), 21 CFR Part 814, Subpart H). The humanitarian use device (HUD) process is relatively rapid because the applicant does not have to conduct clinical trials to demonstrate reasonable assurance of safety and effective, and the statute allows the FDA significantly less time to act on an HUD application than the agency has for a PMA. Rather than provide data to determine the safety and effectiveness of the device, the applicant has only to satisfactorily explain to the FDA why the probable benefit of the device outweighs the risks to patients in the context of other treatments for the disease. However, this regulatory pathway has many requirements, including the disease or condition affects fewer than 4000 patients/year, the device would not otherwise be available for persons with this disease or condition, the device and will not expose patients to unreasonable or significant risks, and the benefits to health from the device's use must outweigh the risk. Because of the provision's narrow scope and limitations, the humanitarian use device exemption is not used frequently. But it can be very valuable in some instances.

PRODUCT DEVELOPMENT PROTOCOL

The product development protocol (PDP) is an alternative to the PMA process, but is rarely used [21 USC § 360e(f)]. The PDP's distinguishing feature is that it involves a close relationship between the FDA and the sponsor in designing appropriate preclinical and clinical investigations to establish the safety and effectiveness of a device. The PDP requires multiple levels of review and approval of study protocols. The requirements for proof of safety and effectiveness are the same as for a PMA. The PDP process thus offers few advantages for a manufacturer over premarket approval processes, particularly for a device that has undergone significant evaluation and investigation. The PDPs also have required much more FDA staff time than PMA processes.

PREMARKET APPROVAL (PMA)

The FDCA's requirements for PMA approval apply to most Class III medical devices, except for a few devices marketed before the 1976 MDA and those being used consistent with an investigational device exemption (IDE) in order to obtain clinical data to establish the device's safety and effectiveness (21 USC § 360e). The FDA has promulgated regulations on PMA requirements and processes (21 CFR Part 814). These regulations include the FDA's procedures for reviewing and acting on a PMA application. Other important sources for information on PMA issues include general guidances, guidances for specific devices, meetings with the agency and advisory panels, and correspondence from the agency.

The regulations specify and describe the general categories of required information in a PMA [21 CFR 814.20(b)]. These categories include an "indication for use" statement, a device description, and data from non-clinical and clinical studies of the device. The foreign and U.S. marketing history, if any, of the device by the applicant or others must be described in the PMA, including a list of countries in the device has been withdrawn from marketing.

INDICATION FOR USE

A PMA's "indication for use" statement must provide a general description of "the disease or condition the device will diagnose, treat, prevent, cure, or mitigate" and "the patient population for which the device is intended" [21 CFR 814.20(b)(3)]. The "indication for use" statement is key to the device's labeling and, if the device is approved, the uses for which it can be legally marketed. In addition to this statement, the application must include a separate description of existing alternative procedures and practices for the indicated use.

DEVICE DESCRIPTION

The device must be described in summary form and then in detail, including manufacturing and trade secret

information where necessary, to allow FDA specialists to evaluate the risks associated with the device. The summary must explain “how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device” [21 CFR 814.20(b)(3)]. The full device description must include detailed drawings, and details of each functional component or ingredient of the device, all properties of the device relevant to the indication for use, the scientific and technical principles of operation of the device, and the quality control methods (good manufacturing practices) used in the manufacture, processing, packing, storage, and installation of the device [21 CFR 814.20(b)(4)]. In addition, the applicant must reference any standard, mandatory or voluntary, that is relevant to the device for the indicated use. If applicable, the applicant must identify how the device deviates from the standard and demonstrate, to the FDA’s satisfaction, how the applicant resolves these deviations.

NONCLINICAL STUDIES

A PMA must include summaries of nonclinical laboratory studies appropriate to the device, including, but not limited to, microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life studies. The PMA must also include a statement that each study was conducted in accordance with the FDA’s good laboratory practices regulations, or explanations as to why not. The study summaries must include descriptions of the objectives, experimental design, data collection and analysis, and results of each study. The results should be described as positive, negative, or inconclusive with regard to the objectives of each study. After each of the studies is summarized, it must be described in sufficient detail to enable the FDA to determine the adequacy of the information for FDA review of the PMA.

CLINICAL STUDIES

Clinical studies involving human subjects with the device must be conducted in accordance with IDE regulations or, if they are conducted outside the United States without an FDA-approved IDE, they must be conducted in accordance with special requirements discussed with the FDA before the PMA is submitted. IRB and human subjects protection requirements and the ICH guidance for good clinical practice also apply. The results of these clinical studies must be summarized first and then discussed in sufficient detail to enable the FDA to determine the adequacy of the information for FDA approval of the PMA. Clinical trial summaries must include the following:

“...a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and

other information from the clinical investigations as appropriate...” [21 CFR 814.20(b)(3)].

Discussion of the results of the clinical investigations must include details regarding:

“...the clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations...” [21 CFR 814.20(b)(6)].

The applicant must identify any investigation conducted under an FDA-approved IDE and provide a written statement with respect to compliance with IRB requirement, or explain the noncompliance. In addition to submitting the data for all the studies conducted by the applicant (or on the applicant’s behalf), the applicant is responsible for submitting a bibliography of all studies (nonclinical as well as clinical) relevant to the device and copies of any studies requested by the FDA or the advisory panel. Also, the applicant must identify, discuss, and analyze:

“...any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience.” [21 CFR 814.20(b)(8)].

LABELING

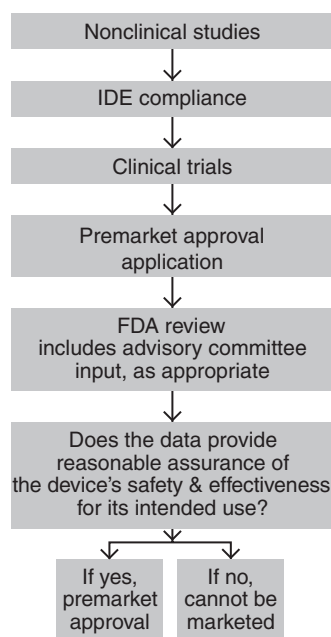
The applicant must submit copies of all proposed labeling for the device, including contraindications, warnings, precautions, and adverse reactions. Labeling typically includes, but is not limited to, physician instructions, an operation manual, a patient brochure, and all applicable information, literature, or advertising materials that constitutes labeling [21 CFR 814.20(b)(10)]. The FDA reviews and revises the proposed labeling prior to PMA approval.

REVIEW STANDARD

The applicant must demonstrate that the nonclinical, clinical, and technical data submitted in the PMA embody valid scientific evidence of reasonable assurance that the device is safe and effective for its intended use. In addition,

the applicant must discuss the benefits and risks (including any adverse effects) of the device, and describe any additional studies or surveillance the applicant intends to conduct following approval of the PMA. In evaluating safety and effectiveness, the FDA defines “valid scientific evidence” broadly and retains final authority on what is acceptable [21 CFR 860.7(c)]. The agency considers a variety of factors in deciding whether reasonable assurance of safety and effectiveness has been submitted for a medical device, including intended use (indication), use conditions, benefit-risk considerations, device reliability, and generally requires well-controlled clinical investigations (21 CFR 860.7).

PMA flow chart



UPDATE REPORT REQUIREMENTS

While the FDA is reviewing a PMA application, the applicant must update it. Such updates are required 3 months after the PMA filing date, following the applicant's receipt of an FDA letter stating the PMA is “approvable”, and at any other time as requested by the FDA. An “approvable” letter is a decision by the FDA that the PMA will be approved after the applicant resolves minor deficiencies.

After a device is approved, periodic and other reports are required. The owner of an FDA-approved PMA device is responsible for periodically updating any safety and effectiveness information on the device that may reasonably affect the FDA's evaluation of the device's safety or effectiveness, or that may reasonably affect statements of contraindications, warnings, precautions, and adverse reactions. If a PMA owner becomes aware of off-label (unapproved) uses of its device that may be unsafe or ineffective, then it is responsible for reporting these unauthorized uses to the FDA, especially if adverse events are associated with them.

POSTMARKET RULES

Major postmarket requirements include adequate labeling, medical device reporting, corrections and removals, and device modifications integrated into a system for manufacturing quality medical devices.

LABELING OVERVIEW

Labeling of medical devices is one of a manufacturer's key postmarket responsibilities. Each device must comply with general labeling requirements, and with the specific requirements and limits identified in the FDA's authorization or approval to market the device.

LABELING: GENERAL REQUIREMENTS

Many general labeling requirements exist for medical devices (21 CFR Part 801, Subpart A). The regulations include details on issues such as how a manufacturer's name is to be listed on a device package label. This article focuses on key concepts in the FDA's regulation of device labeling. These concepts include the FDCA's definition of “labeling”, the regulation's definition of “intended use”, and “adequate directions for use” requirements.

Under the FDCA, “labeling means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article” [21 USC § 321(m)]. This definition is very broad and includes promotional and advertising materials and oral statements about the device. The FDA's regulation of advertising and promotion presents many challenges for medical device companies. Three basic principles are critical: materials must be truthful and not misleading, must contain a fair balance of benefits and risks, and must provide full disclosure for use.

The “intended use” of a medical device is the objective intent of the product as expressed by the manufacturer or distributor of the device (21 CFR 801.4). It includes all conditions, uses, or purposes stated by the manufacturer or distributor orally or in written form. As discussed earlier, “intended use” is an integral part of the FDCA's “medical device” definition. If a manufacturer or distributor promotes an “intended use” different from the one authorized by the FDA, then the device is adulterated and misbranded until and unless the FDA authorizes the new use. This is often referred to as “off-label” use. The regulation further provides that “if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to the article is to be put.” “Intended use” is how the manufacturer intends the device to be used. “Indication for use” is a subset of “intended use” that usually represents a narrowing of the intended use to a specific patient population. In short, why a patient, or a practitioner on a patient's behalf, would use a particular device. Indications for use include a general description of

the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. If differences related to gender, race, ethnicity, age, or other factors exist, they should be reflected as well in the product's labeling.

The FDCA requires device labeling to bear "adequate directions for use," unless the FDA has promulgated regulations exempting a particular device [21 USC § 352(f)]. Under the regulations, "[a]dequate directions for use means directions under which the layman can use a device safely and for the purposes for which it is intended. . ." (21 CFR 801.5). These directions include specification of all applicable use conditions, dose quantity, use frequency, use duration, time of use, method of use, and use preparation. Adequate directions for use on over-the-counter devices must include a statement of indication for use [21 CFR 801.61(b)].

Prescription devices are exempt from the adequate directions for use requirement because, by definition, such directions cannot be prepared for a prescription device (21 CFR 801.109). However, prescription devices must have adequate instructions for the device's use by practitioners, including, but not limited to information on its use and indications, and any adverse events, contraindications, and side effects that may accompany the use of the device. In addition, to qualify for the adequate directions for use exemption for prescription devices, the device must meet other conditions, such as being in the possession of the practitioner. The regulations authorize other exemptions from the adequate directions for use requirement, including ones for medical devices that have common uses known to ordinary individuals, for medical devices used in certain teaching not involving clinical research, and for medical devices used in manufacturing, processing, and repacking (21 CFR Part 801, Subpart D).

LABELING: SPECIFIC DEVICES

Sources for labeling requirements for particular devices include labeling regulations for a few specific kinds of devices, classification regulations that provide "indications for use" statements for most Class I and Class II devices, guidance documents on specific devices, the FDA marketing authorization and approval letters, and approved labeling for PMA-approved devices.

The FDA has issued specific labeling regulations for dentures, eyeglasses and sunglasses, hearing aids, menstrual tampons, latex condoms, and devices that contain natural rubber (21 CFR Part 801, Subpart H). It also has specific labeling regulations for *in vitro* diagnostic devices (21 CFR Part 809, Subpart B). Each approved PMA includes labeling requirements for the device specified in the approval letter, in the summary of safety and effectiveness, and in written instructions for physicians (and other appropriate professionals) and patients.

REPORTING, CORRECTIONS, AND REMOVALS

Entities that manufacture, prepare, process, package, and/or distribute medical devices are subject to certain

requirements regarding device reporting, corrections, and removals. They must track, document, investigate, take action on, and report on events associated with their medical devices. Device user facilities (e.g., hospitals) and importers of medical devices also have responsibilities for reporting certain medical device events (21 CFR Part 803, Subparts A-B and C-D). This article focuses on FDA reporting requirements for device manufacturers (21 CFR Part 803, Subparts A-B and E).

Device manufacturers must report medical device reportable (MDR) events to the FDA with five workdays of becoming aware of a reportable incident if remedial action to prevent an unreasonable risk of substantial harm to the public health, or the event is of a type that the FDA has designated as requiring a report within five work days. Otherwise, MDR events must be reported to the FDA within 30 calendar days. An MDR event is any information that a manufacturer becomes aware of that reasonably suggests that the device marketed by the manufacturer may have "caused or contributed to a death or serious injury" or "malfunctioned. . . and would be likely to contribute to a death or serious injury, if the malfunction were to recur" [21 CFR 803.3(r), 803.50(a)]. By "any information", the regulations mean all information in the manufacturer's possession or that the manufacturer could obtain from user facilities, distributors, initial reporters of the information, or by analysis, testing, or evaluation of the device. The FDA's regulations specify that manufacturers "become aware" of a reportable event when any employee and any manager or supervisor of employees with responsibility for MDR events acquires information reasonably suggesting that a reportable adverse event has occurred. Moreover, MDR events include any information that necessitates "remedial action to prevent an unreasonable risk of substantial harm to the public health", including, but not limited to, trend analysis [21 CFR 803.3(c)].

Manufacturers should be very inclusive of potential MDR reportable events because the regulations define "caused or contributed" factors very broadly to include events due to user error and labeling misunderstandings in addition to manufacturing and design problems, and device failure and malfunction. In addition, the regulations define malfunction to mean the failure of the device to meet performance specifications of the device for the labeled intended use of the device. "Remedial action" means "any action other than routine maintenance or servicing, of a device where such action is necessary to prevent recurrence of a reportable event" [21 CFR 803.3(z)]. For MDR purposes, the regulations define "serious injury" more broadly than a life-threatening illness or injury. Serious injuries are also those that produce permanent functional impairment, or damage to, body structure or that requires treatment to preclude such impairment [21 CFR 803.3(bb)].

Manufacturers should have written procedures in place to identify, evaluate, and document potential MDR reportable events so that reports can be submitted to the agency accurately and within the required timeframes. A manufacturer must maintain files and records of all events associated with its medical devices whether the manufacturer decided that such events were MDR reportable, and

the FDA must be given access to these records upon request. A manufacturer must maintain records of MDR reportable events for ready access by FDA inspectors, and also coordinate these files with the complaint files required by the FDA's Quality System Regulations.

In order to comply with MDR reporting and general record keeping requirements (21 CFR 803.17), a manufacturer must have a system of written procedures to identify, communicate, and evaluate events subject to MDR reporting requirements that is timely and effective; transmit medical device reports to the FDA that are complete and timely; document and record all information that was evaluated in determining if an event was MDR reportable, submitted to the FDA (including MDR reports), used in preparing semiannual reports or certifications to the FDA, and ensure that this documentation and record keeping is readily and promptly accessible to the FDA upon inspection.

Manufacturers also must submit reports to the FDA about medical devices that the manufacturer has corrected in, or removed from, the marketplace to reduce the risk to public health (21 CFR Part 806). A "corrected" medical device is one that the manufacturer has repaired, modified, destroyed, adjusted, relabeled, or inspected at the user location. This includes patient monitoring. A "removed" medical device is one that the manufacturer has physically moved from the user facility to repair, modify, destroy, adjust, relabel, or inspect. Corrections or removals do not have to be reported for devices that have not been distributed to users (stock recovery) or for routine maintenance. However, corrections or removals must be reported for "repairs of an unexpected nature, replacement of parts earlier than their normal life expectancy, or identical repairs or replacements of multiple units" of the device [21 CFR 806.2(k)]. The manufacturer must explain to the agency the reasons for, and estimate the risk to public health of, each correction and removal action within 10 days of initiating the action. The manufacturer must keep records of all corrections and removals, including those not reportable to the FDA, such as those for routine maintenance and stock recovery.

MODIFICATIONS TO MEDICAL DEVICES

Manufacturers must ensure that modifications to their marketed devices are made using design control requirements of the FDA's Quality System Regulations, including, but not limited to, verification and validation processes and updates of the design history file. Manufacturers should also have procedures in place to evaluate whether particular device modifications need to be reported to the FDA. All device modifications must be documented in the company's design and device history files. But some device modifications require prior approval by the agency, some require the opportunity for FDA disapproval prior to implementation, and still others may be reported after the company has implemented the changes. Because a medical device is defined as the physical apparatus and its intended use, significant changes to the product's intended use can require prior authorization from the FDA, even if no physical modification is made to the apparatus; the claim is

only implied by the physical modification made to the apparatus; the manufacturer does not make the change but is aware that an entity to which the company sold the device is making additional substantial claims for the device. In other words, the FDA authorized manufacturer of a medical device can be responsible for the device it manufactures for the entire life cycle of the device.

The FDA's guidances for reporting device modifications for 510(k)-cleared devices and PMA-approved devices are summarized in Table 1 (10,11). Manufacturers should establish policies and principles for the company's medical devices based on these guidance documents and agency guidances specific to the company's devices.

QUALITY SYSTEM REGULATIONS

The two main objectives of the FDA's Quality System Regulations (QSR) (21 CFR Part 820) are to ensure (1) that quality is designed into medical devices, and (2) that management is responsible for the device throughout its life cycle and will be held accountable for shortcomings. The QSR sets forth the agency's current good manufacturing practices (cGMP) requirements for medical devices. Each manufacturer must integrate processes for controlling device modifications, labeling, and actions, reports, and record keeping regarding MDR events, corrections and removals into a quality system that is compliant with QSR. The QSR requires manufacturers to integrate all events associated with the manufacture and distribution of the medical devices into a corrective and preventive action (CAPA) subsystem linked to a record keeping subsystem that includes complaint files. The manufacturer must establish standard operating procedures that define, for example, the criteria for MDR reportable events for each kind of medical device that are manufactured, what actions are required, and the processes that must be followed. The manufacturer is responsible not only for maintaining complaint files and device history files, but for actively evaluating this information to maintain the medical device quality. This system involves using diverse information, including device maintenance, modifications, malfunctions, and failures with complaints from users, off-label (unapproved) use, and adverse reactions for continuous evaluation to ensure that the device is performing as designed. Corrective actions are to be taken as appropriate.

The corrective and preventive action subsystem is only one subsystem in a manufacturer's quality system. A quality system should be formed during the establishment of a company's management responsibilities and reviewed and revised during the initial design phase of device development. In addition to management and design control requirements, the QSR requires systems to control documents, purchasing, identification, traceability, production, processing, acceptance, nonconforming products, labeling, packaging, handling, storage, distribution, installation, servicing, and statistics. The regulations give a manufacturer the flexibility to develop a quality system for its medical devices that is tailored to the characteristics of these medical devices. However, the manufacturer's management team must justify and document the quality system, usually in

Table 1. Device Modification Reporting

Types of Modification	Premarket Notice [510(k)]	PMA Supplement
Changes due to recall or corrective action	Recall or corrective actions imply a safety or effectiveness problem with the device. Therefore, the FDA usually requires submission of a 510(k) notice if a device modification is necessary as part of the corrective action	Submit a “180-Day PMA Supplement” for design changes due to recall or corrective action even if the device still meets design specifications. Submit a “Special PMA Supplement-Changes Being Effected” for manufacturing changes that result from the corrective action
Changes that significantly affect safety or effectiveness	Use quality system, especially design controls, to determine if changes that significantly affect safety or effectiveness and if they do then submit a 510(k) notice	Submit a “180-Day PMA Supplement” for changes in, but not limited to, indications for use, labeling, new facilities, sterilization method, packaging, performance or design specifications, and the expiration date that affect safety or effectiveness. Use the quality system, especially design controls, to determine if changes affect safety or effectiveness. The FDA may issue a formal opinion that permits certain changes to be submitted in a “30-Day Supplement” rather than a “180-Day Supplement”
Labeling changes	Most, but not all, changes in intended use/ indication for use require submission of a 510(k) notice. For example, if the device will be indicated for use in a subset of patients for which the device is already cleared, then a 510(k) may not have to be submitted. Or no notice may be needed if a risk analysis demonstrates no additional risk by expanding the patient population being treated	Submit a “180-Day PMA Supplement”
Technology or performance specifications	Changes in a device’s control mechanism, principles of operation, or energy source usually requires submission of a 510(k) notice. Changes in sterilization method usually do not require 510(k) notification if design verification and validation is adequate	Submit a “180-Day PMA Supplement”
Materials changes	Evaluate the effects of materials changes on the performance characteristics of the device. If the performance characteristics are changed significantly or new labeling must be added then perhaps a 510(k) notice should be submitted to the FDA	Submit a “180-Day PMA Supplement”
Minor incremental changes or changes that do not affect safety or effectiveness	Use design controls to evaluate risks associated with “minor” evolutionary changes in the device. Proactively develop a decision rule about when these incremental changes should be reported to the FDA	Usually does not require FDA approval prior to implementation but describe the modifications in the Annual Report required for the PMA
Minor changes to the manufacturing process	Notice to the FDA not required	File a “30-Day Notice” to the FDA describing the changes in detail. Implement the changes at the end of the 30-day period unless the changes require submission of a “135-Day Supplement” because the 30 day notice to the FDA was inadequate
Changes that improve the safety of the device	Notice to the FDA not required	File a clearly marked “Special PMA Supplement—Changes Being Effected.” The changes that enhance safety include, but are not limited to, changes that strengthen a contraindication, an instruction, or quality controls. They must be described in detail

a quality system manual that specifies each of the sub-systems as identified in the QSR and any deviations from it.

IMPLEMENTATION

Bioengineers and informed specialists developing innovative medical devices must understand the regulatory implications of their scientific and technical innovations in order to develop a realistic business plan for their product. Sometimes the innovations are considerable yet the agency regulatory pathways remain simple. For example, as discussed earlier, CDRH cleared laser-light and water-jet microkeratomes as equivalent to vibrating steel blades to cut the cornea even though the former products use completely different cutting mechanisms than the latter. Similarly, FDA decided that a manufacturer's microscopic dermal fragments should be regulated as human tissues under the same tissue bank rules used to regulate its macroscopic sheets of dermis. The FDA could have decided to regulate microscopic dermis as a medical device because of the additional processing (a decision that would have required requiring premarket authorization of the dermal fragments), but instead decided both were human tissues from a regulatory point of view. On the other hand, innovative products can be subject to profoundly different regulatory pathways. For example, external kidney dialysis products have almost always been regulated as medical devices by the CDRH using the 510(k) process, an efficient process. However, the FDA decided to use the drug-biologics review process (IND/NDA) to regulate an external kidney dialysis filter using human cells, a more complex and costly review process than for devices.

The following analysis of a hypothetical medical device illustrates some of the regulatory implications of innovative medical devices. The hypothetical device is an implanted artificial kidney that can continuously dialyze the human body. Currently, 90% of patients that require kidney dialysis are treated with an external device in which the patient's blood is dialyzed outside the body, an external kidney dialysis device. Some patients are treated with an external kidney dialysis device that infuses the dialysate (the dialysis solution) into the abdominal cavity (the peritoneum) and then drains the waste products out of the peritoneum ~45 min later or continuously overnight. As mentioned above, the FDA currently is regulating an external kidney dialysis product using more burdensome drug-biologic regulatory requirements rather than the simpler 510(k) process used for other dialysis machines. Therefore, if metabolic interaction and/or cells are used in an implanted artificial kidney devices, it is likely that either CDER or CBER will lead the review of the combination product through the FDA's drug-biologics approval process. However, if the implanted artificial kidney device achieved its intended use of dialysis without primarily biochemical or metabolic interaction with the human body, then the implanted artificial kidney likely would be regulated as a medical device by the CDRH. Filter material and microscopic control elements such as valves and motors are likely critical components. This example illustrates that issues imbedded in the scientific and technical characteristics of an innovative medical product could

result in a regulatory pathway that is more complex, and costly, than already marketed alternative products.

Regardless of whether the innovative medical product, an implanted artificial kidney in this example, is reviewed by the FDA as a device, drug, or biologic, or a combination product, agency reviewers may or may not have expertise or knowledge directly relevant to the critical science. In fact, it is unlikely. Therefore, very early in product development the manufacturer should engage FDA reviewers in a dialogue about the cutting edge science or technology used in the device so that a common understanding evolves about key safety and effectiveness issues. This approach should help reduce misunderstandings about necessary nonclinical laboratory studies, animal study protocols, key safety and effectiveness endpoints, and fail-safe mechanisms so that agency reviewers will be comfortable with the risks associated with initial pilot study in humans. Also, the manufacturer should dialogue with agency reviewers about the scientific, clinical, and ethical issues associated with an initial clinical study in humans. In order to maximize control, manufacturers should take the initiative in making study proposals to the FDA rather than simply ask the agency for advice.

REGULATORY CHALLENGES

Medical device developers, academic researchers and engineers, start-up companies, research and development departments of large manufacturers, and other innovators are at the leading edge of scientific, technological, and medical product development, not the FDA. They therefore should be proactive with regard to the issues critical to the development and eventual marketing of the medical device. Developers of medical devices should take advantage of the opportunities to establish conditions for efficient FDA regulation of their devices before making regulatory submissions to the agency by developing a detailed quality system manual tailored to development and manufacture of the company's medical device; implementing good laboratory practices and specific standard operating procedures for nonclinical studies; identifying existing technical standards that are applicable to manufacturing quality devices, developing applicable standards where none exist; identifying the best clinical practices for clinical trials with the device; communicating the science and technology of the device to FDA reviewers; proposing a specific regulatory pathway to the agency based on a risk-benefit analysis of the device; incorporating feedback from discussions with the FDA. These proactive steps are particularly important for devices that are very innovative, and where scientific consensus may not exist on procedures and new standards needed to verify and validate the design of the device.

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See also CODES AND REGULATIONS: RADIATION; HOME HEALTH CARE DEVICES; HUMAN FACTORS IN MEDICAL DEVICES; SAFETY PROGRAM, HOSPITAL.