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Overview of the Legal Framework for Medical Device Regulation in the United States

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This chapter provides an overview of the legal framework for medical device regulation in the United States. This chapter discusses the definition of a medical device and provides a high-level overview of the risk-based regulatory approach embodied in the Federal Food, Drug, and Cosmetic Act (FDCA). Detailed discussions of the Food and Drug Administration (FDA or “Agency”) premarket review processes and postmarket requirements are provided in subsequent chapters. The subsequent chapters also discuss device regulation in the European Union, and the roles that federal and state entities other than FDA play in the regulation of medical devices.

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Regulatory Basics

Statutory Framework

Q 1.1 What law regulates medical devices?

Medical devices are regulated under the FDCA.¹ The basic statutory framework governing the premarket review, testing, manufacturing, and marketing of medical devices was established by the Medical Device Amendments of 1976 (the 1976 Amendments).²

Q 1.2 How did medical device regulation develop?

When the FDCA was enacted in 1938, it required premarket review of drugs but not medical devices. Devices were regulated under the FDCA's provisions prohibiting "adulteration" and "misbranding" (false or misleading labeling) of products. The principal focus of the Food and Drug Administration (FDA) was on enforcement actions against dangerous, fraudulent, and "quack" devices that were being marketed in the 1930s through 1950s. In the late 1950s and early 1960s, medical devices became more complex and sophisticated with the scientific breakthroughs in electronics, plastics, and engineering. These new devices had great potential to save and improve lives, but they also heightened FDA concerns about the potential for harm to patients.

Congress began to consider new device legislation in the 1960s. Congress amended the FDCA with the Drug Amendments of 1962 to require premarket approval of "new drugs" for safety and effectiveness, but medical devices were not included in those amendments. The Department of Health, Education, and Welfare (DHEW) established a Study Group on Medical Devices (known as "the Cooper Committee") that spent years studying medical devices and considering the best regulatory approach to apply to them. The Cooper Committee issued its report in September 1970.

The Radiation Control for Health and Safety Act of 1968 established regulatory requirements applicable to radiation-emitting electronic products, some of which included medical devices such as X-ray machines.

The Medical Device Amendments of 1976 established the basic regulatory framework that is still applicable to medical devices today. Its provisions included, among others, premarket review and approval of medical devices, a risk-based classification scheme, good manufacturing practice requirements, adverse event reporting, and requirements applicable to investigational device studies.

The statute has been amended from time to time, including amendments by the Safe Medical Devices Act of 1990 (the 1990 Act),³ the Medical Device Amendments of 1992 (the 1992 Amendments),⁴ the Food and Drug Administration Modernization Act of 1997 (FDAMA),⁵ the Medical Device User Fee and Modernization Act of 2002 (MDUFMA),⁶

the Food and Drug Administration Amendments Act of 2007 (FDAAA),⁷ and the Food and Drug Administration Safety and Innovation Act (FDASIA),⁸ enacted in July 2012. These amendments have enhanced FDA's postmarket authority over devices, incorporated a "least burdensome" principle for review of device submissions, imposed user fees and premarket submission review guidelines, required clinical trials registration and result reporting, and more.

Q 1.3 What kinds of regulatory requirements apply to medical devices?

The basic regulatory requirements include registration of medical device manufacturers' and distributors' establishments, listing of medical devices distributed in the United States, and premarket review by FDA prior to introducing medical devices into commercial distribution in the United States.

Postmarket requirements include reporting adverse events and device malfunctions (MDR reporting), device tracking, and postmarket surveillance. Medical devices must be manufactured in accordance with FDA's Quality System Regulations (QSRs), which govern design control and validation, and good manufacturing practices (GMPs). Devices may also be subject to performance standards, restrictions on sale, distribution and use, and other controls. The FDCA includes statutory penalties for violations of the law.

This description of the requirements is broad and general, however, and there are many other important details of the statute and regulations.

Definitions and Classifications

Q 1.4 What is a medical device?

Section 201(h) of the FDCA defines a medical device as follows:

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.

There are several key points regarding this definition.

First, a medical device is usually considered to be an instrument, machine, tool, or other similar article. However, it can also include in vitro reagents and other types of products in gel or liquid form.

Second, a device does not achieve its primary intended purpose through chemical action within or on the body, and does not depend on being metabolized.

Third, a medical device is intended for use in the diagnosis of disease or other conditions, or in the treatment or prevention of disease; or it is intended to affect a structure or function of the body.

Finally, the device definition includes an accessory to a device (for example, contact lens solution).

Q 1.5 How do I know whether my product is regulated as a “medical device”?

The definition of “device” is complex and leads to many discussions about the products that are included in the definition.

A major determinant of “device” status is the manufacturer’s intent. The manufacturer’s claims for a product establish the “intended use,” and the same product could be a device or not a device depending upon the claims that are made for it by the manufacturer. For example, exercise equipment intended for maintaining good health would not be a device, while the same equipment with claims for cardiac rehabilitation of heart surgery patients would be a device. As another example, a device for the ear that is claimed to be a sound amplifier to enhance a hunter’s normal hearing to better hear the prey would not be a device, while a hearing aid claimed to help the hearing impaired would be a device.

Q 1.6 How are devices regulated under the statutory framework?

The FDCA establishes a risk-based regulatory framework for medical devices. Under section 513 of the FDCA,⁹ devices are classified according to their level of risk. Class I devices present the least risk and are subject to the act's general controls. Class II devices are subject to both general controls and special controls. Class III devices, such as implants and life-sustaining devices, are subject to the most stringent controls, including premarket approval by FDA.

Q 1.7 What are the premarket requirements for medical devices?

The basic framework for premarket review of medical devices was established in 1976 by the Medical Device Amendments. At that time, many devices were already being marketed. The pathway by which a post-1976 medical device may come to market depends on its risk classification and other factors.

First, almost all Class I devices, and certain Class II devices, are exempt from premarket review.

Second, most Class II devices (and some Class I devices) may be marketed only after FDA clearance of a premarket notification under section 510(k) of the act. This pathway requires that the device be "substantially equivalent" to a "predicate device." A predicate device is a similar product that was first marketed before May 28, 1976 (the date of enactment of the 1976 Amendments), or that was marketed after this date and found by FDA to be substantially equivalent to a legally marketed device previously cleared through a 510(k) notification. Most devices are marketed under this section 510(k) pathway, and the premarket submission is referred to as a "510(k) notification."

Third, Class III devices, including a device that is not substantially equivalent to a predicate device, may not be marketed until: (1) the device has been tested for safety and effectiveness; (2) a premarket approval application (PMA) has been submitted to FDA; and (3) FDA has approved the PMA as demonstrating reasonable assurance that the device is safe and effective for its intended use. FDA can impose conditions of approval on a PMA device, including post-approval study requirements and restrictions on sale, distribution, or use.

Amendments to section 513(f)(2) of the statute in 2007 and 2012 established the de novo classification process. A device for which no legally marketed predicate device exists is automatically classified as Class III. In such a situation, a manufacturer of a low to moderate risk device can submit a de novo request for evaluation of the automatic Class III designation, asking FDA to make a risk-based classification of the device to Class II or Class I. When FDA approves a de novo submission, that device becomes a predicate device for subsequent devices of similar type. Another reclassification pathway is a petition for reclassification, under which a manufacturer can petition to reclassify a Class III device to Class II or Class I.

Clinical testing of safety and effectiveness in humans must be conducted under an “investigational device exemption” (IDE) for “significant risk devices,” or under abbreviated IDE requirements for “non-significant risk devices.”

Q 1.8 What are the key differences between the 510(k) premarket notification and the premarket approval procedures?

The PMA procedure is lengthy and difficult. Testing for safety and effectiveness may take months or years. FDA may take six months to a year (or longer) to review and make a decision on a PMA once it is submitted.

In contrast, a 510(k) notification can be cleared by FDA in ninety days (although it often takes about six months). For these reasons, medical device manufacturers use the 510(k) notification procedure instead of the PMA procedure when possible.

Establishment Registration and Device Listing

Q 1.9 How does FDA know what devices are being marketed in the United States?

Sections 510(b) and 510(c) of the FDCA require a device manufacturer to *register* its establishments. Section 510(j) requires a manufacturer periodically to submit a *list* of its devices to FDA.

The definition of “manufacture” is very broad. As defined in section 510(a)(1) of the act:

[T]he term “manufacture, preparation, propagation, compounding, or processing” shall include repackaging or otherwise changing the container, wrapper, or labeling of any . . . device package in furtherance of the distribution of the . . . device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.

Under this definition, for example, a company is a manufacturer of a device if it repackages the device or changes the wrapper or labeling of the package.

Q 1.10 What are the establishment registration requirements?

Any person “who owns or operates any establishment . . . engaged in the manufacture, preparation, propagation, compounding, or processing” of a device must register its establishment with FDA.¹⁰ The company must register its name, places of business, and all establishments it controls upon first engaging in the activity and annually between October 1 and December 31.¹¹ Registration generally must be accomplished through electronic means, using FDA’s Unified Registration and Listing System (FURLS).¹² Establishments must pay an annual registration fee.¹³ Failure to pay this fee will render registration incomplete.¹⁴

Q 1.11 What are the device listing requirements?

A company must submit a listing of all its devices that are in commercial distribution.¹⁵ The device listing generally must be submitted electronically using FURLS,¹⁶ and must be updated between October 1 and December 31 of each year when a change occurs.¹⁷

Q 1.12 Who is required to register and list?

Under section 807.20(a) of FDA’s regulations, the establishment registration and device listing requirements pertain to any person who:

- initiates or develops specifications for a device that is to be manufactured by a second party;
- manufactures a device either for itself or for another person;
- repackages or relabels a device;

- initially imports a device into the United States; or
- manufactures components or accessories that are ready to be used for a health-related purpose and are packaged or labeled for commercial distribution for that health-related purpose.

Registration and listing requirements do *not* apply to a person who:

- manufactures a component that is distributed only to a finished device manufacturer; or
- acts as a wholesale distributor and does not manufacture, repackage, process, or relabel a device.

Q 1.13 What device listing requirements apply to importers of a device?

The initial importer of a device into the United States has the following device listing obligations:

- If the initial importer also developed the specifications for the device that it imports, it must submit a device listing to FDA and update the information annually between October 1 and December 31 when changes occur.
- If the initial importer repackages or relabels the imported device, it must submit a device listing form and similarly update the information.
- If the initial importer did not initiate or develop the specifications for the device and does not repackage or relabel the device, it is not required to submit a device listing. However, the initial importer must submit, for each device it imports, the name and address of the foreign manufacturer. An initial importer must also be prepared to submit, when requested by FDA, the proprietary name, if any, and the common or usual name of each device for which it is the initial importer.¹⁸

Q 1.14 What information is required under the device listing regulations?

When device listing information is submitted to FDA, it must include the information specified in 21 C.F.R. § 807.25(g). This includes, among other things: FDA classification name and number of the

device, its proprietary name (trade name), and its common or usual name (generic name).¹⁹ The listing must also include the name, FDA registration number, and establishment type of every U.S. or foreign device establishment under joint ownership and control of the owner or operator at which the device is manufactured, repackaged, or relabeled.²⁰

The company that submits a device listing must maintain a historical file containing the labeling and advertisements for the device.²¹ The file must contain the labeling and advertisements in effect at the time of the initial device listing, as well as any labeling or advertisements in which a material change has been made after the initial listing.²² Listing information may be submitted by the parent, subsidiary, or affiliate company for all the domestic or foreign establishments that are under the control of the parent, subsidiary, or affiliate, provided there exists joint ownership and control among all the establishments.²³

Q 1.15 Do the device establishment registration and device listing requirements apply to foreign manufacturers?

Section 510(i) of the FDCA requires any foreign establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a device that is imported or offered for import into the United States to register electronically with FDA upon first engaging in such activity and annually between October 1 and December 31.²⁴

These establishments also must list the devices and designate a U.S. agent.²⁵ The establishment registration and U.S.-agent designation requirements were added to the FDCA in 1997, and FDA completed its rulemaking to implement the requirements in November 2001.²⁶

Premarket Requirements for Lawful Marketing of a Medical Device in the United States

Q 1.16 How can a manufacturer ensure that a medical device meets regulatory requirements to be marketed in the United States?

Class I devices can be marketed without premarket review by FDA, with some limited exceptions.²⁷ The manufacturer must comply with general controls, including establishment registration, device listing, GMP (unless exempted), and recordkeeping and reporting.

Class II devices generally require FDA premarket review (with some exceptions). They must also comply with general controls and are potentially subject to special controls, such as a performance standard or guidance document.

Class III devices require FDA approval of a PMA, in addition to compliance with general controls and any post-approval requirements imposed by the PMA approval order.

The premarket review pathways include 510(k) notification, de novo submission, and PMA application.

510(k) Notification

Q 1.17 What is a 510(k) notification?

Pursuant to section 510(k) of the FDCA, a manufacturer proposing to market a medical device for the first time must submit a notification to FDA before it introduces the device into commercial distribution.

The 510(k) notification must contain proposed labeling and an explanation of how the device is substantially equivalent in intended use and technological characteristics to a predicate device.²⁸ The 510(k) notification must be submitted to FDA at least ninety days before the device will be marketed. FDA reviews the information in the 510(k) to determine whether the device proposed to be marketed is “substantially equivalent” to a predicate device.

Q 1.17.1 What does “substantially equivalent” mean?

To be “substantially equivalent” (SE) to a predicate device, the device must have the same “intended use” as the predicate. Use in a new or broader patient population is considered by FDA to be a new intended use. FDA has issued guidance specifying the principles the Agency will use in determining when a marketed device that is labeled for a general use cannot be the predicate device for a new device labeled with more specific claims.²⁹

In addition to having the same intended use, the device (1) must have the same technological characteristics as the predicate device, or (2) if it has different technological characteristics, must be demonstrated to be as safe and effective as the predicate device and must not raise different questions of safety and effectiveness than the predicate device raises.³⁰

When a device has different technological characteristics than the predicate device, FDA may request information that is “necessary” for it to make a substantial equivalence determination and that constitutes “the least burdensome means of demonstrating substantial equivalence.”³¹ FDA must also consider the extent to which reliance on postmarket controls may expedite clearance.³²

Q 1.17.2 What information must be included in a 510(k) notification?

A 510(k) notification must include all relevant information to establish that the device is substantially equivalent to the predicate device, including information on the performance characteristics, safety and effectiveness of the device. For some devices, clinical study data may be required in a 510(k) notification.

A 510(k) notification must also include either (1) a “510(k) Summary,” which is a brief summary of the information establishing substantial equivalence and the performance of the device, or (2) a “510(k) Certification” stating that the 510(k) notification will be made available upon request.³³ Any summary submitted with a 510(k) notification will be made available to the public by FDA within thirty days of a substantial equivalence determination.³⁴

Q 1.17.3 How long does it take to receive marketing clearance of a device under the 510(k) notification pathway?

FDA has ninety days in which to respond to a 510(k) notification.³⁵ FDA's response might be a request for additional information. FDA can issue a determination that the device is “substantially equivalent” (SE) or “not substantially equivalent” (NSE). Even if the Agency does not meet the statutory ninety-day deadline, however, a manufacturer must await FDA's determination.³⁶

Q 1.17.4 Can review of a 510(k) notification be expedited?

Priority review of a 510(k) notification may be available when a device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition and the device addresses an unmet medical need. The device must meet one of the following conditions: (1) the device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology; (2) no approved alternative exists; (3) the device offers significant clinically meaningful advantages over existing approved alternatives; or (4) the availability of the device is in the best interest of patients.³⁷

Q 1.17.5 What happens if FDA determines that the device is “not substantially equivalent”?

If FDA determines that a device is not substantially equivalent (NSE) to the proposed predicate, the device is automatically classified as a “Class III” device. The device would then require an approved PMA in order to be marketed.

Alternatively, after receiving an NSE determination, the 510(k) submitter has thirty days to request a review of the otherwise-automatic Class III classification of the device.³⁸ This process is intended to allow for de novo classification of low-risk devices that were determined to be NSE due to lack of a predicate device. Under statutory amendments enacted in the FDASIA, a manufacturer can submit a request for de novo classification without first submitting a 510(k) notification, where the manufacturer cannot identify a predicate device.³⁹ If a request for de novo review is submitted, FDA must classify the device within 120 days.⁴⁰

Q 1.17.6 What happens after FDA determines a device to be “substantially equivalent”?

After a substantial equivalence (SE) determination has been issued by FDA, the device may be marketed. The device must comply with Quality System Regulations and meet other applicable regulatory requirements. The SE determination is also referred to as a 510(k) clearance.

A device that is cleared under a 510(k) cannot be referred to as an “approved” device; use of the word “approved” is limited to devices marketed under an approved PMA.

FDA proposed a regulation specifying the grounds for rescission of a decision that a device is substantially equivalent to a legally marketed device and providing for administrative review of rescission orders.⁴¹ This regulation has not been finalized.

Q 1.17.7 How does FDA determine the “intended use” of a device?

FDA’s determination of intended use, for purposes of determining substantial equivalence, must be based upon the proposed labeling submitted in the 510(k) notification.⁴²

If, however, the Director of the Office of Device Evaluation (ODE) determines that there is a “reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling” and “such use could cause harm,” FDA can require an appropriate statement in the labeling concerning the off-label use, such as a warning or a contraindication.⁴³ FDA must provide an opportunity for consultation to the party that submitted the 510(k) notification.⁴⁴ Although FDA may specify labeling changes in this situation, it may not refuse to clear a device for marketing based on concerns about potential harm from an unlabeled use.⁴⁵

Q 1.17.8 Why are some Class III devices marketed under a 510(k) notification?

Certain pre-1976 devices were classified as Class III after enactment of the Medical Device Amendments of 1976, but they were allowed to remain on the market (for example, all pre-Amendments electroconvulsive therapy devices). Until FDA issues a regulation requiring PMAs for these devices, a 510(k) notification may be submitted

for new devices that are substantially equivalent to these pre-1976 Class III predicate devices. Once FDA promulgates a regulation triggering the PMA requirement, however, all devices within that type will require PMAs, regardless of whether they are pre- or post-Amendments devices. The statutory requirement for a regulation has been changed to an administrative order, and new provisions have been added regarding the reclassification process.⁴⁶

Q 1.17.9 Can a manufacturer make changes to its device after receiving 510(k) clearance?

If a manufacturer wishes to make substantial changes to its 510(k)-cleared device, a new 510(k) notification may be required.⁴⁷ Certain modifications can be made to a device without a new 510(k) submission, provided the changes are documented in a letter to file. An FDA guidance document describes the types of modifications that a manufacturer may make using the “letter to file” procedure.⁴⁸

If the device changes could affect the safety and effectiveness of the device and do not qualify for the letter to file procedure, a new 510(k) notification is required.

A manufacturer intending to modify its own legally marketed device may submit a “Special 510(k)” for the modified device.⁴⁹ The manufacturer must conduct the risk analysis and necessary verifications and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements.⁵⁰ The basic contents of a Special 510(k) are the same as those of a Traditional 510(k), but it also should include a “Declaration of Conformity” with design control requirements. One advantage of a Special 510(k) is that FDA will review it within thirty days of receipt.

Q 1.17.10 Are there other types of 510(k) notifications?

An “Abbreviated 510(k)” may be submitted for a device when: (1) an FDA guidance document exists; (2) a special control has been established; or (3) FDA has recognized a relevant consensus standard.⁵¹ An Abbreviated 510(k) must contain either a summary describing how the guidance document or special controls were used during device development and testing, or a declaration of conformity

to the consensus standard. A manufacturer submitting an Abbreviated 510(k) may use a third party to assess conformance with the recognized standard. FDA expects that its review of an Abbreviated 510(k) will be more expeditious than review of a Traditional 510(k), which would contain more data.

Premarket Approval Application (PMA)

Q 1.18 When is a PMA required?

If the manufacturer makes a determination that its device is not substantially equivalent to a predicate device, or if the device meets the definition of a Class III device, an approved premarket approval application (PMA) is required before the device can be lawfully marketed.

If FDA determines that a device is not substantially equivalent to a predicate device, the new device is automatically classified as a Class III device under section 513(f) of the FDCA. As such, the device cannot be marketed until FDA approves a PMA for it or reclassifies the device to Class II under the de novo reclassification procedure or otherwise.

Q 1.18.1 What if a manufacturer is uncertain whether a 510(k) or a PMA is required for its device?

In most cases, the manufacturer submits a 510(k) notification and learns after FDA review that FDA considers a PMA to be necessary.

If there is a question whether the device is new and requires a PMA, the manufacturer may ask FDA. This can be done informally in a meeting with the Agency. Alternatively, the manufacturer can submit a request for a formal opinion under section 513(g) of the FDCA about the classification of the device.

Q 1.18.2 What information is required in a PMA?

A PMA must contain a complete description of the device, each of its functional components, its principles of operation, manufacturing methods and controls, labeling and directions for use, and all publications containing data or information relevant to an evaluation of its safety or effectiveness.⁵² A PMA must contain detailed test data,

including clinical study data, demonstrating reasonable assurance of the product's safety and effectiveness.

FDA must “rely on the conditions of use included in the proposed labeling” as the basis for determining whether there is a reasonable assurance of safety and effectiveness, provided the proposed labeling is neither false nor misleading.⁵³ FDA must also consider whether the extent of the effectiveness data that otherwise would be required for approval of the PMA can be reduced through reliance on postmarket controls.⁵⁴

Under section 513(a) of the FDCA, FDA must meet with a prospective PMA applicant, if the applicant so chooses, prior to its submission of the PMA. The purpose of the meeting is to determine the type of clinical data that will be necessary to demonstrate the effectiveness of the device for its proposed conditions of use. Within thirty days after the meeting, FDA must specify in writing any clinical data necessary to provide a reasonable assurance of effectiveness. FDA must consider, in consultation with the applicant, “the least burdensome appropriate means” of evaluating device effectiveness that would have “a reasonable likelihood of resulting in approval.”⁵⁵ FDA's determination as to the necessary data binds the Agency, “unless such determination . . . could be contrary to the public health.”⁵⁶

Q 1.18.3 What if the PMA does not include all the required information?

FDA may refuse to file a PMA if any of the following applies: (1) the PMA does not on its face contain all of the information required under section 515(c)(1) of the FDCA; (2) it does not contain each of the items required under 21 C.F.R. § 814.20 and the justification for omission of any item is inadequate; (3) the applicant has a pending premarket notification under section 510(k) for the same device, and the Agency has not determined that the device is a Class III device subject to PMA requirements; (4) the PMA contains a false statement of material fact; or (5) the PMA is not accompanied by the financial disclosure statements required under 21 C.F.R. Part 54.⁵⁷ FDA has issued a guidance document clarifying the criteria that govern the Agency's decision to file a PMA.⁵⁸

Q 1.18.4 What is a “modular PMA”?

Under a policy announced in 1998, FDA allows applicants to submit the contents of a PMA on a rolling basis. This is called a “modular PMA.” FDA has issued guidance clarifying the expected content of each module and explaining the sequence and timing for their submission.⁵⁹ Congress codified the modular review approach in 2003.⁶⁰

Q 1.18.5 How long does it take to get approval of a PMA?

Section 515(d) of the FDCA provides that a PMA must be reviewed within 180 days. Prior to enactment of MDUFMA, FDA routinely exceeded that statutory time limit. When Congress enacted MDUFMA, the Secretary of Health and Human Services identified specific performance goals for PMA review in Fiscal Years 2003–07.⁶¹ Performance goals for PMA review in Fiscal Years 2008–12 were specified when Congress enacted FDAAA.⁶² Performance goals were updated in 2012 with enactment of the FDASIA reauthorizing user fees for the next five years.⁶³

Q 1.18.6 How does the PMA review proceed?

After a PMA is submitted, FDA conducts an in-depth analysis. FDA may request additional data or information from the applicant.

A PMA generally will be referred to an advisory panel of outside experts for their review and recommendation. Referral to an advisory panel can be done at FDA’s initiative or the applicant’s request. Such referral may not be necessary, however, for a device that presents issues substantially similar to those presented by an innovator device that was previously approved under a PMA. The advisory panel reviews the data submitted by the applicant and provides its advice to FDA. The meeting of the advisory panel is open to the public, although the panel can meet in a closed session to discuss confidential commercial information and trade secrets.

FDA will conduct a preapproval inspection of the manufacturing facility, to assure compliance with quality system regulations (QSRs), including good manufacturing practices (GMPs).⁶⁴

Upon written request, FDA must meet with the applicant not later than 100 days after the PMA has been filed as complete, for the purpose of discussing the review status of the application.⁶⁵ Prior to the meeting, FDA must provide in writing a description of any deficiencies that have been identified, based on an interim review of the entire application, as well as the information required to correct the deficiencies. FDA must also promptly notify the applicant in writing of any deficiency subsequently identified.

If FDA approves the PMA, it will notify the public of its decision by making available a summary of the safety and effectiveness data upon which the approval is based.⁶⁶ Any interested person can file a petition with the Agency to seek review of the approval.

Q 1.18.7 Can review of a PMA be expedited?

Under section 515(d) of the FDCA, FDA must provide review priority for devices that are intended to treat or diagnose life-threatening or irreversibly debilitating diseases or conditions and can address unmet medical needs. These are devices: (1) representing breakthrough technologies; (2) for which no approved alternatives exist; (3) that offer significant advantages over existing approved alternatives; or (4) the availability of which is in the best interests of patients.⁶⁷

Q 1.18.8 Can another company show that its device is substantially equivalent to a PMA device and receive a 510(k) notification?

An approved PMA traditionally has been viewed as a personal license to market a particular device. A manufacturer seeking to market a similar device ordinarily must submit its own PMA.

Under section 520(h) of the FDCA, FDA may use certain data and information from a manufacturer's PMA six years after its approval. Specifically, the Agency may use data from clinical and preclinical tests or studies demonstrating safety or effectiveness, but may not use "descriptions of methods of manufacture and product composition and other trade secrets."⁶⁸ FDA may use this data and information to approve another PMA, or to classify or reclassify a device.

Q 1.18.9 What if a manufacturer wants to modify a PMA device?

Generally, a PMA supplement must be filed for any change to an approved device that affects safety or effectiveness.⁶⁹ A supplement is not required, however, if the change is a modification in a manufacturing procedure or method of manufacturing and the PMA holder submits a written notice describing the change, summarizing the data and information supporting the change, and informing FDA that the change has been made in accordance with QSR/GMP requirements.⁷⁰ Such notices must be submitted thirty days before distribution of any device subject to the manufacturing change. After thirty days, the device may be distributed, unless FDA has acted within that time to notify the PMA holder that the thirty-day notice was not adequate and has described the additional information or action required. If FDA requires a preapproval supplement, it will notify the applicant that a supplement is needed. FDA then must review the supplement within 135 days.

In reviewing a PMA supplement submitted for an incremental change in the design of a device that affects safety or effectiveness, FDA must approve the supplement if: (1) nonclinical data demonstrate that the design modification creates the intended additional capacity, function, or performance of the device, and (2) clinical data, from the approved application and any supplement to it, provide a reasonable assurance of safety and effectiveness for the changed device.⁷¹ FDA may request additional clinical data when necessary to evaluate the design modification.

Investigational Use of a Device

Q 1.19 What requirements apply to clinical studies of a device in human subjects?

To conduct a clinical study of an investigational device, the sponsor must obtain approval from an institutional review board (IRB), which reviews the protocol for conducting the study and the form of consent.⁷² IRB review is intended to protect the individuals who will be subjects in the study.

Each subject must be informed of the potential risks and benefits and must provide informed consent to participation in the study.⁷³

In addition to IRB approval and informed consent, sponsors must comply with FDA's investigational device exemption (IDE) regulations, in 21 C.F.R. Part 812.

Q 1.20 What do the IDE regulations require?

For a “significant risk device,” as defined in 21 C.F.R. § 812.3(m), FDA approval is required before a sponsor may begin clinical trials.⁷⁴ Significant risk devices include implants, devices that sustain or support life, and devices that otherwise pose a serious risk to health.

The sponsor of a proposed clinical study files an application for an investigational device exemption (IDE) and must obtain FDA approval of the IDE application before beginning the study. The IDE application must include an investigational plan and a report of prior investigations. The sponsor of the study, and physician-investigators under the IDE, must comply with recordkeeping and reporting requirements. With an approved IDE, an applicant may lawfully ship—for the sole purpose of conducting investigations—a device that would otherwise require an approved PMA to be shipped.

FDA approval of an IDE is not required for clinical investigations of a “nonsignificant risk device,” provided that the device sponsor obtains IRB approval, obtains informed consent to the research from the subjects in the study, and complies with the recordkeeping and reporting requirements in 21 C.F.R. §§ 812.140 and 812.150. These are the “abbreviated IDE” requirements. FDA has issued guidance listing examples of the devices that it considers “significant risk devices” and “nonsignificant risk devices.”⁷⁵

Q 1.21 Can a sponsor modify an investigational device, or change the study protocol, in the middle of an IDE clinical study?

Modification of an investigational device or study protocol subject to an IDE ordinarily requires the submission of an IDE supplement and approval of that supplement by FDA. However, certain modifications to investigational devices and study protocols may be made without submission of an IDE supplement. These are: (1) developmental

changes that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the investigation; and (2) changes or modifications to clinical protocols that do not affect (a) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol; (b) the scientific soundness of an investigational plan submitted in the IDE; or (c) the rights, safety, or welfare of the human subjects involved in the investigation.⁷⁶ The sponsor may make changes in the device or protocol if it determines the applicable conditions are met and gives FDA notice no later than five days after making the change or modification.⁷⁷

Q 1.22 How does a sponsor find out from FDA what clinical data are required for a PMA or 510(k) notification?

FDA provides informal guidance on preclinical and clinical data requirements through a “Pre-Submission” process.⁷⁸ The sponsor submits a pre-submission document that describes the device, summarizes the preclinical testing of the device and any clinical data, includes a proposed clinical trial protocol, and poses specific questions to which FDA is asked to respond. A meeting or teleconference is held between FDA and the sponsor at which the questions and other issues can be discussed.

A more formal process is provided under section 520(g)(7) of the FDCA. FDA must offer the sponsor an opportunity for Agency review of a clinical trial protocol for any Class III device or implantable device prior to submission of an application for an IDE. The purpose of this review is to reach agreement with the applicant regarding the investigational plan. FDA must meet with the applicant within thirty days of a written request for such a meeting.

Any agreement between FDA and the applicant regarding the clinical plan becomes part of the administrative record and may not be changed except (1) with the written agreement of the applicant, or (2) upon a decision by the Director of the Office of Device Evaluation (ODE) “that a substantial scientific issue essential to determining the safety or effectiveness of the device involved has been identified.”⁷⁹

Q 1.23 Can a sponsor charge for an investigational device?

A sponsor or investigator may not commercialize an investigational device by charging the subjects or investigators a price higher than that necessary to recover the costs of manufacture, research, development, and handling.⁸⁰ If the device is to be sold, the IDE application must include an explanation why the sale does not constitute commercialization.⁸¹

Humanitarian Device Exemption**Q 1.24 What options are available to device manufacturers who want to develop a device for a disease or condition affecting a small number of people?**

Section 520(m) of the FDCA contains a “humanitarian device exemption” to encourage the development and use of medical devices intended in the treatment or diagnosis of rare diseases or conditions.⁸² This section provides an exemption from the effectiveness requirements of section 515, relating to PMA approval, and section 514, relating to performance standards.

Q 1.25 What are the requirements for obtaining a humanitarian device exemption?

FDA may grant a humanitarian device exemption if:

- (1) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States per year;
- (2) the device would not be available to a person with the disease or condition unless FDA granted the exemption and there is no comparable device (other than another humanitarian use device) available to treat or diagnose the disease or condition;
- (3) the device will not expose patients to an “unreasonable or significant risk” of illness or injury; and
- (4) the probable benefit to health from the use of the device outweighs any risk of illness or injury from its use.

FDA must issue an order granting or denying an application requesting a humanitarian device exemption within seventy-five days after receiving that application.

Q 1.26 What requirements apply to use of a humanitarian device?

Use of a humanitarian device requires prior approval from an institutional review board (IRB). An exception to this prior approval requirement exists if a physician determines in an emergency situation that the resultant delay could cause serious harm or death to the patient. In this situation, the physician must notify the IRB's chair after use of the device.

Q 1.27 Can a sponsor charge for a humanitarian use device?

The sponsor can charge a price for a humanitarian use device that generally may not exceed the cost of research, development, fabrication, and distribution.⁸³

This limitation does not apply if: (1) the device is intended for treatment or diagnosis of a disease or condition that occurs in pediatric patients or a pediatric subpopulation; (2) the device is labeled for use in a pediatric population or subpopulation in which the disease or condition occurs; (3) the device was not approved under section 520(m) for this use before September 27, 2007; (4) the number of devices distributed during any calendar year does not exceed the "annual distribution number" set by FDA in granting the exemption; (5) the person immediately notifies FDA if the number of devices distributed in a given year exceeds the annual distribution number; and (6) the request for exemption is submitted prior to October 1, 2012.⁸⁴

These provisions limiting charging for a humanitarian device were amended by section 613 of the FDASIA. In addition to applying to pediatric patients, the exemption from the prohibition on a profit will apply to humanitarian devices for adults where intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients, or that occurs in pediatric patients

in such small numbers that development of the device for pediatric patients is impossible, highly impracticable, or unsafe. The FDASIA also amended the provisions relating to the “annual distribution number.”

Q 1.28 Are there other limitations on the humanitarian device exemption?

FDA may require the applicant to demonstrate continued compliance with the requirements of section 520(m) if the Agency believes that the criteria for exemption are no longer met, that the conditions for charging a non-cost recovery price are no longer met, or that such a demonstration is necessary to protect the public health.

FDA may suspend or withdraw a humanitarian device exemption only after providing notice and an opportunity for an informal hearing.

Reporting Requirements and Postmarket Surveillance

Medical Device Reporting Requirements

Q 1.29 Are device manufacturers required to submit reports to FDA after obtaining marketing clearance or approval of a medical device?

Manufacturers, importers, and device user facilities are subject to the medical device reporting (MDR) requirements of section 519 of the FDCA and 21 C.F.R. Part 803 of the Agency’s regulations.⁸⁵ These regulations require reporting to FDA regarding deaths, serious injuries, and certain malfunctions associated with use of a medical device.

Q 1.30 What MDR requirements apply to a device manufacturer?

A device manufacturer must report to FDA whenever it becomes aware of information reasonably suggesting that one of its marketed

devices: (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that device, or a similar device marketed by that manufacturer, would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.⁸⁶

A “serious injury” is an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.⁸⁷ “Malfunction” is the failure of a device to meet its performance specifications or otherwise perform as intended.⁸⁸

Q 1.31 When must a manufacturer’s MDR report be submitted?

The manufacturer must report to FDA within thirty days of becoming aware of information that reasonably suggests that a reportable event of death or serious injury has occurred.⁸⁹ Generally, the manufacturer would file a separate MDR report for each such event. Supplemental reports are required within thirty days of obtaining additional information.

FDA regulations also require manufacturers to submit an MDR report within thirty days of receiving information that a device has malfunctioned, and the malfunction could cause or contribute to a death or serious injury if it were to recur. Under FDAAA, Congress amended the malfunction reporting requirements in section 519, but FDA has not implemented those changes through new regulations. Under the amended statutory provision, manufacturer reports of device malfunctions would be required within thirty days where the malfunction occurs with: (1) Class III devices, (2) Class II devices that are permanently implantable, life supporting, or life sustaining, and (3) other devices for which FDA has indicated—in a letter to the manufacturer or a *Federal Register* publication—that Part 803 will apply.⁹⁰ Manufacturer malfunction reports for other devices would be made in summary form, on a quarterly basis.⁹¹

Q 1.32 What MDR requirements apply to importers of a device?

Importers must report deaths and serious injuries to both FDA and the manufacturer, but should report malfunctions only to the manufacturer.⁹²

Q 1.33 What MDR requirements apply to a device user facility?

Device user facilities must report patient deaths to both FDA and the manufacturer, and must report serious illness or injuries to the manufacturer.⁹³

Device user facilities must also submit, on an annual basis, a summary of the user reports they submitted in the prior year.⁹⁴

Q 1.34 What MDR requirements apply to distributors of a device?

Distributors must establish and maintain device complaint records relating to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device.⁹⁵ Distributors do not have reporting obligations.

Notice of Correction and Removal**Q 1.35 Are other kinds of reports required to be submitted to FDA?**

Section 519(g) of the FDCA requires manufacturers and importers to report promptly certain “corrections” and “removals” of medical devices.

Q 1.36 When is a notice of correction and removal required?

A report to FDA is required within ten working days of initiating a correction or removal (1) to reduce a risk to health posed by the device, or (2) to remedy a violation of the FDCA where the device may present a risk to health.⁹⁶

A device poses a “risk to health” if (1) there is a “reasonable probability” that use of the device will cause serious adverse health consequences or death, or (2) use of the device may cause temporary or medically reversible adverse health consequences or an outcome where the probability of serious adverse health consequences is remote.⁹⁷

Postmarket Surveillance

Q 1.37 Does FDA monitor postmarket experience with devices in other ways?

FDA may issue an order, under section 522 of the FDCA, requiring a manufacturer to conduct postmarket surveillance for a Class II or Class III device if (1) the failure of the device would be reasonably likely to have serious adverse health consequences; (2) the device is expected to have significant use in pediatric populations; (3) the device is intended to be implanted for more than one year; or (4) the device is life-sustaining or life-supporting and used outside a device user facility.⁹⁸

Q 1.38 What happens if a manufacturer receives a postmarket surveillance order?

Within thirty days of receiving an order requiring postmarket surveillance, a manufacturer is required to submit to FDA, for approval, a plan for the required surveillance. Within sixty days of receipt of the plan, FDA must determine, among other things, if the plan will result in “the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health.”⁹⁹ A manufacturer may request review of any postmarket surveillance order or condition under the dispute resolution process established in section 562 of the FDCA.

Q 1.39 How long must postmarket surveillance be conducted?

FDA generally may order a prospective surveillance period of up to thirty-six months. A longer period of surveillance generally must be arranged by mutual agreement between FDA and the manufacturer.

FDA may order a longer period without manufacturer agreement if the device is expected to have significant use in pediatric populations and FDA deems a longer period necessary to assess the impact of growth, development, and other factors on safe and effective use of the device.

Device Tracking

Q 1.40 Does FDA have any special recordkeeping or reporting requirements for high-risk devices?

FDA may order manufacturers of certain types of high-risk devices to use a method of tracking them. Device tracking requirements can be imposed under section 519(e) of the FDCA.

Q 1.41 What kinds of devices might be subject to device tracking requirements?

FDA may order a manufacturer to adopt a method of tracking a Class II or Class III device if: (1) the failure of the device would be reasonably likely to have serious adverse health consequences; (2) the device is intended to be implanted for more than one year; or (3) the device is life-sustaining or life-supporting and used outside a device user facility.¹⁰⁰

In addition to these statutory criteria (one of which must be met for a tracking order to issue), FDA has indicated it will consider the following factors in determining whether it will issue a tracking order: (1) the likelihood of sudden, catastrophic failure, (2) the likelihood of significant adverse clinical outcome, and (3) the need for prompt professional intervention.¹⁰¹ Prior to enactment of FDAMA in 1997, some devices were subject to mandatory tracking.

Q 1.42 What is the purpose of the device tracking requirements?

Tracking information may be used to facilitate notification and recalls ordered by FDA in the case of serious risks to health presented by a device.¹⁰² A patient who receives a device subject to tracking may

refuse to release, or refuse permission to release, his or her name, address, Social Security number, or other identifying information for the purpose of tracking.¹⁰³

Unique Device Identification

Q 1.43 Are manufacturers required to have a method of tracking every device they market?

Section 519(f) of the FDCA directed FDA to promulgate regulations creating a unique device identification (UDI) system for medical devices. This system generally requires device labels to bear a UDI that adequately identifies the device through distribution and use.¹⁰⁴ FDA's UDI regulations are set forth in 21 C.F.R. Part 801.

Restricted Devices

Q 1.44 Does FDA have authority to restrict the distribution of medical devices?

Under section 520(e) of the FDCA,¹⁰⁵ FDA may restrict the sale, distribution, or use of a medical device. A device may be restricted if the Secretary determines that, because of the device's potentiality for harmful effect or the collateral measures necessary to its use, "there cannot otherwise be reasonable assurance of its safety and effectiveness." FDA imposes restrictions by a regulation issued under section 520(e), or by a PMA approval order pursuant to section 515(d)(1)(B)(ii) (which references section 520(e)).

Q 1.45 What kinds of restrictions can FDA impose?

FDA may limit the use of a device to persons with specific training or experience, or may require that certain kinds of labeling or other information must accompany the device.

When FDA imposes restrictions on sale, distribution, or use under section 520(e), the Agency has jurisdiction over advertising for the restricted devices.¹⁰⁶

Quality and Performance Requirements

Quality System Regulations and Good Manufacturing Practice Requirements

Q 1.46 Does FDA regulate the manufacturing of medical devices?

FDA has promulgated quality system regulations (QSRs) that impose requirements of design control and validation for devices, and governing device manufacturing, labeling, recordkeeping, and reporting.¹⁰⁷

The QSRs specify requirements for design controls and validation, quality controls, measurement equipment, production and process controls, packaging and labeling controls, device inspection, failure investigation, and recordkeeping requirements.¹⁰⁸ The QSRs include good manufacturing practices (GMP) requirements that apply to all manufacturers of finished medical devices. The QSR requirements are intended to assure that finished medical devices will be safe and effective and otherwise in compliance with statutory requirements.

Q 1.47 How does FDA enforce the QSR requirements?

FDA conducts facility inspections to determine compliance with QSR requirements. The FDCA directs FDA to inspect domestic manufacturers of Class II and Class III medical devices at least once every two years.¹⁰⁹ Section 704(g) of the FDCA authorizes FDA to establish a voluntary fee-based third-party inspection program for manufacturers meeting eligibility criteria.¹¹⁰

Following an inspection, FDA issues a notice of inspectional observations, referred to as a Form 483, if the investigators identify issues of concern. FDA may subsequently issue a Warning Letter to a company if the issues are considered violations of the FDCA. The failure to comply with an applicable regulation renders the device “adulterated” under section 501(h) of the FDCA.

Performance Standards

Q 1.48 Are manufacturers required to conform to standards in designing or manufacturing a medical device?

FDA can establish a performance standard for a Class II or Class III device, under section 514 of the FDCA, if the Agency determines that a performance standard is appropriate and necessary to provide reasonable assurance of the safety and effectiveness of the device.

In addition, FDA may recognize an appropriate standard established by a nationally or internationally recognized standards development organization. A manufacturer may certify compliance with such a standard for the purpose of meeting an applicable premarket submission requirement—for instance, as part of a substantial equivalence showing in a 510(k) notification.¹¹¹

Q 1.49 What is a “Declaration of Conformity”?

A manufacturer that elects to rely on a recognized standard may provide a Declaration of Conformity to FDA, certifying that the device is in conformity with the standard. A manufacturer that submits a Declaration of Conformity with a listed standard can be required, at any time, to submit the data and information relied upon in making the declaration. The falsification of a Declaration of Conformity, and the refusal to submit the underlying data or information, are both prohibited acts under section 301 of the FDCA. FDA must accept the declaration unless it finds that the standard is not applicable to the particular device, or the submitted data and information do not demonstrate that the device conforms to the standard.

Q 1.50 What happens if a device fails to conform to an applicable standard?

A device is adulterated if it fails to conform to a standard established by FDA for that device, or if it is represented to be in conformity with a recognized standard and fails to be in conformity with that standard.¹¹²

Dispute Resolution

Q 1.51 What can a manufacturer do if it does not agree with a decision that has been made by an FDA employee during IDE, 510(k), or PMA review?

A manufacturer who does not agree with a decision by an FDA official can appeal to the next level supervisor pursuant to the regulations in 21 C.F.R. § 10.75 for internal Agency review of decisions.

FDA has issued a guidance document describing informal and formal appeal processes for resolution of disputes regarding clinical studies, premarket evaluation of products, regulatory compliance issues, and complaints about conflict of interest or employee misconduct.¹¹³

Q 1.52 What can a manufacturer do if there is a scientific dispute with FDA that does not seem to be resolvable within the Agency?

Section 562 of the FDCA requires FDA to make appropriate use of independent scientific experts to review any “scientific controversy” between the Agency and any sponsor, applicant, or manufacturer.¹¹⁴ The Center for Devices and Radiological Health (CDRH) has established a Medical Devices Dispute Resolution Panel (MDDRP) for this purpose. A guidance document describes the MDDRP and dispute resolution procedures.¹¹⁵

Statutory Penalties and Enforcement

Q 1.53 What if a device does not comply with a requirement of the FDCA?

Section 301 of the FDCA sets forth numerous prohibited acts that can lead to enforcement actions and penalties.

The introduction into interstate commerce of any medical device that is “adulterated” or “misbranded” is a prohibited act. Sections 501 and 502 define “adulterated” and “misbranded” for these purposes.

For example, a device is adulterated if its manufacturer has failed to comply with QSR requirements, and a device is misbranded if the manufacturer fails to comply with applicable requirements for labeling, recordkeeping, and reporting. The failure to register as a medical device establishment (including failure to pay the establishment registration fee) and the failure to provide the information required in a 510(k) notification are also prohibited acts.

Q 1.54 What are the enforcement actions that can result from a prohibited act?

A device that is adulterated or misbranded is subject to seizure. If a device is imported into the United States, it will be refused admission if it is adulterated or misbranded.

A company and individuals responsible for a violation of the FDCA are subject to injunction and criminal penalties. In addition, under section 303(f) of the FDCA, a person who violates a requirement relating to medical devices is subject to a civil penalty up to \$15,000 for each violation, not to exceed \$1 million for all such violations adjudicated in a single proceeding; there are certain restrictions on when civil penalties can be assessed, and other statutes that enhance the amounts of civil penalties.

Q 1.55 Can FDA require a product recall?

Device manufacturers may elect to conduct a voluntary recall of a device, including a correction or withdrawal, if the device fails to perform properly or is misbranded. Voluntary recalls are conducted in accordance with FDA regulations in 21 C.F.R. Part 7.

FDA may require a device recall, pursuant to section 518(e) of the FDCA, if there is a reasonable probability that the device would cause serious adverse health consequences or death. As part of any recall order, FDA must provide notice to individuals subject to the risks associated with the use of the device. Mandatory device recalls are governed by 21 C.F.R. Part 810.

The FDASIA added a new section 518A to the FDCA, directing FDA to establish a program to improve the device recall system. This system will include developing criteria for determining whether a person

has conducted an effective correction or action plan for a recall, systematically assessing information relating to device recalls, and documenting the basis for an FDA termination of a recall.

Q 1.56 Can FDA withdraw marketing authorization for a device?

FDA is authorized, under section 515(e)(3) of the FDCA, to suspend temporarily the approval of a PMA if there is a reasonable probability that continued distribution of the device would cause serious adverse health consequences or death. If FDA issues a suspension order, it must proceed expeditiously to withdraw approval of the PMA application in accordance with the procedures of section 515(e)(1).

FDA has taken the position that it can rescind a 510(k) notification, although there is no specific statutory basis for doing so and no regulations setting forth any such procedure.

Q 1.57 Do other agencies or entities regulate medical devices?

Other federal and state agencies can regulate medical devices in various ways. For example, the Federal Trade Commission regulates medical device advertising. States can regulate devices under their state laws, although the FDCA contains an express preemption provision under which FDA regulation can preempt state laws. United States Attorneys can bring enforcement actions relating to devices under various federal laws, including the False Claims Act. Many other examples exist.

Notes to Chapter 1

1. Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended, 21 U.S.C. §§ 301 *et seq.*
2. Pub. L. No. 94-295, 90 Stat. 539 (1976).
3. Pub. L. No. 101-629, 104 Stat. 4511 (1990).
4. Pub. L. No. 102-300, 106 Stat. 238 (1992).
5. Pub. L. No. 105-115, 111 Stat. 2296 (1997).
6. Pub. L. No. 107-250, 116 Stat. 1588 (2002); *see also* Medical Devices Technical Corrections Act, Pub. L. No. 108-214, 118 Stat. 572 (2004).
7. Pub. L. No. 110-85, 121 Stat. 823 (2007).
8. Pub. L. No. 112-144, 126 Stat. 993 (2012).
9. Federal Food, Drug, and Cosmetic Act § 513, 21 U.S.C. § 360c [hereinafter FDCA].
10. FDCA § 510(b)(2), (c); 21 U.S.C. § 360(b)(2), (c).
11. *Id.*
12. FDCA § 510(p), 21 U.S.C. § 360(p); How to Register and List, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/ucm053165.htm (last visited May 22, 2013).
13. FDCA § 738(a)(3); 21 U.S.C. § 379j(a)(3).
14. FDCA § 738(f)(2); 21 U.S.C. § 379j(f)(2).
15. FDCA § 510(j); 21 U.S.C. § 360(j).
16. FDCA § 510(p); 21 U.S.C. § 360(p); How to Register and List, www.fda.gov/cdrh/registration/howto.html (last visited Aug. 4, 2008).
17. FDCA § 510(j)(2); 21 U.S.C. § 360(j)(2).
18. 21 C.F.R. § 807.20(a)(5) (77 Fed. Reg. 45,941, Aug. 2, 2012).
19. FDCA § 510(j)(2); 21 U.S.C. § 360(j)(2); 21 C.F.R. § 807.25(g)(3).
20. 21 C.F.R. § 807.25(g)(1).
21. 21 C.F.R. § 807.26.
22. *Id.*; 21 C.F.R. § 807.26(b).
23. 21 C.F.R. § 807.20(a).
24. FDCA § 510(i)(1); 21 U.S.C. § 360(i)(1).
25. FDCA § 510(i)(2); 21 U.S.C. § 360(i)(2); 21 C.F.R. § 807.40(a), (b).
26. 66 Fed. Reg. 59,138 (Nov. 27, 2001).
27. A Class I device is exempt from the section 510(k) notification requirement unless it is intended for a use of substantial importance in preventing impairment of human health, or it presents a potential unreasonable risk of illness or injury. FDCA § 510(l); 21 U.S.C. § 360(l). FDA has also exempted certain Class II devices from section 510(k) notification, in accordance with section 510(m) of the act. *See, e.g.*, 21 C.F.R. § 890.5720.

28. 21 C.F.R. § 807.87.
29. Guidance for Industry: General/Specific Intended Use (FDA Nov. 4, 1998).
30. FDCA § 513(i); 21 U.S.C. § 360c(i); 21 C.F.R. § 807.100.
31. FDCA § 513(i)(1)(D)(i); 21 U.S.C. § 360c(i)(1)(D)(i).
32. FDCA § 513(i)(1)(C); 21 U.S.C. § 360c(i)(1)(C).
33. FDCA § 513(i)(3)(A); 21 U.S.C. § 360c(i)(3)(A); 21 C.F.R. §§ 807.87(h), 807.92, 807.93.
34. FDCA § 513(i)(3)(B); 21 U.S.C. § 360c(i)(3)(B).
35. FDCA § 510(n); 21 U.S.C. § 360(n).
36. FDA may use accredited third-party reviewers to review certain 510(k) notifications and make recommendations to FDA regarding the initial classifications of devices. FDCA § 523, 21 U.S.C. § 360m; *see generally* Guidance for Third Parties and FDA Staff: Third Party Review of Premarket Notifications (FDA Sept. 28, 2004).
37. Guidance for Industry and FDA Staff: Priority Review of Premarket Submissions for Devices (May 17, 2013).
38. FDCA § 513(f)(2)(A)(i); 21 U.S.C. § 360c(f)(2)(A)(i).
39. FDCA § 513(f)(2)(A)(ii); 21 U.S.C. § 360c(f)(2)(A)(ii).
40. FDCA § 513(f)(2)(A)(iii); 21 U.S.C. § 360(f)(2)(A)(iii). FDA has issued a guidance document outlining the process and timelines for reviewing submissions under this section of the FDCA. New Section 513(f)(2)—Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff (FDA Feb. 19, 1998). FDA issued for comment a draft guidance on August 14, 2014, which if adopted would be intended to provide more clarity about the *de novo* process and the necessary data.
41. 66 Fed. Reg. 3523 (Jan. 16, 2001) (proposed 21 C.F.R. § 807.103).
42. FDCA § 513(i); 21 U.S.C. § 360c(i).
43. *Id.*
44. *Id.*
45. *Id.* The provisions relating to consideration of unlabeled uses were scheduled to “sunset” in 2002, but Congress struck the sunset clause when it enacted MDUFMA. The Agency issued new guidance shortly afterwards. *See* Guidance for CDRH Staff: Determination of Intended Use for 510(k) Devices (FDA Dec. 3, 2002).
46. FDASIA § 608, amending FDCA §§ 513(e)(1), 515(a) & (b); 21 U.S.C. §§ 360c(e)(1), 360e(a) & (b).
47. 21 C.F.R. § 807.81(a)(3).
48. Blue Book Memorandum No. K97-1, Deciding When to Submit a 510(k) for a Change to an Existing Device (FDA Jan. 10, 1997). FDA issued for comment a draft guidance document dated July 27, 2011, which was intended to update the existing guidance document, but the FDASIA required FDA to withdraw this draft.
49. *See* The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications (FDA Mar. 20, 1998); *see also* Guidance for Industry: Frequently Asked Questions on the New 510(k) Paradigm (FDA Oct. 22, 1998).

50. The New 510(k) Paradigm, *supra* note 49, at 4.
51. *Id.* at 9.
52. 21 C.F.R. § 814.20.
53. FDCA § 515(d)(1)(A); 21 U.S.C. § 360e(d)(1)(A).
54. FDCA § 513(a)(3)(C); 21 U.S.C. § 360c(a)(3)(C). The Agency has issued guidance interpreting this requirement. The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry (FDA Oct. 4, 2002).
55. FDCA § 513(a)(3)(D)(v); 21 U.S.C. § 360c(a)(3)(D)(v).
56. FDCA § 513(a)(3)(D)(iii); 21 U.S.C. § 360c(a)(3)(D)(iii).
57. 21 C.F.R. § 814.42(e).
58. Guidance for Industry and FDA Staff: Acceptance and Filing Reviews for Premarket Approval Applications (PMAs) (Dec. 31, 2012).
59. Guidance for Industry and FDA Staff: Premarket Approval Application Modular Review (FDA Nov. 3, 2003).
60. FDCA § 515(c)(4); 21 U.S.C. § 360e(c)(4).
61. 148 CONG. REC. S11,549 (daily ed. Nov. 19, 2002) (statement of Sen. Kennedy), www.fda.gov/cdrh/mdufma/pgoals.html (last visited July 27, 2008).
62. 153 CONG. REC. S12,420–21 (daily ed. Oct. 2, 2007) (statement of Sen. Kennedy), www.govtrack.us/congress/record.xpd?id=110-s20071002-23 (last visited Aug. 7, 2008).
63. MDUFA Performance Goals and Procedures Commitment Letter (4/18/12), www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm.
64. *See* Guidance for Industry and FDA Staff: The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations (FDA Jan. 8, 2008).
65. FDCA § 515(d); 21 U.S.C. § 360e(d).
66. 21 C.F.R. § 814.44(d)(1).
67. FDCA § 515(d)(5); 21 U.S.C. § 360e(d)(5); *see also* Guidance for Industry and FDA Staff: Priority Review of Premarket Submissions for Devices (FDA May 17, 2013).
68. FDCA § 520(h)(4)(A); 21 U.S.C. § 360j(h)(4)(A).
69. FDCA § 515(d)(6)(A); 21 U.S.C. § 360e(d)(6)(A).
70. FDA has issued guidance describing the changes that generally will qualify for thirty-day notice and describing the contents of that notice. Guidance for Industry and FDA Staff—30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (FDA Apr. 13, 2011) (supersedes 30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH (FDA Feb. 19, 1998)). The Agency also released a guidance document on PMA supplements that provides additional recommendations on these points. Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process (Dec. 11, 2008).

71. FDCA § 515(d)(6)(B); 21 U.S.C. § 360e(d)(6)(B).
72. 21 C.F.R. pt. 56.
73. 21 C.F.R. pt. 50.
74. 21 C.F.R. § 812.20.
75. Information Sheet Guidance for IRBs—Significant Risk and Nonsignificant Risk Medical Device Studies (FDA Jan. 2006), www.fda.gov/oc/ohrt/irbs/devrisk.pdf (last visited May 25, 2016).
76. FDCA § 520(g)(6)(A); 21 U.S.C. § 360j(g)(6)(A).
77. FDCA § 520(g)(6)(B); 21 U.S.C. § 360j(g)(6)(B).
78. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program (Feb. 18, 2014).
79. FDCA § 520(g)(7)(B); 21 U.S.C. § 360j(g)(7)(B).
80. 21 C.F.R. § 812.7(b).
81. 21 C.F.R. § 812.20(b)(8).
82. 21 U.S.C. § 360j(m); *see also* 21 C.F.R. §§ 814.100–814.126.
83. FDCA § 520(m)(3); 21 U.S.C. § 360j(m)(3).
84. FDCA § 520(m)(6)(A); 21 U.S.C. § 360j(m)(6)(A).
85. FDCA § 519(a)–(c); 21 U.S.C. § 360i(a)–(c); 21 C.F.R. pt. 803.
86. FDCA § 519(a)(1); 21 U.S.C. § 360i(a)(1); 21 C.F.R. § 803.50(a).
87. 21 C.F.R. § 803.3.
88. *Id.*
89. 21 C.F.R. § 803.50(a).
90. FDCA § 519(a)(1)(A)(i); 21 U.S.C. § 360i(a)(1)(A)(i).
91. FDCA § 519(a)(1)(A)(ii); 21 U.S.C. § 360i(a)(1)(A)(ii).
92. 21 C.F.R. § 803.40.
93. FDCA § 519(b)(1); 21 U.S.C. § 360i(b)(1); 21 C.F.R. § 803.30.
94. FDCA § 519(b)(1)(C); 21 U.S.C. § 360i(b)(1)(C); 21 C.F.R. § 803.33. In 1997, Congress directed FDA to plan and implement a new system for user facility reporting, pursuant to which a representative subset of facilities would report device-related deaths and serious illnesses or injuries (*i.e.*, “sentinel” rather than “universal” reporting). FDCA § 519(b)(5); 21 U.S.C. § 360i(b)(5). The Agency conducted a pilot study but has not yet proposed new regulations.
95. 21 C.F.R. § 803.18(d)(1).
96. 21 C.F.R. § 806.10.
97. 21 C.F.R. § 806.2. This definition is the same as the definitions for Class I and Class II recalls in 21 C.F.R. § 7.3(m).
98. FDA finalized regulations implementing section 522 in June 2002. 67 Fed. Reg. 38,878 (June 6, 2002); 21 C.F.R. pt. 822. These regulations have not yet been updated to reflect changes to section 522 implemented by FDAAA.
99. FDCA § 522(b); 21 U.S.C. § 360i(b).
100. FDCA § 519(e); 21 C.F.R. § 360i(e); *see also* 21 C.F.R. § 821.1(a).
101. Medical Device Tracking; Guidance for Industry and FDA Staff (FDA Jan. 25, 2010).

102. See 21 C.F.R. § 821.1(b).
103. 21 C.F.R. § 821.55(a).
104. FDA has issued regulations to implement the UDI requirements, 78 Fed. Reg. 58,786 (Sept. 24, 2013).
105. FDCA § 520(e); 21 U.S.C. § 360j(e).
106. FDCA § 502(r); 21 U.S.C. § 352(r).
107. 21 C.F.R. pt. 820.
108. With respect to Class I devices, design controls apply only to those devices listed in 21 C.F.R. § 820.30(a)(2). 21 C.F.R. § 820.1(a).
109. FDCA § 510(h); 21 U.S.C. § 360(h).
110. FDCA § 704(g); 21 U.S.C. § 374(g).
111. Guidance for Industry and for FDA Staff: Use of Standards in Substantial Equivalence Determinations (FDA Mar. 12, 2000).
112. FDCA § 501(e); 21 U.S.C. § 351(e).
113. Guidance for Industry and FDA Staff: Center for Devices and Radiological Health Appeals Processes (May 17, 2013).
114. FDCA § 562; 21 U.S.C. § 360bbb-1.
115. Guidance for Industry and FDA Staff: Center for Devices and Radiological Health Appeals Processes (May 17, 2013).