Chapter 18

Medical Device Submissions

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OBJECTIVES

- ❑ To provide an overview of medical device requirements and their complexity for marketing a product in the US
- ❑ To examine the classification structure for devices
- ❑ To view the formats for regulatory submissions which include the 510(k), PMA, IDE, 513(g) and their supplements
- ❑ To understand labeling and advertising regulations for devices

LAWS, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

- ❑ 21 CFR 801 Labeling
- ❑ 21 CFR 803 Medical Device Reporting
- ❑ 21 CFR 807 Establishment Registration and Device Listing, Premarket Notification
- ❑ 21 CFR 812 Investigational Device Exemptions
- ❑ 21 CFR 814 Premarket Approval
- ❑ 21 CFR 821 Medical Device Tracking Requirements
- ❑ 21 CFR 822 Postmarket Surveillance
- ❑ 21 CFR 860 Medical Device Classification Procedures

Introduction

Medical devices were first regulated by the *Federal Food, Drug and Cosmetic Act* of 1938 (*FD&C Act*). It is enforced by the US Food and Drug Administration (FDA). Under the act, devices were examined for adulteration and misbranding but no provision was made for review of safety or effectiveness prior to marketing. In the late 1960s, FDA started to concentrate on devices that posed problems with safety and effectiveness, requiring recalls and replacements.

The *FD&C Act* was amended in 1976 to include premarket review of medical devices. Under the act's amendments, FDA was authorized to set standards, with premarket clearance for some devices and premarket approval for a second group. Devices posing little or no risk to users or patients were exempted from standards and premarket clearance but not necessarily from manufacturing under parts of the Good Manufacturing Practices requirements (21 CFR 820).

FDA, through the Center for Devices and Radiological Health (CDRH), is responsible for assuring that medical devices are safe and effective. The agency bears this responsibility through authority granted by the *FD&C Act*, which is carried out in accordance with the regulations found in 21 CFR. Medical devices, referred to as "devices," are defined in Section 201(h) of the *FD&C Act*:

> "The term "device" means 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 Pharmacopeia*, 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."

Medical Device Classification System

Medical devices are regulated based upon a classification system that evaluates the risk posed by the product and the level of control needed to adequately assure safety. The device classification system has been modified by subsequent amendments, but generally remains as originally intended. The act defines three classes of medical devices according to increasing complexity and regulatory control:

- Class I: General Controls
- Class II: General Controls and Special Controls
- Class III: General Controls, Special Controls and Premarket Clearance or Premarket Approval

Class I devices are generally low-risk devices, such as nonprescription sunglasses, for which safety and effectiveness can be assured by adherence to a set of guidelines or "general controls." General controls include compliance with the applicable portions of FDA's Quality System Regulation (QSR) for manufacturing and recordkeeping, requirements to issue notices about repair, replacement or refund of devices presenting an unreasonable risk of substantial harm, facility registration and product listing, reporting of adverse medical events, and appropriate, truthful and nonmisleading labeling, advertising and promotional materials. Some Class I devices, although very few, also require premarket clearance by FDA through the 510(k) premarket notification process.

Class II devices are intermediate-risk devices, such as blood glucose test systems and infusion pumps, where general controls are not sufficient to ensure safety and effectiveness of these devices. Class II devices are subject to general controls, as well as "special controls." Special controls include appropriate performance standards, FDA-issued guidance documents, special labeling requirements, device tracking of implantable devices and any other actions that FDA determines are necessary to assure safety and effectiveness. Most Class II devices are subject to premarket review and clearance by FDA through the 510(k) premarket notification process. At times, the review and requirements are just as rigorous as for a Class III device.

Class III devices, such as life-sustaining, life-supporting or implantable devices, are considered by FDA to pose the greatest risk. Devices that have a new intended use or employ a unique, new technology that is not substantially equivalent to a legally marketed predicate device are also placed into Class III. These Class III devices are subject to the most rigorous controls, including general controls (as per Class I and Class II devices), any relevant special controls (as per Class II devices) and, in most cases, premarket approval, which requires the submission of evidence to establish reasonable assurance of the device's safety and effectiveness. Detailed manufacturing information may also be required. There is the further possibility that FDA may require a panel of outside experts to recommend the action to be taken on the Class III device. However, the agency is not compelled to take the panel's advice.

Unless expressly exempted, a sponsor must notify FDA of its intent to market a new Class I or Class II device in interstate commerce. The sponsor alerts FDA by submitting a premarket notification under Section 510(k) of the act at least 90 days before marketing the device in the US. In order to obtain permission to market the device, the 510(k) premarket notification must demonstrate that the medical device is "substantially equivalent" to a "predicate device." An acceptable predicate device is one that was:

- legally marketed prior to 28 May 1976, the date when the *Medical Device Amendments* of 1976 were enacted
- not on the market prior to 28 May 1976, but which FDA subsequently classified in Class I or Class II
- otherwise cleared for marketing by FDA through the 510(k) process

A medical device is determined to be substantially equivalent to a predicate device if the new device has the same intended use and FDA has determined that it has either the same technological characteristics as the predicate device or different technological characteristics but is as safe and effective as a legally marketed device (*FD&C Act* Section 513(i)). If the device is determined by FDA not to be substantially equivalent, the device is automatically placed in Class III and subject to premarket approval requirements.

Class III devices may, under certain circumstances, be the subject of a 510(k) premarket notification. This occurs for either: preamendment devices subsequently classified by FDA as Class III devices; or postamendment devices that are determined through the 510(k) process to be substantially equivalent to Class III preamendment devices, for which FDA has not yet issued a final rule requiring submission of a premarket approval application (Section 515(b) of the *FD&C Act*). One such device was an assay that determined the presence of the antibody to herpes simplex 2 in blood.

Request for Designation

There are times when it is not clear under which classification a device would fall. A provision of the act in Section 513(g) allows the device submitter to request an

assignment of classification from FDA. This requires a letter with a description of the device and a fee payment. The agency usually responds within 60 days with a classification assignment based upon the material presented.

510(k) premarket notifications are subject to the content requirements of 21 CFR 807.87, which include: the device name and class, an establishment registration number, an "Indications for Use Statement," a 510(k) summary, proposed labeling, substantial equivalence comparison with the predicate device, supporting performance data and a statement that all data and information submitted are truthful and accurate and that no material fact has been omitted. In particular, the Indications for Use Statement provides the specific indications, clinical settings, target population, anatomical sites, device configuration and other information critical to how the device is intended to be used clinically.

The Indications for Use Statement must be consistent with the device labeling, advertising and instructions for use. When FDA completes its review of the 510(k) and determines the device to be substantially equivalent, the Indications for Use Statement is made available to the public on the Internet.

Content and Format of a 510(k)

The information required in a 510(k) is detailed in 21 CFR 807.87. Information that must be submitted includes:

1. Table of contents
2. Action taken by the sponsor to comply with performance standards. Note: Mandatory performance standards have been established for a variety of medical devices. Even if an applicable performance standard does not exist, the item must be addressed in the submission. An acceptable response is: "No applicable mandatory performance standards or special controls exist for this device."
3. Proposed labels, labeling, instructions for use, intended use and promotional materials. Note: Although not specifically required, it is advisable to include copies of labeling for the device to which substantial equivalence is claimed.
4. Indications for Use (IFU) statement, identified as such and listed separately in the table of contents. Note: indications for use are those specific diagnostic or treatment uses for which the sponsor is applying. IFUs are sometimes distinguished from "intended uses," which are the marketing claims—whether written or verbal—made for a device by a sponsor's employee or representative.
5. Description of the device and its operating principles, including photographs and engineering drawings. Labeled diagrams are very helpful to FDA.
6. Statement that the device is similar to a legally marketed predicate device. This statement typically includes additional supporting information to document substantial equivalence and a table of side-by-side comparisons to the predicate device's technical characteristics. The side-by-side table is critical to the 510(k) clearance and presents the FDA reviewer with immediate information that demonstrates equivalence. The items chosen for comparison must be properties that demonstrate safety and efficacy.
7. Appropriate supporting data to show that the effects proposed changes to the sponsor's legally marketed device might have on the 510(k) device's safety and effectiveness have been carefully considered.
8. Summary of the submission's safety and effectiveness information that forms the basis for a substantial equivalence determination. In the past, it was acceptable to put in a statement that the sponsor would make such a summary available upon the request of any interested person. However, the current practice is to include the summary. In addition, the cleared document should be prepared for public release when requested from the agency by a third party. This preparation should include redacting confidential information.
9. Disclosure of any financial arrangements between the sponsor and clinical investigators who performed studies included in the submission, or a certification on FDA Form 3454 attesting to the absence of any financial arrangements (see 21 CFR 54).
10. For a 510(k) claiming substantial equivalence to a Class III device on the market prior to 1 December 1990 and for which a PMA has not been required, a Class III summary must include:
    a. information about safety and effectiveness problems with the type of device to which the 510(k) device is being compared
    b. citations to the information that forms the basis of the summary
    c. certification that a reasonable search of all known information about the Class III device and other similar, legally marketed Class III devices has been conducted (for Class III certification, see 21 CFR 807.94)
11. A "truthful and accurate statement," i.e., a statement attesting to the truthfulness and accuracy of the information contained within the submission
12. Any additional information, when requested by FDA

Requirements for a 510(k) submission's content and format are detailed on FDA's website.[1] The statement required by item six and the supporting data required in item seven represent the sponsor's rationale for a determination of substantial equivalence. Over the years, these requirements have been the focal points for the increasing rigor of FDA's documentation expectations. FDA requires a "substantial equivalence comparison," preferably in table format, as noted above, which describes the proposed indications for the 510(k) device's use, design, materials, performance specifications and other key characteristics, compared side-by-side with the same characteristics of

the predicate device. These sections need to be prepared carefully and thoroughly to demonstrate that the 510(k) device is as safe and effective as the predicate device to which it is being compared.

Generally, clinical studies are not required for 510(k) devices. However, if the 510(k) device cannot be shown to be as safe and effective as the predicate device using laboratory tests such as biocompatibility, engineering, bench performance, design verification and voluntary standards tests, clinical studies may be required.

The truthful and accurate statement carries significant legal implications and should be taken seriously by the individual signing it. It essentially amounts to a certification, and should FDA subsequently determine that false information or misstatement of material facts were included in the submission, or that material facts were omitted, judicial action could be taken against the person who signed the statement. It is prudent to conduct a formal audit of the information in the 510(k), including all pertinent development information, documentation and raw data, prior to signing this statement.

As noted above, the required truthful and accurate statement, which must be signed by a designated and accountable person within the company requesting market clearance, is specified by regulation at 21 CFR 807.87(k) to be:

> "A statement that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted."

Unless a Class III device is the subject of a 510(k) premarket notification, FDA approval of a Premarket Approval (PMA) application is required before a sponsor may market the device. The PMA process is much more demanding and rigorous than the 510(k) premarket notification process. A PMA application is intended to demonstrate that the device is safe and effective, and generally must be supported by extensive data, including data from preclinical studies and, frequently, human clinical trials. It also must contain a full description of the device and its components; the methods, facilities and controls used for manufacturing; and the proposed labeling.

Additionally, the fee for filing a PMA can be much higher than the fee for filing a 510(k), so the 510(k) approach may be more desirable for the submitting company. Note that clinical trials may also be required for Class II devices such as some in vitro diagnostics.

Labeling and Advertising

Section 502 of the *FD&C Act* specifies that a medical device is misbranded if, among other violations, its labeling is false or misleading in any particular or, in the case of a restricted device, its advertising is false or misleading. A restricted device is one that can only be sold on oral or written authorization by a licensed practitioner. The sale and distribution of a misbranded device are prohibited by Section 301 of the act. Violators of Section 301 are subject to fines, injunction or imprisonment, and misbranded medical devices are subject to seizure.

FDA considers most advertising for medical devices to be labeling. The term "labeling" as defined in Section 201(m) of the *FD&C Act* "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." FDA interprets labeling to include a wide variety of written, printed or graphic matter that bears a textual relationship to a device.

Under Section 502(f)(1) of the *FD&C Act* and 21 CFR 801.109(c), labeling for restricted devices must be included on or within the package from which the restricted device is to be dispensed, or the product is deemed misbranded on the grounds that it lacks adequate directions for use. To comply with the *FD&C Act*'s requirement of adequate directions for use, a restricted device's labeling must contain, among other items, information addressing product hazards and other risks, as specified in 21 CFR 801.109(d).

Advertising of restricted devices is also required to disclose risk and other information. Section 502(r) of the *FD&C Act* requires advertisements for restricted devices to include "a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications …". Furthermore, Sections 502(q)(1) and 201(n) of the act require that restricted device advertisements not be false or misleading.

Advertising is not defined in the *FD&C Act*, but is defined in FDA's regulations to "include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."[3]

FDA has issued detailed regulations on the information that must be included in advertising and promotion and the manner in which it is to be presented. The regulations note that advertisements must contain a "true statement of information in brief summary relating to side effects, contraindications, warnings, precautions and indications for use." The brief summary must be close to, and not separated from, the ad. Advertising that appears in medical journals is usually accompanied by a brief summary. Promotional labeling, on the other hand, must contain the full text of the approved labeling.

A sponsor has not met FDA's requirements if the labeling and advertising:

- are false or misleading
- do not present a "fair balance" between side effects and contraindications and effectiveness information
- fail to reveal material facts

Fair balance requires a presentation of both favorable and unfavorable information, i.e., the risks and benefits

that can influence prescribing. Healthcare providers may employ products for unapproved uses, but to advertise such uses is misbranding, or adulteration, if the unapproved use requires PMA approval. Only information consistent with the approved labeling can be used in advertising.

FDA will pre-review advertising that is voluntarily submitted for review, although it is under no time constraint to do so.

For devices, promotional labeling cannot make claims beyond the intended use for which the device was cleared. The CDRH promotion and advertising staff is responsible for restricted devices.

According to Section 520(e) of the *FD&C Act*, restricted devices have the potential for harmful effects or require collateral measures for use and for which there cannot otherwise be reasonable assurance of safety and effectiveness. However, the approval order for a PMA or FDA's recommendations for many devices cleared for marketing via a 510(k) may restrict their sale, distribution and use as a condition of approval. Labeling must bear the statement: "Caution: Federal law restricts this device to sale, distribution and use by or on the order of a healthcare provider." Current device regulations require an indication if a prescription is required. A form is marked accordingly.

In determining whether a device is misbranded because the labeling or advertising is false or misleading, Section 201(n) of the *FD&C Act* requires FDA to consider, among other things, not only representations made or suggested by statement, word, design, device or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material to consequences that may result from the use of the article under the conditions of use prescribed therein.

Information provided in device labeling must be accurate in terms of the cleared intended use(s) of the product. In 21 CFR 801.4, FDA defines the term "intended use" to include claims made in advertising:

> "The words *intended uses* or words of similar import…refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives."

Representing a device for intended uses and claims that are not cleared or approved by FDA constitutes misbranding, which is prohibited by law.

FDA regulations provide certain other specific representations that constitute misbranding such as: a false or misleading representation with respect to another device or a drug or food or cosmetic;[4] any representation that creates an impression of official approval because of establishment registration or listing;[5] or any representation that creates an impression of official approval because of compliance with 510(k) requirements.[6] Additionally, specific labeling requirements exist for certain devices in 21 CFR 801 Subpart H—Special Requirements for Specific Devices. The phrase "granted FDA approval" is understood among FDA regulatory experts to mean the approval by FDA of a PMA or a PMA Supplement. However, non-experts consider clearance and approval to be the same as permission to market. As noted above, the original 510(k) clearance cannot be represented as an "approval."

Expedited Review

Devices Appropriate for Expedited Review

FDA considers a device or combination product containing a device appropriate for expedited review if the device or combination product:

1. is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition
2. addresses an unmet medical need, as demonstrated by one of the following:
   a. The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology. Breakthrough technologies should be demonstrated to lead to a clinical improvement in the treatment or diagnosis of the life-threatening or irreversibly debilitating condition.
   b. No approved alternative treatment or means of diagnosis exists.
   c. The device offers significant, clinically meaningful advantages over existing approved alternative treatments. The device should provide for a clinically important earlier or more accurate diagnosis, or offer important therapeutic advantages in safety and/or effectiveness over existing alternatives. Such advantages may include demonstrated superiority over current treatments for effects on serious outcomes, the ability to provide clinical benefit for those patients unable to tolerate current treatments, or the ability to provide a clinical benefit without the serious side effects associated with current treatments.
   d. The availability of the device is in the best interest of patients. That is, the device provides a specific public health benefit, or meets the need of a well-defined patient population. This may also apply to a device that was designed or modified to address an unanticipated serious failure occurring in a critical component of an approved device for which there are no alternatives, or for which alternative treatment would entail substantial risk of morbidity for the patient.

Device Modifications

A new 510(k) application is required for changes or modifications to an existing device when the modifications could significantly affect the device's safety or effectiveness, or if the device is to be marketed for a new or different indication.

When a 510(k) holder decides to modify an existing device, it must determine whether the proposed modification(s) requires submission of a 510(k). All changes in indications for use require the submission of a 510(k). A change in indication for use includes a switch from prescription use to over-the-counter use.

Examples of modifications that may require a 510(k) submission include, but are not limited to:

- sterilization method
- structural material
- manufacturing method
- operating parameters or conditions for use
- patient or user safety features
- sterile barrier packaging material
- stability or expiration claims
- design

Special 510(k)

If a new 510(k) is needed for a device's modification and if the modification does not affect the device's intended use or alter its fundamental scientific technology, summary information resulting from the design control process can serve as the basis for clearing the application along with the required elements of a 510(k).

To optimize the chance that a Special 510(k) will be accepted and promptly cleared, submitters should evaluate each modification against the considerations described below to insure that the particular change does not:

- affect the intended use
- alter the device's fundamental scientific technology

Intended Use

Modifications to the indications for use or any labeling change that affects the device's intended use will not be accepted as a Special 510(k). Therefore, it is recommended that Special 510(k) submitters highlight or otherwise prominently identify all changes in the proposed labeling that may result from modifications to the legally marketed device. In addition, it should be clearly stated in the Special 510(k) that the intended use of the modified device has not changed as a result of the modification(s). Note that a labeling change from prescription to over-the-counter use, or vice versa, is considered a change in intended use and is not eligible for a Special 510(k) submission.

Fundamental Scientific Technology

Special 510(k)s will not be accepted for modifications that have the potential to alter the device's fundamental scientific technology. These types of changes generally include modifications to the device's operating principle(s) or mechanism of action. Specific examples that illustrate types of changes that alter the fundamental scientific technology and should not be submitted as Special 510(k)s include:

- a change in a surgical instrument that uses a sharpened metal blade to one that cuts with a laser
- a change in an in vitro diagnostic device (IVD) that uses immunoassay technology to one that uses nucleic acid hybridization or amplification technology
- incorporation of a sensing mechanism in a device to allow it to function "on demand" rather than continuously

Device modifications that should be appropriate for review as Special 510(k)s include the following:

- energy type
- environmental specifications
- performance specifications
- ergonomics of the patient-user interface
- dimensional specifications
- software or firmware
- packaging or expiration dating
- sterilization

A sponsor may make changes to the device that do not change the intended use or alter the technology and may not require a 510(k) submission. These changes may be minor but do require an addendum to the Design History File (DHF) and follow appropriate change control to the Master Device (Batch) Record (MDR).

Abbreviated 510(k)

An Abbreviated 510(k) relies on the use of guidance documents, special controls and recognized standards. An Abbreviated 510(k) submission must include required elements. Under certain conditions, the submitter may not need to include test data.

Device sponsors may choose to submit an Abbreviated 510(k) when:

- a guidance documents already exists
- a special control has already been established
- FDA has recognized a relevant consensus standard

In an Abbreviated 510(k) submission, sponsors provide summary reports on the use of guidance documents and/or special controls, or declarations of conformity to recognized standards, to expedite submission review.

Guidance Documents

An Abbreviated 510(k) that relies upon a guidance document should include a summary report that describes the way in which the relevant guidance document was employed. It should also note how the guidance was used during device development and testing. The summary report

should include information regarding the sponsor's efforts to conform to the guidance and outline any deviations.

Special Controls

Special controls are a way of providing reasonable assurance of a Class II device's safety and effectiveness. Special controls are defined as those controls (such as performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations and other appropriate actions) that establish reasonable assurance of the device's safety and effectiveness. The device classification regulations list special controls for the device, if any.

An Abbreviated 510(k) that relies upon a special control(s) includes a summary report that describes adherence to the special control(s). It also notes how the special control(s) was used during device development and testing, including how it was used to address a specific risk or issue. The summary report includes information regarding the sponsor's efforts to conform to the special control(s) and should outline any deviations.

FDA Recognized Standards

Recognized standards could be cited in guidance documents or individual policy statements, or established as special controls that address specific risks associated with a type of device.

An Abbreviated 510(k) that relies upon a recognized standard must include a Declaration of Conformity to the recognized standard. Under certain conditions, conformance test data are not required to be submitted in the 510(k). FDA has recognized more than 400 standards to which 510(k) submitters can declare conformity.

If FDA determines that an Abbreviated 510(k) is not eligible for review, the reviewer will notify the sponsor of this decision and offer the option of having the document converted to a traditional 510(k) or withdrawing it for future submission. If the 510(k) is withdrawn and a new one submitted, a new user fee will apply. If the 510(k) is converted, the original receipt date remains as the start of the review period. Also, sponsors should be aware that, in most cases, additional information will be necessary for converted documents.

Conformance Assessment

In the Abbreviated 510(k) process, a sponsor must assess the device's conformance to a recognized standard. Once the sponsor has ensured the satisfactory completion of this process, the Abbreviated 510(k) may be submitted.

In addition, the sponsor has the option of using a third party to assess conformance to the recognized standard. The third party will perform a conformance assessment with the standard for the sponsor and should provide the sponsor with a statement to this effect. For example, a third party may be used to assess conformance to the standard for electromagnetic interference testing and shock hazards, IEC 60601-1-2.

The Abbreviated 510(k) should include a declaration of conformity signed by the sponsor, while the third party's statement should be maintained in the DMR and DHF (21 CFR 820.30). The responsibility for conformance to the recognized standard rests with the manufacturer, not the third party.

Declaration of Conformity to a Recognized Standard

Declarations of conformity to recognized standards should include the following:

- identification of applicable recognized consensus standards met
- specification for each consensus standard that all requirements were met except inapplicable requirements or deviations
- identification for each consensus standard of any way in which it may have been adapted for submission to the device under review
- identification for each consensus standard of any requirements not applicable to the device
- specification of any deviations from each applicable standard that were applied
- specification of the differences that may exist between the tested device and the device to be marketed, along with a justification of the test results in these areas of difference
- name and address of any test laboratory or certification body involved in determining the conformance of the device, along with applicable consensus standards and a reference to any of those organizations' accreditations

It should be clearly understood that not all changes to a device require a new submission to FDA. The sponsor must determine whether the submission criteria are met and proceed accordingly. As noted above, if a submission is not deemed to be necessary, any changes made to the device must appear in the MDR after appropriate change control measures have been taken and must also be placed in the DHF.

Exemptions

Most Class I devices—and occasionally some Class II devices—are exempt from premarket notification requirements. These devices are subject to the limitations on exemptions; however they are not exempt from general controls. All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be appropriately packaged and be properly labeled. The establishment needs to be registered and the device listed with FDA. Establishment registrations and listings are in the public domain.

Additionally, some Class I devices are exempt from

GMP requirements, with the exception of complaint files and general recordkeeping requirements.

Class I/II Devices Exempt from 510(k) and Class I Devices Exempt from GMPs

Devices exempt from 510(k):

- preamendment devices not significantly changed or modified
- Class I/II devices specifically exempted by regulation

A "preamendment device" is one legally marketed in the US before 28 May 1976 that has not been significantly changed or modified and for which a regulation requiring a PMA application has not been published by FDA.

Devices meeting this description are referred to as "grandfathered" and do not require a 510(k).

The *FD&C Act* authorizes FDA to exempt certain generic types of Class I devices from the premarket notification requirement. FDA has exempted more than 800 generic types of Class I devices and 60 Class II devices from the premarket notification requirement. Exemptions occur on a periodic basis and are published in the *Federal Register*. The 510(k) exemption has certain limitations. Before deciding that a device is exempt, the sponsor must determine the device's classification status and limitations.

A premarket notification application and FDA clearance are not required before marketing the device in the US if a sponsor's device falls into a generic category of exempted Class I devices.

Even though a 510(k) may not be required, it is necessary to meet other requirements for marketing, which include:

- registration
- listing
- labeling
- GMPs

PMA Content and Format

The information required in a PMA is detailed in 21 CFR 814.20(b). In addition to voluntary completion of the applicable sections of a cover sheet, other required information includes:

1. table of contents showing the volume and page number for each item
2. summary of information in the submission, including:
   a. general description of the indications for use
   b. explanation of how the device functions, the scientific concepts upon which the device is based, general physical and performance characteristics, and a brief description of the manufacturing process, if it aids understanding
   c. generic, proprietary and trade name of the device
   d. description of existing alternative practices and procedures for which the device is intended
   e. brief description of the device's foreign and US marketing history by the applicant and/or any other person, including a list of the countries in which it has been marketed and from which marketing was withdrawn because of adverse safety and effectiveness experiences
   f. summary of studies and reports submitted with the PMA, including:
      i. nonclinical laboratory studies
      ii. human clinical investigations, other data, information or reports relevant to an evaluation of the device's safety and effectiveness from any source, known or that reasonably should be known to the applicant
      iii. discussion demonstrating that data and information in the submission constitute valid scientific evidence providing reasonable assurance of the device's safety and effectiveness, and conclusions drawn from the studies with a discussion of risk/benefit considerations and adverse effects
3. complete description of:
   a. device, including photos, drawings and schematics
   b. each functional component and/or ingredient
   c. device properties relative to its specific indications for use
   d. principles of operation
   e. methods, facilities and controls used to manufacture, process, package, store and, if appropriate, install the device
4. references to any performance standard in effect or proposed at the time of submission and any voluntary standard relevant to the device's safety or effectiveness, including adequate information to demonstrate compliance with the applicable standards and an explanation of any deviation from the standards
5. technical sections containing data and information in sufficient detail to enable approval or disapproval of the application, including results of:
   a. nonclinical laboratory studies in a separate section, including a statement that each study was conducted in accordance with Good Laboratory Practices (21 CFR 58)
   b. human clinical investigations in a separate section, including a statement that each study was conducted in accordance with IRB rules (21 CFR 56), informed consent rules (21 CFR 50) and IDE rules (21 CFR 812)
6. bibliography of all published reports that are known or reasonably should be known concerning the device's safety or effectiveness not submitted under number 5 above:
   a. identification, analysis and discussion of any

other data, information and reports relevant to the evaluation of the device's safety and effectiveness from any source that are known or reasonably should be known

b. copies of all reasonably obtainable published and unpublished reports described in 3d and 3e, if requested by FDA or an FDA advisory committee

7. samples of the device and its components, if requested by FDA, submitted or available at a named location if impractical to submit
8. copies of all proposed labeling including labels, instructions for use, installation, maintenance and servicing, and any information, literature and/or advertising that constitutes labeling (Section 201(m) of the *FD&C Act* and 21 CFR 801 or 809)
9. environmental assessment in accordance with 21 CFR 25.20(n) or justification for categorical exclusion under 21 CFR 25.30 and 25.34
10. disclosure of any financial arrangements between the sponsor and clinical investigators who performed studies included in the submission, or a certification on FDA Form 3454 attesting to the absence of any financial arrangements (21 CFR 54)
11. any other information requested by FDA

Omission of any required information must be identified and justified in a statement attached as a separate section of the PMA. A DMF or other applicable information in FDA files may be incorporated by reference. However, if this information was not submitted by the PMA applicant, it must receive permission from the filer of the information for it to be reviewed by FDA.

The sponsor is required to periodically update a pending PMA with new or newly learned safety and effectiveness information that could reasonably affect the device's evaluation and labeling (21 CFR 814.20(e)). To ensure adherence to all content and format requirements, manufacturers should carefully review the regulations in 21 CFR 814.20(a)–(h), as well as FDA's guideline on the arrangement and format of a PMA

The PMA Supplement

When a significant change to the device approved under a PMA affects the device's safety or effectiveness, a supplement to the original PMA is required. This became law when the *FD&C Act* was amended by Section 515(d)(6).

PMA supplements that are required include:

- " new indication for use of the device;
- labeling changes;
- the use of a different facility or establishment to manufacture, process, sterilize, or package the device;
- changes in manufacturing facilities, methods, or quality control procedures;
- changes in sterilization procedures;
- changes in packaging;
- changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device; and
- extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. [If the protocol has been previously approved by FDA, a supplement is not submitted but the change must be reported to FDA in the postapproval periodic reports as described in the §814.39(b).]"[7]

There are several ways of filing a PMA supplement:

PMA Supplement (180 days)—814.39(a)

This is for significant changes that affect the device's safety and effectiveness and will require an in-depth review and approval by FDA before implementing the change. This may also need an advisory panel review.

Special PMA Supplement—Changes Being Effected (CBE)—814.39(d)

The CBE is generally used when the change enhances or increases the device's safety. It does not require FDA approval before making the change. Examples are labeling changes that add more revelant information and increase quality control testing.

30-day Notice and 135 PMA Supplement—814.39(f)

This is used for modifications to manufacturing procedures or methods that affect the device's safety and effectiveness. If FDA does not respond within 30 days after notification, the change can be made to the device and it can be marketed accordingly.

PMA Manufacturing Site Change Supplement

When the manufacturing site is changed, a supplement needs to be filed. The site must have received a Quality System/GMP inspection within the last two years. If requirements are not met, a 180-day PMA Supplement must be submitted.

Changes can also be reported in the Annual Report instead of a formal supplement. However, to use this approach, one should seek an advisory opinion from FDA. Supplements that are pending can also be amended with more information.

The Investigational Device Exemption (IDE)

The IDE regulations are found in 21 CFR 812. The intent of the IDE regulations is to establish the safety and efficacy of significant risk devices. A "significant risk device" is defined in 21 CFR 812.3(m) as:

- intended as an implant and poses a serious risk to patient health
- purported or represented to be of use in supporting or sustaining life and presents a serious risk to patient health
- of substantial importance for diagnosing, curing, mitigating or treating disease or preventing impairment of health and poses a serious risk to patient health
- otherwise presents a potential for serious risk to patient health

Filing an IDE and its components is similar to filing an Investigational New Drug Application.[8] Both give FDA an opportunity to review background information, such as animal testing, bench testing and the clinical protocol, to determine whether the product is safe for testing in humans and whether efficacy can be shown based upon the protocol requirements.

> Quoting the regulations:
> "An IDE approved under 812.30 or considered approved under 812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) except for the requirements found in 820.30, if applicable (unless the sponsor states an intention to comply with these requirements under 812.20(b)(3) or 812.140(b)(4)(v)) and color additive requirements under section 721."

Many devices, considered to have approved applications, are exempt from the IDE requirements. These include nonsignificant risk devices, basically devices in commercial distribution prior to 28 May 1976, a device, other than a transitional device, "introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence." In addition a diagnostic device that is noninvasive, a device for veterinary use, research on animals, and a custom device unless it is being used to establish safety and efficacy for commercial distribution are also exempt. Note that a "transitional device" is one that FDA considered to be a new drug before 28 May 1976.

The IDE consists of the following:

1. sponsor name and address
2. a complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in 812.25(a) through (e) or, in lieu of the summary, the complete plan; a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate or if FDA requests them
3. a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage and, where appropriate, installation of the device, in sufficient detail that a person generally familiar with Good Manufacturing Practices can make a knowledgeable judgment about the quality control used in the manufacture of the device
4. an example of the agreements to be entered into by all investigators to comply with investigator obligations, and a list of the names and addresses of all investigators who have signed the agreement
5. a certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all who are participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement
6. a list of the name, address and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB
7. name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with the regulations
8. if the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device; the submitter will also need to demonstrate cost recovery if sale is approved
9. a claim for categorical exclusion under 21 CFR 25.30 or 25.34 or an environmental assessment under 25.40
10. copies of all device labeling
11. copies of all forms and informational materials to be provided to subjects to obtain informed consent
12. any other relevant information FDA requests for review of the application
    a. additional information—FDA may request additional information concerning an investigation or revision in the investigational plan. This constitutes a clinical hold. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing.
    b. information previously submitted—information previously submitted to CDRH need not be resubmitted, but may be incorporated by reference.

Of critical importance is that FDA requires a risk analysis under 21 CFR 812.25 Investigational Plan. This is a description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex and condition.

The Pre-IDE Meeting

Prior to the submission of an IDE—although not required—it is suggested that the sponsor meet with FDA to determine first whether sufficient information is available to submit the IDE and second to alert FDA about the program and device. The meeting serves to inform FDA about the program. FDA may furnish information based upon its experience with similar products.

To request an FDA meeting, the following format should be followed, based upon the guidance entitled, *Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products* (February 2000).

1. product name and application number
2. device name
3. proposed indications(s) or intended use
4. type of meeting being requested (A, B, C)
5. brief statement of the meeting purpose
6. list of specific objectives/outcomes expected from the meeting
7. preliminary proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s)
8. draft list of specific questions, grouped by discipline
9. list of all individuals (including titles) who will attend the proposed meeting from the sponsor's or applicant's organization and consultants
10. list of agency staff requested by the sponsor or applicant to participate in the proposed meeting (If a sponsor or applicant is not sure which agency officials should attend the meeting, the specific individuals do not need to be included in the request, but requested disciplines, if known, should be.)
11. approximate date on which supporting documentation will be sent to the review division
12. suggested meeting dates and times (i.e., morning or afternoon)

It is important to establish a good working relationship with the FDA project officer. Any need for questioning the minutes and obtaining clarification of ideas and suggestions may be expedited by the project officer.

Supplemental Applications

Supplemental Applications are required for changes in the investigational plan. Changes that require prior approval also include an exception to informed consent, in which case a a separate IDE is required. The same changes also require IRB notification.

Institutional Review Board (IRB) Approval

FDA makes it very clear in 21 CFR 812.42 that IRB approval is necessary before an investigation begins. For further information on IRB regulations and consent forms, see 21 CFR 50 and 56, respectively.

Device Reclassification

The rules and procedures for establishing a device's classification and requesting a change in device classification are contained in 21 CFR 860. A primary advantage of reclassification from a PMA to a 510(k) route to marketing is the reduction of the fee required by FDA to review the submission. In Fiscal 2009, the PMA review fee was more than $200,000, while the 510(k) processing fee was approximately $3,700.

Since 1976, the primary reclassification activity has been geared toward downclassifying Class III devices into Class II or I. Generating reclassification data requires considerable effort and resources, although if one is successful in this course of action, the reclassified device and any substantially equivalent device can be cleared for marketing through the less-burdensome 510(k) process.

Special controls did not exist prior to the 1976 amendments, and Class II devices were defined only by performance standards. Under the 1976 amendments, reclassification to Class II was dependent upon whether a performance standard could, in all probability, assure a device's safety and effectiveness.

It was the intent of Congress that reclassification play a potentially significant role in the medical device clearance process, although CDRH's interpretation of its mandate has not permitted the reclassification process from being meaningfully utilized. The primary obstacle has been the high level of scientific information that CDRH requires to support a device's reclassification.

The Product Development Protocol (PDP)

The PDP was authorized several years ago as an alternative to the IDE and PMA in *FD&C Act* Section 515(f). For Class III devices subject to premarket approval, the successful completion of a PDP results in market clearance and essentially is a PMA approval.

One intent of the *Medical Device Amendments* of 1976 was to create an alternate pathway for device approval and marketing by having the sponsor and FDA agree early in the development process on items needed for successful completion of the safety and efficacy analysis of the Class III device.

Once agreement is reached, the PDP contains all the information about design and development activities and acceptance criteria. A project timeline is established and information is furnished to FDA to review in a sequential fashion.

The PDP consists of:

- a description of the device and any changes that may be made to the device
- a description of the preclinical trials, if any
- a description of the clinical trials, if any
- a description of the manufacturing methods, facilities and controls
- a description of any applicable performance standards
- specimens of proposed labeling
- any other information "relevant to the subject matter of the protocol"

Upon completion of clinical studies, reports are furnished to FDA, which has 120 days to act on a PDP. Currently, the PDP approach to approval is sparsely employed.

Combination Products

Until 1990 and the *Safe Medical Devices Act*, there was no formal process to establish which FDA center would regulate combination products consisting of drugs or biologics and devices.

Regulations have now established that FDA makes a determination about the primary mode of action of the combination product. By making this determination, the agency in effect decides if the item is a drug, device or biologic. Then, FDA determines which center ((Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) or CDRH)) is the primary reviewer. However, representatives of the other appropriate centers will be on the review committee.

If it is not clear whether the combination product is a device or drug, the manufacturer may file a Request for Designation with FDA. This compels the agency to classify the combination product and indicate which center which will be the primary review group. The agency must respond within 60 days.

For more information, see "Chapter 25 Combination Products."

Medical Device Reporting (MDR)

The MDR requirements are another mechanism to ensure a device's safety. It is a postmarket control that refers to Classes I through III. Manufacturers, importers and user facilities must inform FDA (and/or sponsors) of any adverse events associated with marketed devices. This does not apply to devices in clinical studies that have not been approved or cleared by FDA. Adverse events are reported in the appropriate filing and/or the IDE Annual Report and to the IRB.

There are three types of reports: five-day and 30-day reports for manufacturers and 10-day reports for importers and user facilities. While these reports contain essentially the same information and are, in fact, submitted on the same forms, it is important to note that manufacturers, importers and user facilities face different reporting obligations.

Manufacturers are defined as:

"....[A]ny person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedure. The term includes any person who: (1) repackages or otherwise changes the container, wrapper or labeling of a device in furtherance of the distribution of the device from the original place of manufacture; (2) initiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specification; (3) manufactures components or accessories which are devices that are ready to be used and are intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient."

Under the MDR regulations, only certain adverse events are reportable. These are

1. when a device may have caused or contributed to a death or serious injury
2. when a device has malfunctioned and when that device or a similar one marketed by the manufacturer would be reasonably likely to cause or contribute to a death or serious injury if the malfunction were to recur

Serious injury as an injury or illness that:

- is life-threatening
- results in permanent impairment of a body function or permanent damage to a body structure
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

A malfunction is defined as:

"....[t]he failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed....".

Therefore the manufacturer must determine whether it is reportable. Generally, if the question about reportability arises, the incident it should be reported.

As guidance, FDA indicates that a device malfunction is considered reportable if any of the following is true:

- the likelihood of the recurrence of the device malfunction causing the event is not remote or minute
- the malfunction affects the device in a catastrophic manner that may lead to a death or serious injury
- the malfunction causes the device to fail to perform its essential function and compromises its therapeutic, monitoring or diagnostic effectiveness, which could cause or contribute to a death or serious injury

- the device is a long-term implant or a device that is considered to be lifesupporting or life-sustaining
- the manufacturer takes or would be required to take action to reduce a risk to health as a result of the malfunction
- a malfunction of the same type has actually caused or contributed to a death or serious injury in the past

Importers face the same reporting timeframes as user facilities. Under the MDR regulations, importers must file reports as soon as practicable, but not later than 10 working days after becoming aware of an MDR-reportable event.

A user facility is defined as:

"...a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility ... which is not a 'physician's office'.... School nurse offices and employee health units are not device user facilities."

It appears that MDRs may be underreported from user facilities because of the possibility of malpractice litigation. This situation has not been addressed.

Device Exports

Export requirements and procedures are explained in the *FDA Export Reform and Enhancement Act* of 1996. The regulations for exporting unapproved human drugs, biological products and devices were simplified. Where FDA-cleared or -approved devices are concerned, no notification for export is required by FDA.

Export Procedures for Unapproved Devices

The following information is taken directly from the FDA website describing the requirements for exporting unapproved devices.

Exporting Medical Devices Via Section 801(e)(1) *Requirements*

A medical device which would be considered to be adulterated or misbranded, may be exported under Section 801(e)(1) of the *FD&C Act* provided the device is intended solely for export. Although such a device would not meet the requirements of the *FD&C Act* to be sold domestically for commercial distribution, it may be exported legally and without FDA permission in accord with Section 801(e)(1) provided the device is:

- in accordance with the specifications of the foreign purchaser;
- not in conflict with the laws of the country to which it is intended for export;
- labeled on the outside of the shipping package that it is intended for export; and
- not sold or offered for sale in domestic commerce.

Once an adulterated or misbranded device is sold or offered for sale in commercial distribution in the US., it may not be exported under Section 801(e)(1) as an alternative to bringing the device into compliance with the requirements of the Act. Devices that have been imported are considered to be in domestic commerce.

Unapproved Devices due to Lack of 510(k) Marketing Clearance

The FDA is aware that in certain instances there may be devices which firms may wish to manufacture solely for export, or which they may wish to export during the interim period while their Premarket Notification 510(k) is under review. FDA allows the export of a device that does not have a 510(k) marketing clearance without prior FDA clearance if it meets two conditions:

- the device meets the requirements of 801(e)(1) listed above, and
- it is reasonably believed that the device could obtain 510(k) marketing clearance in the US if reviewed by FDA.

This includes only devices which are similar in design, construction, and intended use to class I or class II devices or which the firm reasonably believes would be "substantially equivalent" to class I or class II devices. Devices which would not be included under this consideration are:

- Preenactment class III devices for which FDA has called for the submission of a PMA
- Postenactment class III devices, i.e. placed on the market after May 28, 1976, or
- Devices evaluated by a firm and found to be *not substantially equivalen*t to a 510(k)'d device.

Recordkeeping Requirements

Persons exporting an article under section 801(e)(1) of the act or an article otherwise subject to section 801(e)(1) of the act must maintain records demonstrating that the product meets the requirements of section 801(e)(1) of the act. These records must be maintained for the same period of time as required for records subject to good manufacturing practice or quality systems regulations applicable to the product. That is, all records must be retained for a period of time equivalent to the design and expected life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer (21 CFR 820.180). The records must be made available to the Food and Drug Administration (FDA), upon request, during an inspection for review and copying by FDA. The records required to be maintained under 21 CFR 1.101.

Exporting Medical Devices via Section 802 *Requirements*

Unapproved Class III devices and devices required to meet a performance standard under section 514 of the *FD&C Act* may be exported under section 802 if the firm and the device meets certain criteria. These devices

include investigational devices, unapproved devices which would not be able to obtain a PMA (or for which a PMA has not been approved), and banned devices. (At the present time synthetic hair fibers intended for implant is the only banned medical device.) In order to qualify for export under 802, devices must meet the requirements under 801(e)(1) and pass the restrictions set forth in 802(f).

That is, the devices must:

- meet the requirements of section 801(e)(1). The device is
- in accordance with the specifications of the foreign purchaser;
- not in conflict with the laws of the country to which it is intended for export;
- labeled on the outside of the shipping package that it is intended for export; and
- not sold or offered for sale in domestic commerce.
- substantially meet Quality Systems Regulation (also known as Good Manufacturing Practices) or an international quality standard recognized by FDA (currently, none are recognized),
- not be adulterated other than by the lack of marketing approval,
- not be the subject of a notice by Department of Health and Human Services that re-importation would pose an imminent hazard, nor pose an imminent hazard to the receiving country, and
- not be mislabeled other than by possessing the language, units of measure, or any other labeling authorized by the recipient country. In addition, the labeling must comply with the requirements and conditions of use in the listed country which gave marketing authorization, and must be promoted in accordance with its labeling.

In addition to the requirements above, the device must comply with the laws of the receiving country and have valid marketing authorization by the appropriate authority in a listed (Tier 1) country. This means that a firm whose device has received marketing authorization in any of the Tier 1 countries can export that device to any country in the world as long as the device meets applicable requirements of the *FD&C Act* and the marketing authorization by the Tier 1 country is acceptable to the appropriate authorities in the importing country. Some South American countries, for example, now permit marketing of any medical device with a CE mark. If the appropriate authorities of a non-Tier 1 country will not accept the marketing authorization of a Tier 1 country, you can obtain an export permit under section 801(e)(2).

The complete requirements of Section 802 can be found in the *FD&C Act* and a detailed discussion is contained in the February 1998 *FDA Guidance Document.*

The intent of *FDERA* was to expedite the export of products which do not comply with US law, but which are in compliance with the laws of foreign countries. The primary advantage to exporting under section 802 instead of 801(e)(2) is that approval from FDA, i.e. submitting a request for and obtaining an Export Permit is not necessary in order to export. The exporter must submit a "Simple Notification" as per section 802(g) to FDA when the firm begins to export. No approval from FDA is required.

If the firm or device does not comply with the above criteria, the device cannot be exported under section 802. However, the device may qualify for exportation under section 801(e)(2).

Listed (Tier 1) Countries

The listed (or "Tier 1") countries are: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, a member of the European Union (United Kingdom, Spain, Ireland, Denmark, Greece, Belgium, Portugal, Germany, France, Italy, Luxembourg, Netherlands, Sweden, Finland, and Austria), or the European Economic Area (includes the European Union countries and Norway, Iceland, and Liechtenstein). As of May 2004, the European Union also includes Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia.

Simple Notification

Persons exporting a device under section 802 of the act must provide written notification to FDA. The notification must identify:

- The product's trade name;
- The type of device;
- The product's model number; and
- The country that is to receive the exported article if the export is to a country not listed (non-tier 1 country). The notification may, but is not required to, identify the listed (tier 1) countries or may state that the export is intended for a listed (tier 1) country without identifying the listed country.

In addition for unapproved or cleared devices, the FDA may issue a Certificate of Exportability to the importing country if required. The certificate states

"Under Section 802 of the Act, a drug or device not approved for marketing in the United States may be exported if it is manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practice requirements. The manufacturing plant(s) in which the product(s) is produced is subject to periodic inspections. The last such inspection showed that the plant(s), at that time, appeared to be in substantial compliance with current good manufacturing practice requirements for the product(s) listed below. The company has certified to the Food and Drug Administration that:

- The product(s) accords to the specifications of the foreign purchaser;

- The product(s) is not in conflict with the laws of the country to which it is intended for export;
- The shipping package for the product(s) is labeled on the outside that it is intended for export; and
- The product(s) is not sold or offered for sale in the United States.

Based on the information above, the product(s) listed below may be exported pursuant to Section 802 of the Act."

Much more information on exporting devices is available that is beyond the scope of this review. Readers are referred to the FDA *Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996*.

Summary

- FDA regulations for devices comprise sets of rules that classify devices that require agency clearance or approval. Devices may be classified into Class I, II or III or de novo. Classes I, II and de novo may require clearance or exemption and Class III devices require a Premarket Approval Application.
- Regulations for labeling and advertising of devices have been enhanced.
- Clinical studies for significant risk devices require an Investigational Device Exemption.
- Medical Device Reporting is highly regulated and is particularly significant for the manufacturer and end user.
- In 1996, FDA made exporting of devices less onerous through the *Export Reform and Enhancement Act*.

References

1. Content of a 510(k) www.fda.gov/cdrh/devadvice/314312.html.
2. *Federal Register* (56 Fed. Reg. 46,191).
3. 21 CFR 202.1(l)(1).
4. 21 CFR 801.6.
5. 21 CFR 807.39.
6. 21 CFR 807.97.
7. www.fda.gov/cdrh/advice/pma/supplement.html.
8. 21 CFR 312.

Recommended Reading

- Kahan JS. *Medical Device Development: A Regulatory Overview*. Parexel International Corporation, Waltham, MA (2000).
- Food and Drug Administration. Labeling: Regulatory Requirements for Medical Devices. HHS Publication FDA 89-4203 (August 1989).
- *Medical Device Amendments* of 1976 (Pub. L. No. 94-295)
- Trautman KA. *The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices*. ASQ Quality Press, Milwaukee, WI (1997).

Review Questions

1. True or False—A special control for a medical device may be used for Class III devices.

2. True or False—Many Class I devices are exempt from premarket approval.

3. A device modification always requires either a 510(k) or a PMA filing.

4. Post marketing activities can be considered as special controls.

5. Which item is generally not required for a 510(k) submission?
   a. Labeling
   b. Quality Control Specifications
   c. Predicate device information
   d. Comparison information to the predicate device
   e. None of the above

6. An IDE must be filed for all clinical studies which support a PMA application.

Answers

1. True
2. False
3. False
4. True
5. b
6. False