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FDA Regulation of Medical Devices

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Summary

Prior to and since the passage of the Medical Device Amendments of 1976, Congress has debated how best to ensure that consumers have access, as quickly as possible, to new and improved medical devices and, at the same time, prevent devices that are not safe and effective from entering or remaining on the market. Medical device regulation is complex, in part, because of the wide variety of items that are categorized as medical devices; examples range from a simple tongue depressor to a life-sustaining heart valve. The regulation of medical devices can affect their cost, quality, and availability in the health care system.

In order to be legally marketed in the United States, many medical devices must be reviewed by the Food and Drug Administration (FDA), the agency responsible for protecting the public health by overseeing medical products. FDA's Center for Devices and Radiological Health (CDRH) is primarily responsible for medical device review. CDRH activities are funded by congressional appropriations and user fees collected from device manufacturers, which together comprise the program level budget. User fees account for 43% of FDA's total FY2016 program level and 28% of CDRH's FY2016 program level. The CDRH program level budget in FY2016 is $450 million, including $127 million in user fees. FDA's authority to collect medical device user fees, originally authorized in 2002 (P.L. 107-250), has been reauthorized in five-year increments and was reauthorized through FY2017 in the FDA Safety and Innovation Act (FDASIA, P.L. 112-144).

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), all medical device manufacturers must register their facilities and list their devices with FDA and follow general controls requirements. FDA classifies devices according to the risk they pose to consumers. The FFDCA requires premarket review for moderate- and high-risk devices. There are two main paths that manufacturers can use to bring such devices to market. One path consists of conducting clinical studies and submitting a *premarket approval* (PMA) application that includes evidence providing reasonable assurance that the device is safe and effective. The other path involves submitting a *510(k) notification* demonstrating that the device is *substantially equivalent* to a device already on the market (a *predicate device*) that does not require a PMA. The 510(k) process results in FDA *clearance* and tends to be much less expensive and less time-consuming than seeking FDA approval via PMA. Substantial equivalence is determined by comparing the performance characteristics of a new device with those of a predicate device. Demonstrating substantial equivalence does not usually require submitting clinical data demonstrating safety and effectiveness. Once its device is approved or cleared for marketing, a manufacturer must comply with regulations on manufacturing, labeling, surveillance, device tracking, and adverse event reporting. In 2015, FDA approved 98% of PMAs accepted for review and 85% of 510(k)s accepted for review were determined to be substantially equivalent.

Problems related to medical devices can have serious consequences for consumers. Defects in medical devices, such as artificial hips and pacemakers, have caused severe patient injuries and deaths. Reports published in 2009 through 2011—by the Government Accountability Office (GAO), the Department of Health and Human Services Office of the Inspector General, and the Institute of Medicine—have voiced concerns about FDA's device review process. In 2009, 2011, 2013, and 2015 FDA's oversight of medical products was included on the GAO list of high-risk areas. In response to these concerns, FDA has conducted internal reviews and has implemented changes, including plans for a new National Evaluation System for health Technology (NEST).

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Introduction

Medical device regulation is complex, in part because of the wide variety of items that are categorized as medical devices. They may be simple tools used during medical examinations, such as tongue depressors and thermometers, or high-tech life-saving devices that are implanted in the patient, like pacemakers and coronary stents. The medical device market has been described as consisting of eight industry sectors: surgical and medical instrument manufacturing, surgical appliance and supplies, electromedical and electrotherapeutic apparatus, irradiation apparatus, ophthalmic goods, dental equipment and supplies, dental laboratories, and in vitro diagnostic products (IVDs, or laboratory developed tests).[1]

The federal agency responsible for regulating medical devices is the Food and Drug Administration (FDA)—an agency within the Department of Health and Human Services (HHS). A manufacturer must obtain FDA's prior approval or clearance before marketing many medical devices in the United States. FDA's Center for Devices and Radiological Health (CDRH) is primarily responsible for medical device premarket review. Another center, the Center for Biologics Evaluation and Research (CBER), regulates devices associated with blood collection and processing procedures, cellular products and tissues.[2]

CDRH activities are funded by congressional appropriations and user fees collected from device manufacturers, which together comprise the program level budget.[3] In general, CDRH user fees may be used only for medical device premarket review activities, not other CDRH activities.[4] User fees account for 43% of FDA's total FY2016 program level and 28% of CDRH's FY2016 program level.[5] The CDRH program level budget in FY2016 is $450 million, including $127 million in user fees. FDA's authority to collect medical device related user fees, originally authorized in 2002 (P.L. 107-250), has been reauthorized in five-year increments and was reauthorized through FY2017 by the 112th Congress via Title II of the FDA Safety and Innovation Act (FDASIA, P.L. 112-144).[6]

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[1] The Lewin Group, for AdvaMed, *State Economic Impact of the Medical Technology Industry*, June 7, 2010, p. 19. *In vitro* diagnostic products (IVDs, or laboratory developed tests) have their own unique premarket requirements and are not discussed further in this report. For more information on the regulation of IVDs see CRS Report R43438, *Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests*, by Amanda K. Sarata and Judith A. Johnson.

[2] Jurisdiction of the centers' medical device review is governed by the FDA Intercenter Agreement between CBER and CDRH (October 31, 1991). FDA, *Devices Regulated by the Center for Biologics Evaluation and Research*, http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/510kProcess/ucm133429.htm.

[3] For more information on medical device user fees, see CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*, by Judith A. Johnson.

[4] Fees "shall only be available to defray increases in the costs of resources allocated for the process for the review of device applications." FFDCA 738(i)(2)(A)(ii). The law specifically defines "costs of resources allocated for the process for the review of device applications" [FFDCA 737(9)] and what activities are considered part of the "process for the review of device applications" [FFDCA 737(8)] For example, *costs* include management of information [FFDCA 737(9)(B); and, *activities* associated with the process for review include inspections of manufacturing establishments [FFDCA 737(8)(C). The process for review of device applications focuses solely on activities involved in premarket approval, with one exception: the evaluation of postmarket studies that are required as a condition of approval of certain premarket applications or reports [FFDCA 737(8)(J)].

[5] FDA, *Justification of Estimates for Appropriation Committees, FY2017*, Washington, DC, February 2016, pp. 20 and 135. FDA also funds some device and radiological health activities with fees collected under the Mammography Quality Standards Act (MQSA, P.L. 102-539), and device user fees fund some non–device-specific activities at FDA.

[6] Title VI of FDASIA addresses the regulation of medical devices; for further information see CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144)*, coordinated by Susan Thaul.

Congress has historically been interested in balancing the goals of allowing consumers to have access, as quickly as possible, to new and improved medical devices with preventing devices that are not safe and effective from entering or remaining on the market. The goals of device availability and device safety may exert opposite pulls, with implications for consumers, the health care system, and the economy.

Private investment in medical device development reportedly reached a high of $3.7 billion in 2007. Investment has slowed somewhat to $2.5 billion in 2012, $2.3 billion in 2013, $2.7 billion in 2014, and $2.8 billion in 2015.[7] According to one report, the U.S. medical technology industry generated $336 billion in revenue in 2013 and employed almost 671,000 workers.[8] The "medical technology industry" includes "medical device, diagnostic, drug delivery and analytic/life science tool companies" but does not include "distributors and service providers" such as contract research or contract manufacturing organizations.[9] A 2011 analysis found that "32 of the 46 medical technology companies with more than $1 billion in annual revenue are based in the United States."[10] Although the largest companies dominate the market for devices in terms of sales, some believe it is often the small device companies that make a significant contribution to early innovation. Small companies may partner with larger companies to bring products to market if they lack access to the capital and resources to conduct clinical trials and navigate regulatory and reimbursement hurdles.

Manufacturers make decisions about pursuing new devices based in part on the cost of their development. Additional regulatory requirements may escalate these costs, while other incentives, such as tax breaks or market exclusivity extensions, may diminish them. If the device development cost is too high, the eventual result may be that consumers are denied access to new devices because new products are not developed or brought to market. Access problems have led to proposals for, and the enactment of, incentives to develop medical devices for rare diseases and pediatric populations. However, if the regulation and oversight of device development are not adequate, unsafe or ineffective products may reach the market and cause harm to consumers.

Problems related to medical devices can have serious consequences for consumers. Relatively recent examples in the media that have caused severe patient injuries and deaths include metal-on-metal hip implants; pacemakers, defibrillators, and associated leads (wires); stents; endoscopes; surgical mesh; and, power morcellators.[11] The metal-on-metal hip has "been implanted in millions of patients [worldwide], many of whom suffered serious harm and, as a result, needed additional procedures to replace the device."[12] An estimated 500,000 patients in the United States have received this type of hip replacement.[13]

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[7] PriceWaterhouseCoopers / National Venture Capital Association, "Medical Devices and Equipment," *Money Tree Report*, data provided by Thomson Reuters, at http://www.pwcmoneytree.com.

[8] Ernst and Young. *Pulse of the industry: Medical technology report, 2014*, p. 27. http://www.ey.com/Publication/vwLUAssets/ey-pulse-of-the-industry-report/$FILE/ey-pulse-of-the-industry-report.pdf.

[9] Ibid., p. 70.

[10] PwC (PricewaterhouseCoopers), *Medical Technology Innovation Scorecard: The race for global leadership*, January 2011, p. 8, http://www.pwc.com/us/en/health-industries/health-research-institute/innovation-scorecard.

[11] For example, see Barry Meier and Janet Roberts, "Hip implant complaints surge, even as the dangers are studied," *The New York Times*, August 22, 2011, pp. A1, A16; Information on recalls is available by searching the database at FDA, *Medical & Radiation Emitting Device Recalls*, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm.

[12] Corinna Sorenson and Michael Drummond, "Improving medical device regulation: the United States and Europe in Perspective," *The Milbank Quarterly*, vol. 92, no. 1 (2014), p. 127.

[13] Barry Meier, "F.D.A. Seeks to Tighten Regulation of All-Metal Hip Implants," *The New York Times*, January 16, 2013.

These device problems have raised questions as to whether adequate enforcement tools, resources, and processes are in place at FDA to ensure that marketed devices are safe and effective. Reports by the Government Accountability Office (GAO), the Department of Health and Human Services Office of the Inspector General, and the Institute of Medicine (IOM) have voiced concerns about FDA's device review process.[14] In 2009, 2011, 2013, and 2015 GAO included FDA's oversight of medical products on the GAO list of high-risk areas.[15]

This report provides a description of FDA's medical device review process and related policy issues. The report is divided into two parts: premarket requirements and postmarket requirements. **Appendix A** provides a comparison of elements comprising the FDA premarket review of drugs and medical devices. **Appendix B** provides a brief history of laws governing medical device regulation, and **Appendix C** provides a table of acronyms used in the report.

The Medical Device Review Process: Premarket Requirements

FDA requires all medical product manufacturers to register their facilities, list their devices with the agency, and follow general controls requirements.[16] FDA classifies devices according to the risk they pose to consumers. Many medical devices, such as plastic bandages and ice bags, present only minimal risk and can be legally marketed upon registration alone. These low-risk devices are deemed *exempt* from premarket review and manufacturers need not submit an application to FDA prior to marketing.[17] In contrast, most moderate- and high-risk devices must obtain the agency's permission prior to marketing. FDA grants this permission when a manufacturer meets regulatory premarket requirements and agrees to any necessary postmarket requirements which vary according to the risk that a device presents.[18]

[14] U.S. Government Accountability Office, *Medical Devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process*, GAO-09-190, January 2009; Daniel R. Levinson, *Adverse Event Reporting for Medical Devices*, Department of Health and Human Services, Office of Inspector General, Washington, DC, October 2009; and, IOM (Institute of Medicine), *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011.

[15] GAO regularly reports on government operations that it identifies as high risk due to their greater vulnerability to fraud, waste, abuse, mismanagement or the need for transformation to address economy, efficiency or effectiveness challenges. See GAO, *High-Risk Series: An Update*, GAO-09-271, January 2009; GAO, *High-Risk Series: An Update*, GAO-11-278, February 2011; GAO, High-Risk Series: An Update, GAO-13-283, February 2013; and, GAO-15-290, High-Risk Series: An Update, February 2015.

[16] 21 C.F.R. §807.

[17] The term *manufacturer* is used throughout this report for simplicity, but regulations also apply to any person, organization, or sponsor that submits an application to FDA to market a device.

[18] *In vitro* diagnostic products (IVDs, or laboratory-developed tests) have their own unique premarket requirements and are not discussed further in this report. For more information on the regulation of IVDs see CRS Report R43438, *Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests*.

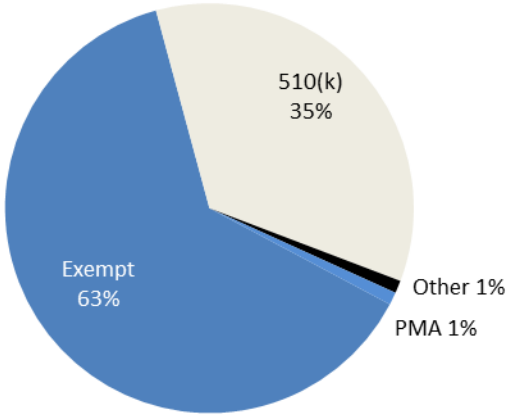
PMA vs. 510(k)

There is a fundamental difference between the PMA and 510(k) pathways. In a PMA review, FDA determines if the device is reasonably safe and effective for its intended use. In a 510(k) review, FDA determines if the device is substantially equivalent to another device already on the market whose safety and effectiveness may not have been assessed previously.

There are two main paths that manufacturers can use to bring moderate- and high-risk devices to market with FDA's permission. One path consists of conducting clinical studies, submitting a *premarket approval* (PMA) application, and requires evidence providing reasonable assurance that the device is safe and effective.[19] The PMA process is generally used for novel and high-risk devices and results in a type of FDA permission called *approval.*

The other path is shorter and less costly. It involves submitting a *510(k) notification* demonstrating that the device is *substantially equivalent* to a device already on the market (a *predicate device*) that does not require a PMA.[20] The 510(k) process is unique to medical devices and results in FDA *clearance*. Substantial equivalence is determined by comparing the performance characteristics of a new device with those of a predicate device. To be considered substantially equivalent, the new device must have the same intended use and technological characteristics as the predicate; clinical data demonstrating safety and effectiveness are usually not required. The manufacturer selects the predicate device to compare with its new device. However, FDA has the ultimate discretion in determining whether a comparison is appropriate.

Figure 1. Medical Devices Listed with FDA, FY2016, by Premarket Review Process



Source: FDA, May 23, 2016.

Notes: "Other" includes devices that were allowed to enter the market via other means, such as through the humanitarian device exemption process that allows market entry, without adherence to effectiveness requirements, for devices benefiting patients with rare diseases or conditions. See "Humanitarian Device Exemption (HDE)." Nonexempt devices are reviewed by FDA via the PMA process or the 510(k) process.

Of the unique devices that are listed by manufacturers with FDA in FY2016, as shown in **Figure 1**, about 63% were exempt from premarket review; the remainder entered the market via the

[19] The PMA is somewhat similar to the process FDA uses to approve a new prescription drug. For information on the drug approval process, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Susan Thaul.

[20] To be a predicate, a device must have either been on the market before 1976 when the Medical Device Amendments (MDA) took effect, or it could have been cleared for marketing after 1976, but must have the same intended use as a device classified in the Code of Federal Regulations (C.F.R.).

510(k) process (35%), the PMA process (1%), or other means (such as the "Humanitarian Device Exemption (HDE)]").[21]

Device Classification

Under the terms of the Medical Device Amendments of 1976 (MDA, P.L. 94-295), FDA classified all medical devices that were on the market at the time of enactment—the *preamendment* devices—into one of three classes. Congress provided definitions for the three classes—Class I, Class II, and Class III—based on the risk (low-, moderate-, and high-risk respectively) to patients posed by the devices.[22] Examples of each class are listed in **Table 1**.

Table 1. Medical Device Classification

Device Classification	Examples	Safety/Effectiveness Controls	Required Submission
Class I	elastic bandages, examination gloves, hand-held surgical instruments	General Controls	Registration only unless 510(k) specifically required
Class II	powered wheelchairs, infusion pumps, surgical drapes	General Controls & Special Controls	510(k) notification unless exempt -IDE possible
Class III	heart valves, silicone gel-filled breast implants, implanted cerebella stimulators	General Controls & Premarket Approval	PMA application -IDE probable
	metal-on-metal hip joint, certain dental implants	*General Controls*	*510(k) notification*

Source: FDA, Overview of Medical Device Regulation, General and Special Controls, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm.

Note: IDE means investigational device exemption. Some Class III devices have been cleared via the 510(k) process; these are Class III devices that entered the market prior to regulation calling for a PMA application.

Device classification determines the type of regulatory requirements that a manufacturer must follow. Regulatory requirements for each class are described below in more detail. *General controls* apply to all three classes of FDA-regulated medical devices, unless exempted by regulation, and are the only level of controls that apply to Class I devices.[23] Examples of general controls include establishment registration, device listing, premarket notification, and good manufacturing practice requirements.

Class I devices are those under current law for which general controls "are sufficient to provide reasonable assurance of the safety and effectiveness of the device."[24] Many Class I devices are *exempt* from the premarket notification and/or the Quality System (QS) regulation requirements,

[21] Email from Ann M. Ferriter and David R. Gartner, Division of Analysis and Program Operations, Office of Compliance, CDRH/FDA, May 23, 2016.

[22] FFDCA §513(a)(1); see also 21 C.F.R. §860.3(c). The agency has developed classifications for over 1,700 distinct types of devices and grouped them into 16 *classification panels*, such as "cardiovascular devices" or "ear, nose, and throat devices." FDA, Medical Devices, *Classify Your Medical Device*, December 3, 2012, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm.

[23] See FDA, Medical Devices, *Regulatory Controls*, 06/26/2014, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#gen.

[24] FFDCA §513(a)(1)(A).

though they still have to comply with the other general controls.[25] A device is exempt if FDA determines that it presents a low risk of illness or injury to patients.[26]

Class II devices are those under current law "which cannot be classified as class I because the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device."[27] Class II includes devices that pose a moderate risk to patients, and may include new devices for which information or *special controls* are available to reduce or mitigate risk.[28] Special controls are usually device specific and may include special labeling requirements, mandatory performance standards, and postmarket surveillance. Currently "15% of all device types classified in Class II are subject to special controls."[29] Although most Class II devices require premarket notification via the 510(k) process, a few are exempt by regulation.[30]

Class III devices are those under current law which "cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device," and "cannot be classified as a class II device because insufficient information exists to determine that the special controls ... would provide reasonable assurance of [their] safety and effectiveness," and are "purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," or present "a potential unreasonable risk of illness or injury, [are] to be subject ... to premarket approval to provide reasonable assurance of [their] safety and effectiveness."[31]

In other words, general and/or special controls are not sufficient to assure safe and effective use of a Class III device. Class III includes devices which are life-supporting or life-sustaining, and devices which present a high or potentially unreasonable risk of illness or injury to a patient. New devices that are not Class I or II are automatically designated as Class III unless the manufacturer files a request or petition for reclassification.[32]

Although most Class III devices require *premarket approval* (PMA), some Class III devices may have been cleared via the 510(k) process. In fact, during the first 10 years following enactment of MDA, over 80% of postamendment Class III devices entered the market on the basis of 510(k) submissions showing substantial equivalence to preamendment devices.[33] These are Class III devices that entered the market prior to regulation calling for a PMA application.[34] FDA explains the situation as follows:

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[25] QS regulation is found in 21 C.F.R. §820.

[26] See 21 C.F.R. §§862- 92.

[27] FFDCA §513(a)(1)(B).

[28] See FDA, Medical Devices, *Regulatory Controls*, 06/26/2014, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#special.

[29] Institute of Medicine, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 40.

[30] FDA, Overview of Medical Device Regulation, Medical Device Classification, Class I/II Exemptions, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051549.htm.

[31] FFDCA §513(a)(1)(C).

[32] FFDCA §513(f)(2).

[33] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 81.

[34] FDA, PMA Historical Background, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm046769.htm; and, FDA, Medical Devices, Special Considerations, Class III Certification and Summary, at: http://www.fda.gov/MedicalDevices/

> When FDA's medical device regulation program began in the late 1970s, FDA regulated over 170 Class III device types through the 510(k) program, and those devices were never required to submit PMAs, like a typical Class III device. The intent was that FDA's regulation would be temporary and that, over time, the FDA would reclassify those device types into Class I or II, or sustain the classification in Class III and call for PMA applications. This reclassification process is described in Section 515 of the Federal Food, Drug and Cosmetic Act (FD&C Act). Over the years, the FDA made significant progress on the original list of 170 devices; however, as of 2009, 26 medical device regulations still required final action.[35]

At the time that the MDA of 1976 was drafted, "relatively few medical devices were permanently implanted or intended to sustain life. The 510(k) process was specifically intended for devices with less need for scientific scrutiny, such as surgical gloves and hearing aids."[36] Over time, FDA's 510(k) review process was "challenged as new devices changed more dramatically and became more complex."[37]

In late 2009, FDA implemented the 515 Program Initiative "to facilitate action on these remaining Class III device types."[38] Examples of Class III devices that were still regulated via the 510(k) program include the metal-on-metal hip implant, certain dental implants, automated external defibrillator, electroconvulsive therapy device, pedicle screw spinal system, intra-aortic balloon and control system, and several device types related to pacemakers.[39] In 2012, FDASIA changed the process for the reclassification of a device from rulemaking to an administrative order.[40] As a result, since 2013 FDA has published a number of final orders in the *Federal Register* to reclassify many of these remaining Class III device types.[41]

Medical Device Marketing Applications

As stated above, in general, before a nonexempt medical device may be legally marketed, a manufacturer must submit to FDA either: a PMA application, and the agency may *approve* the device; or, a 510(k) notification, and the agency may *clear* the device. FDA makes its determination—either approval or clearance—based on information the manufacturer submits to the agency. The information that is required—in other words, the type of submission the manufacturer must make (if any)—is determined based on the *risk* that the device poses, if used according to the manufacturer's instructions. FDA typically evaluates more than 4,000 510(k) notifications and about 40 original PMA applications each year.[42]

DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134578.htm#classiii.

[35] FDA, CDRH Transparency, 515 Program Initiative, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm240310.htm.

[36] Diana M. Zuckerman, Paul Brown, and Steven Nissen, "Medical device recalls and the FDA approval process," *Archives of Internal Medicine*, Online publication 2011, p. E2.

[37] Ibid., p. E2.

[38] FDA, 515 Program Initiative, at http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhtransparency/ucm240310.htm.

[39] FDA, CDRH Transparency, 515 Program Status, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm240318.htm.

[40] Section 608(b) of FDASIA amended FFDCA Section 515(b).

[41] For further details, see FDA, CDRH Transparency, 515 Program Status, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm240318.htm.

[42] U.S. Congress, Senate Special Committee on Aging, *A Delicate Balance: FDA and the Reform of the Medical Device*

The Food and Drug Administration Modernization Act of 1997 (FDAMA; P.L. 105-115) gave FDA the authority to establish procedures for meeting with manufacturers prior to preparing a submission.[43] The procedures aim to speed the review process by giving FDA and a manufacturer the opportunity to address questions and concerns about the device and/or the planned studies that will be used to support the marketing application before the studies are initiated and the application is submitted.

Generally speaking, under the Federal Food, Drug and Cosmetic Act (FFDCA), manufacturers

- are prohibited from selling an adulterated product;[44]
- are prohibited from misbranding a product;[45]
- must register their facility with FDA and list all of the medical devices that they produce or process;
- must file the appropriate premarket submission with the agency at least 90 days before introducing a *nonexempt* device onto the market; and
- must report to FDA any incident that they are aware of that suggests that their device may have caused or contributed to a death or serious injury.[46]

Under the terms of the Medical Device User Fee Act (MDUFA), manufacturers must pay a fee for most types of submissions. In FY2016, the user fee for FDA review of a PMA submission is $261,388 or $65,347 for a small business; the user fee for FDA review of a 510(k) submission is $5,228 or $2,614 for a small business.[47] GAO found that in 2005, the average cost for FDA to review a PMA was $870,000 and the average cost to review a 510(k) submission was $18,200.[48] User fees account for 43% of FDA's total FY2016 program level and 28% of CDRH's program level.[49] The CDRH program level budget in FY2016 is $450 million, including $127 million in user fees.

Approval Process, Testimony of William Maisel, Deputy Center Director for Science, FDA/CDRH, 112th Cong., 1st sess., April 13, 2011.

[43] For guidance on the procedures established, see *Early Collaboration Meetings Under the FDA Modernization Act*; Final Guidance for Industry and CDRH Staff, February 28, 2001, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm.

[44] A device is adulterated if it includes any filthy, putrid, or decomposed substance, or if it is prepared, packed, or held under unsanitary conditions. The FFDCA further states that a device is adulterated if its container contains any poisonous or deleterious substance, or if its strength, purity or quality varies significantly from what the manufacturer claims. For higher class devices, a device can be considered adulterated if it fails to meet performance requirements outlined in its approval, or if it is in violation of other Good Manufacturing Practice requirements.

[45] A device is misbranded when all or part of the labeling (i.e., the FDA-approved printed material providing information about the device) is false, misleading, or missing.

[46] See FDA, Medical Devices, Regulatory Controls, 06/26/2014, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#gen.

[47] A small business is defined as a business that has $100 million or less in gross receipts or sales, including all affiliates. Those small businesses with gross receipts or sales of $30 million or less are eligible to have their first PMA fee waived. FDA, Medical Devices, Important Information on the Medical Device User Fee Rates for FY2016, at http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm457438.htm.

[48] U.S. Government Accountability Office, *Medical Devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process*, GAO-09-190, January 2009.

[49] FDA, *Justification of Estimates for Appropriation Committees, FY2017*, Washington, DC, February 2016, pp. 20 and 135. FDA also funds some device and radiological health activities with fees collected under the Mammography Quality Standards Act (MQSA, P.L. 102-539), and device user fees fund some non–device-specific activities at FDA.

The following sections describe the PMA and 510(k) submissions in more detail, and provide information about making changes to a PMA device using a supplement, the Humanitarian Device Exemption, special types of 510(k) submissions, and parallel review of a device by FDA and the Centers for Medicare & Medicaid Services (CMS).

Premarket Approval (PMA)

A PMA is "the most stringent type of device marketing application required by FDA" for new and/or high-risk devices.[50] PMA approval is based on a determination by FDA that the application contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s).[51] In contrast to a 510(k), PMAs generally require some clinical data prior to FDA making an approval decision.[52]

All clinical evaluations of investigational devices (unless exempt) must have an investigational device exemption (IDE) before the clinical study is initiated.[53] An IDE allows an unapproved device (most commonly an invasive or life-sustaining device) to be used in a clinical study to collect the data required to support a PMA submission.[54] The IDE permits a device to be shipped lawfully for investigation of the device without requiring that the manufacturer comply with other requirements of the FFDCA, such as registration and listing. In August and in November 2011, FDA released draft guidance intended to ensure the quality of clinical trials and streamline the IDE process by clarifying the criteria for approving clinical trials.[55] Final guidance on these topics was issued in 2013 and 2014.[56] All clinical studies must also receive prior approval by an institutional review board (IRB).[57]

A PMA must contain (among other things) the following information:

- summaries of nonclinical and clinical data supporting the application and conclusions drawn from the studies;

[50] FDA, Medical Devices, Premarket Approval (PMA), at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm.

[51] FFDCA §513(a)(1)(C); 21 C.F.R. §814.

[52] 21 C.F.R. §814.

[53] See 21 C.F.R. §812. Devices are exempt from IDE requirements when testing is noninvasive, does not require invasive sampling, does not introduce energy into a subject, and is not stand alone (i.e., is not used for diagnosis without confirmation by other methods or medically established procedures). See 21 C.F.R. §812.2(c)(3).

[54] FDA, *Device Advice: Investigational Device Exemption (IDE)*, July 9, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm.

[55] FDA, "FDA seeks comment on proposed guidance for high-quality clinical studies," FDA, press release, August 15, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268000.htm; and, "FDA issues two draft guidance documents to facilitate investigational medical device studies in humans," press release, November 10, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279459.htm.

[56] See *Design Considerations for Pivotal Clinical Investigations for Medical Devices*, at http://www.fda.gov/RegulatoryInformation/Guidances/ucm373750.htm, *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies*, at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf, and *FDA Decisions for Investigational Device Exemption Clinical Investigations*, at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf.

[57] An IRB is a group, generally comprised of volunteers, that examines proposed and ongoing scientific research to ensure that human subjects are properly protected. See 45 C.F.R. §46.107.

- a device description including significant physical and performance characteristics;
- indications for use, description of the patient population and disease or condition that the device will diagnose, treat, prevent, cure, or mitigate;
- a description of the foreign and U.S. marketing history, including if the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device;
- proposed labeling; and
- a description of the manufacturing process.[58]

Approval is based not only on the strength of the scientific data, but also on inspection of the manufacturing facility to ensure that the facility and the manufacturing process are in compliance with the quality system (QS) regulation.[59] FDAMA made it easier for manufacturers to submit the required sections of a PMA in a serial fashion as data are available ("modular PMA").

When a PMA is first received by FDA, it has 45 days to make sure the application is administratively complete. If not, the application is returned. If the application is complete, it is formally filed by FDA. The agency then has 75 days to complete the initial review and determine whether an advisory committee meeting will be necessary.

Advisory committees may be convened to make recommendations on any scientific or policy matter before FDA.[60] They are composed of scientific, medical, and statistical experts, and industry and consumer representatives. An advisory committee meeting allows interested persons to present information and views at a public hearing.[61] FDA typically accepts advisory committee recommendations for an application (approvable, approvable with conditions, or nonapprovable). However, there have been cases where FDA's decision has not been consistent with the committee's recommendation. CDRH will hold joint advisory committee meetings with other FDA centers when necessary. Though FDA regulations allow 180 days to review the PMA and make a determination, total review time can be much longer.[62] MDUFA performance goals have been established to reduce the review time for PMAs.[63]

As a condition of approval for a PMA device, FDA may order a post-approval study to obtain information on device safety, effectiveness, and/or reliability over long-term use of the device in

[58] FDA, Medical Devices, PMA Application Contents, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050289.htm.

[59] 21 C.F.R. §820.

[60] For further information, see http://www.fda.gov/AdvisoryCommittees/.

[61] 21 C.F.R. §14.

[62] For example, see *1st Quarter FY2016 Package, MDUFA III (FY2013-2017) Performance*, February 18, 2015, p. 15, at http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM487953.pdf. See also 21 C.F.R. §814.40.

[63] FDA officials meet with industry leaders to agree upon mutually acceptable fee types, amounts, and performance goals. The agreement specifies that, in return for the additional resources provided by medical device user fees, FDA is expected to meet performance goals defined in a letter, generally referred to as the "FDA Commitment Letter," from the HHS Secretary to the Chairmen and Ranking Minority Members of the Committee on Health, Education, Labor and Pensions of the U.S. Senate and the Committee on Energy and Commerce of the U.S. House of Representatives. This process is similar to the one used for prescription drug user fees under the Prescription Drug User Fee Act (PDUFA). For further information on MDUFA, see CRS Report R44517, *The FDA Medical Device User Fee Program: MDUFA IV Reauthorization*, by Judith A. Johnson. For further information on PDUFA, see CRS Report RL33914, *The Prescription Drug User Fee Act: History Through the 2007 PDUFA IV Reauthorization*, by Susan Thaul.

real world populations (as opposed to clinical studies).[64] A report published in November 2014 by *JAMA Internal Medicine* analyzed 223 post-approval studies of 158 medical devices ordered to be conducted by FDA between 2005 and 2011.[65] The report found that delays in launching and completing such studies were common. The report found limited information on the causes of study delays and variable detail provided on the reason a post-approval study (PAS) was ordered. According to the authors, "the FDA has never issued a warning letter to a manufacturer for failing to start or complete a mandated PAS, which may undermine its authority in ordering these studies. The most common effect of a PAS was a change to device labeling. The influence of such label changes is unknown."[66]

In 2015, 98% of PMAs accepted for filing were approved by FDA.[67] After FDA notifies the applicant that the PMA has been approved, a notice is posted on the Internet for the approved PMA, making available a summary of the safety and effectiveness data upon which the approval is based and providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.[68]

PMA Supplements

If a manufacturer wants to make a change to an approved PMA device, it must submit to FDA one of several different types of PMA supplements to request agency approval of the device change.[69] The various types of PMA supplements and associated fees are briefly described in **Table 2**. The manufacturer is also required to pay a user fee, except in the case of the Special PMA Supplement. FDA provides information about approved PMA supplements on the FDA website.[70]

Table 2. Types of PMA Supplements

Type of Supplement	Types of Changes to Device	Data Required	User Fee FY2016 (small business fee)	Reviewer	Year Introduced
Panel-track[a]	Significant design change; new indication	Clinical; limited preclinical data in some cases	$196,041 ($49,010)	Panel of subject matter experts and/or FDA staff	1990

[64] For further information, see FDA, Medical Devices, *Post-Approval Studies (PAS) - Frequently Asked Questions (FAQ)*, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovaStudies/ucm135263.htm, and *Post-Approval Studies*, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovaStudies/default.htm.

[65] Ian S. Reynolds, Joshua P. Rising, and Allan J. Coukell, et al., "Assessing the Safety and Effectiveness of Devices After US Food and Drug Administration Approval: FDA-Mandated Postapproval Studies," *JAMA Internal Medicine*, vol. 174, no. 11 (November 2014), pp. 1773-1779.

[66] Ibid., p. 1777.

[67] *1st Quarter FY2016 Package, MDUFA III (FY2013-2017) Performance*, February 18, 2015, p. 22, at http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM487953.pdf.

[68] FDA, Medical Devices, PMA Approvals, at http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/pmaapprovals/default.htm.

[69] FFDCA §515(d)(6); 21 C.F.R. §814.39. For further information on PMA supplements, see FDA, *Guidance for Industry and Staff, Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision-Making Process*, December 11, 2008, at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM270606.pdf.

[70] FDA, Medical Devices, PMA Approvals, at http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/pmaapprovals/default.htm.

Type of Supplement	Types of Changes to Device	Data Required	User Fee FY2016 (small business fee)	Reviewer	Year Introduced
180-day[b]	Significant design change; labeling change	Preclinical; confirmatory clinical data in some cases	$39,208 ($9,802)	FDA staff	1986
Real-time[c]	Minor design change to device, software, sterilization, or labeling	Preclinical only	$18,297 ($4,574)	FDA staff	1997
30-day notice[d]	Manufacturing change	No specific data requirements	$4,182 ($2,091)	FDA staff	1997
Special[e]	Labeling change that enhances device safety	No specific data requirements	No fee.	FDA staff	1986

Source: Based on table in Benjamin N. Rome, Daniel B. Kramer, and Aaron S. Kesselheim, "FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012," *JAMA*, vol. 311, no. 4 (January 22/29, 2014), p. 386, and current user fee information at http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm452519.htm.

a. Defined at FFDCA §737(4)(B). Not all panel-track supplements require a Panel meeting of an independent panel of experts. FDA, *Guidance for Industry and Staff, Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision-Making Process*, p. 7.

b. Defined at FFDCA §737(4)(C). A Manufacturing Site Change Supplement is considered to be a type of 180-Day Supplement. FDA, *Guidance for Industry and Staff, Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision-Making Process*, p. 21.

c. Defined at FFDCA §737(4)(D). FDA staff meets with the manufacturer and usually issues a same day decision on the supplement. FDA, *Guidance for Industry and FDA Staff, Real-Time Premarket Approval Application (PMA) Supplements*, April 28, 2006, at http://www.fda.gov/RegulatoryInformation/Guidances/ucm089602.htm.

d. Defined at FFDCA §737(5). The device may be distributed 30 days after FDA receives the notice unless the agency finds the notice to be inadequate. Then FDA will inform the manufacturer in writing that a 135-day PMA supplement is required. FDA, *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*, April 13, 2011, at http://www.fda.gov/RegulatoryInformation/Guidances/ucm080192.htm.

e. This is a "narrow exception to the general rule that prior FDA approval of changes to a PMA, including the labeling for a device, is a condition of lawful distribution." It is used when a manufacturer has "newly acquired safety-related information" and "the information involves labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction." FDA, *Guidance for Industry and Staff, Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision-Making Process*, p. 17.

Devices approved via a PMA supplement have smaller fees, shorter review times, and often do not require the collection of premarket clinical data. Clinical data refers to data obtain during a clinical trial involving human subjects and preclinical data refers to mechanical engineering tests as well as animal studies. The features of the PMA supplement "encourage manufacturers to implement evolving technologies to create new models of devices that are incrementally different from previously approved additions. This helps facilitate rapid improvement in device

technology, but also means that high-risk medical devices can gain PMA approval as supplements without any direct clinical study of the specific change made to the device."[71]

Evaluations of the PMA and PMA Supplement Process

As mentioned above, FDA considers a PMA to be the most stringent type of device marketing application required for new and/or high-risk devices. However, studies in the academic medical literature have questioned the quality of the data submitted to the agency in support of PMA applications.

Randomized controlled trial (RCT): participants are randomly assigned to two or more groups. One group receives the intervention (the new treatment), while the control group receives current therapy or placebo. Randomization ensures that any patient characteristics that might affect the outcome will be roughly equal across each group in the study. Any difference in outcomes between the groups is then likely due to the intervention. The RCT is often called the gold standard of evidence for a clinical trial.

Blinded clinical trial: participants, caregivers, and outcome assessors are prevented from knowing which intervention was received by the participants until the trial has ended. Using a blinded trial design is, along with randomization, another mechanism to help ensure that the trial results are not biased in favor of the intervention.

A December 2009 report in *JAMA (Journal of the American Medical Association)* reviewed data submitted to support PMAs for high-risk cardiovascular devices that received FDA approval between 2000 and 2007. The authors found that 65% of the PMA applications were based on a single study that often was not a high-quality randomized controlled clinical trial.[72] This is in contrast to drug applications, which require two randomized well-controlled trials.[73] For a comparison of FDA premarket review processes for drugs and devices, see **Table A-1**. The *JAMA* report found that only 27% of all cardiovascular PMAs were based on a randomized trial and only 14% of the trials of cardiovascular devices used a blinded design.

In addition, the 2009 *JAMA* report also found that a majority (88%) of the cardiovascular studies used surrogate end points, "which may not be reliable predictors of actual patient benefit."[74] A surrogate end point of a clinical trial "is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives."[75] An example of a surrogate is measurement of cholesterol level that is used as a surrogate marker for the clinical end point, death from heart disease. A drug that lowers cholesterol, however, may not lengthen life.

The authors of the 2009 *JAMA* study chose to examine cardiovascular devices "because it was expected they would undergo the most stringent approval process given their far-reaching impact on morbidity and mortality and their increasing use."[76] The authors stated that their findings "raise questions about the quality of data on which some cardiovascular device approvals are

[71] Benjamin N. Rome, Daniel B. Kramer, and Aaron S. Kesselheim, "Approval of High-Risk Medical Devices in the US: Implications for Clinical Cardiology," *Current Cardiology Reports*, vol. 16, no. 6 (June 2014), pp. 489-502.

[72] Sanket S. Dhruva, Lisa A. Bero, and Rita F. Redberg, "Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices," *JAMA*, vol. 302, no. 24 (December 23, 2009), pp. 2679-2685.

[73] FFDCA §505(d); 21 C.F.R. §314.126.

[74]. Sanket S. Dhruva, Lisa A. Bero, and Rita F. Redberg, "Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices," *JAMA*, vol. 302, no. 24 (December 23, 2009), p. 2683.

[75] Ibid., p. 2681.

[76] Ibid., p. 2680.

based."[77] They argue that in comparison with drug approval, "the bar for evidence of benefit should be higher for devices because they are implanted and cannot simply be discontinued, as drugs can."[78] The importance of FDA device approval versus clearance is significant, as it may preempt consumer lawsuits on device safety leaving injured patients no avenue of legal recourse or redress.[79]

Decisions by physicians and patients could be more informed regarding the use of high-risk devices, such as cardiovascular devices, if the clinical trial data that FDA reviews to support approval were more accessible. A June 2015 *BMJ (British Medical Journal)* report found selective reporting problems in the medical literature regarding the published trials of high-risk cardiovascular medical devices.[80] Reporting bias is a well-documented problem in the drug-related medical literature. Those who have analyzed clinical trial information in FDA new drug applications and compared it with the corresponding publications in the medical literature have found the selective reporting of favorable results in the literature. "Results favoring the new drug over the comparator were significantly more likely to be reported in the literature than unfavorable results. The selective publication of favorable results for drugs includes several types of reporting bias," including failure to publish entire studies and failure to publish unfavorable outcomes.[81]

The June 2015 *BMJ* report, the first of its kind, found that "half (51%) of clinical studies of novel high risk cardiovascular devices remain unpublished over two years after FDA approval.... When these studies are published, there are often clinically relevant discrepancies between FDA documents and corresponding publications."[82] According to the authors, these findings "point to the importance of mandatory registration on a public clinical trials platform. Clinicaltrials.gov is an important step in this direction, but recent data show that published trials often have discrepant findings between clinicaltrial.gov and publications."[83] The authors state that "the accessibility and user friendliness of FDA reports needs to be considerably improved. As clinicians can use devices immediately after FDA approval, it is in the public interest that all of the data be available to clinicians at that time."[84]

A January 2014 *JAMA* report examined FDA approval of cardiac implantable electronic devices (CIEDs)—such as pacemakers, implantable cardioverter-defibrillators (ICDs), and other cardiac devices—via the PMA process and the PMA supplement process.[85] CIEDs were chosen as "a

[77] Ibid., p. 2684.

[78] Ibid.

[79] The interaction between state tort laws and the federal regulation of medical devices and drugs has been a source of constant litigation in recent years. In the past two decades, the Supreme Court has issued several decisions concerning whether the FFDCA preempts state tort law. The results have been mixed: in some cases, a person injured by an allegedly defective drug or device is barred from suing a manufacturer, whereas in other cases, the Supreme Court has allowed a lawsuit to proceed. Following these decisions, ambiguities exist concerning the scope of federal preemption in these medical device and drug cases. For further information, see CRS Report R43218, *Preemption of Drug and Medical Device Claims: A Legal Overview*, by Andrew Nolan and Jennifer A. Staman.

[80] Lee Chang, Sanket S. Dhruva, Janet Chu, et al., "Selective reporting in trials of high risk cardiovascular devices: cross sectional comparisons between premarket approval summaries and published reports," *BMJ*, vol. 350 (June 10, 2015), pp. 1-7.

[81] Ibid.

[82] Ibid., pp. 1, 5.

[83] Ibid., p. 6

[84] Ibid.

[85] Benjamin N. Rome, Daniel B. Kramer, and Aaron S. Kesselheim, "FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012," *JAMA*, vol. 311, no. 4 (January 22/29,

useful case study because they have been the subject of substantial evolution over the past 30 years," and the authors sought to "characterize the nature of the changes in each supplement and understand the data supporting these changes."[86] The first CIED was approved by FDA via the PMA process in 1979. The report found that from 1979 to 2012, FDA approved 77 CIED PMAs and 5829 PMA supplements based on those 77 original CIED PMAs. That represents a median of 50 supplements per original PMA. The authors warn clinicians and patients that "clinical data are rarely collected as part of PMA supplement applications prior to marketing."[87] Of the 5829 PMA supplements, almost half (2,754, 47%) were allowed onto the market via the 30-day notice supplement, about a quarter were 180-day supplements (1,538, 26%), and another quarter were real-time supplements (1,312, 23%) and special supplements (108, 2%); only a small fraction used the more rigorous panel-track supplement (15, 0.3%).[88]

Medtronic Sprint Fidelis and St Jude Medical Riata

The Sprint Fidelis and the Riata leads are specific models of cardiac electrodes (thin wires) that connect an implantable cardioverter-defibrillator (ICD) directly to the heart. An ICD monitors heart rhythms and can deliver an electrical shock to restore normal rhythm if life-threatening, irregular heartbeats are detected. The ICD keeps the heart from going too fast and is surgically implanted in patients who may be at risk of sudden cardiac arrest. Both the Medtronic Sprint Fidelis and the St Jude Medical Riata were recalled because of the potential for wire fracture, causing the ICD to deliver an unnecessary shock or to not operate at all. Deaths and serious injuries were reported in which a fractured Sprint Fidelis or Riata lead may have been a possible or likely contributing factor. As of October 4, 2007, there had been about 268,000 Sprint Fidelis leads implanted worldwide, including 172,000 Sprint Fidelis leads implanted in the United States. More than 227,000 Riata leads had been distributed worldwide and as of 2011, about 79,000 Riata leads remained implanted in U.S. patients.

Sources: FDA website at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm103022.htm and http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314930.htm.

Two medical device recalls that were widely reported in the media—the Medtronic Sprint Fidelis and St Jude Medical Riata ICD leads—both entered the market via the PMA supplement process. The Medtronic Sprint Fidelis was a 180-day supplement, and the St Jude Medical Riata was a real-time supplement; neither was studied in human trials prior to FDA approval. According to the authors of the January 2014 *JAMA* report, the "FDA's approval of many supplements without new human trials, as in the case of these recent ICD changes, highlights the importance of collecting rigorous postapproval performance data."[89] Yet the January 2014 *JAMA* report states that postapproval studies for devices on the market via a PMA supplement are uncommon.[90] PMA supplements "allow patients to benefit from incremental innovation in device technology by providing efficient and inexpensive FDA review pathways for smaller device changes."[91] However, many such minor design changes may add up to a substantial difference from the device approved in the original PMA application.[92] Therefore, the

2014), pp. 385-391.

[86] Ibid., p. 386.

[87] Ibid., p. 389.

[88] Ibid., p. 387. Data were missing for 102 supplements (2%).

[89] Ibid., p. 389.

[90] Ibid., p. 390.

[91] Ibid., p. 386.

[92] Ibid., p. 390.

authors of the January 2014 *JAMA* study recommend "more widespread implementation of rigorous postmarket studies to evaluate device performance once approved for clinical use."[93]

As stated previously in this section, others might also argue that because such devices are implanted within the patient, and cannot be easily removed without the risk of causing major complications, the evidence of benefit should be higher for devices during the FDA premarket review process in comparison with the evidence for drugs. Allowing innovative but potentially defective devices to quickly enter the market may leave large numbers of patients and their physicians with very difficult decisions.

For example, the failure rate for the Sprint Fidelis lead was 2.8% per year.[94] When the lead fails, it can deliver a painful and unnecessary shock (750 volts) to the patient's heart. According to one cardiologist, "[m]ost patients can tolerate one shock, as the pain is over almost before the brain has time to process the magnitude of the insult. But almost no one can tolerate multiple shocks. The first shock starts the fear cycle. First is extreme anxiety, but after a second or third shock, anxiety from the possibility of more shocks progresses quickly to near terror."[95]

The risk of major complications in replacing the lead is 15.3%.[96] The leads "run a long course through the veins into the heart. The body's natural healing process forms scar tissue at multiple sites along the lead that can create strong attachments to the wall of a blood vessel or a heart chamber. Freeing a lead from these attachments requires considerable skill and experience and is more difficult and risky than implanting the leads in the first place."[97] Therefore, if a lead does not show signs of malfunction, most patients would be closely watched rather than receive prophylactic surgery to remove the lead.

In two announcements, dated October 2015 and February 2016, the Department of Justice (DOJ) stated that over 500 hospitals in 43 states had been fined more than $280 million for implanting ICDs in "Medicare patients in violation of Medicare coverage requirements.... In terms of the number of defendants, this is one of the largest whistleblower lawsuits in the United States."[98] The DOJ announcement provides further details about the settlement:

> Medicare coverage for the device, which costs approximately $25,000, is governed by a National Coverage Determination (NCD). [CMS] implemented the NCD based on clinical trials and the guidance and testimony of cardiologists and other health care providers, professional cardiology societies, cardiac device manufacturers and patient advocates. The NCD provides that ICDs generally should not be implanted in patients who have recently suffered a heart attack or recently had heart bypass surgery or angioplasty. The medical

[93] Ibid.

[94] Robert G. Hauser, William H. Maisel, and Paul A. Friedman, et al., "Longevity of Sprint Fidelis Implantable Cardioverter-Defibrillator Leads and Risk Factors for Failure: Implication for Patient Management," *Circulation*, vol. 123 (February 1, 2011), pp. 358-363.

[95] John Mandrola, "Double counting...," July 14, 2010, http://www.drjohnm.org/2010/07/double-counting/.

[96] Jeanne E. Poole, Marye J. Gleva, and Theofanie Mela, et al., "Complication Rates Associated with Pacemaker or Implantable Cardioverter-Defibrillator Generator Replacements and Upgrade Procedures: Results from the REPLACE Registry," *Circulation*, vol. 122 (October 19, 2010), pp. 1553-1561.

[97] Eric Buch, Noel G. Boyle, and Peter H. Belott, "Pacemaker and Defibrillator Lead Extraction," *Circulation*, March 22, 2011, pp. e378-e380.

[98] Department of Justice, Office of Public Affairs, "Fifty-One Hospitals Pay United States More Than $23 Million to Resolve False Claims Act Allegations Related to Implantation of Cardiac Devices," press release, February 17, 2016, https://www.justice.gov/opa/pr/fifty-one-hospitals-pay-united-states-more-23-million-resolve-false-claims-act-allegations; and, "Nearly 500 Hospitals Pay United States More Than $250 Million to Resolve False Claims Act Allegations Related to Implantation of Cardiac Devices," press release, October 30, 2015, https://www.justice.gov/opa/pr/nearly-500-hospitals-pay-united-states-more-250-million-resolve-false-claims-act-allegations.

> purpose of a waiting period—40 days for a heart attack and 90 days for bypass/angioplasty—is to give the heart an opportunity to improve function on its own to the point that an ICD may not be necessary. The NCD expressly prohibits implantation of ICDs during these waiting periods, with certain exceptions. The Department of Justice alleged that from 2003 to 2010, each of the settling hospitals implanted ICDs during the periods prohibited by the NCD.[99]

According to Dr. Rita Redberg, a cardiologist at the University of California, San Francisco, and editor of *JAMA Internal Medicine*, "Hospitals put ICDs in people outside the coverage guidelines who would not get a benefit and likely suffer. It's a big invasive procedure, and the guidelines are there to make sure that for people who are getting the procedure the benefits outweigh the harm."[100] Dr. Redberg reviewed cases for the DOJ and indicated that "many, if not most of the cases we looked at not only violated the CMS guidelines, but were also unjustified by any clinical data other than the MD's opinion, and were clearly outside any boundaries of good or appropriate care."[101]

Bryan Vroon, the attorney who represented the whistleblowers in the Medicare ICD false claims suit, states that "since the beginning of the DoJ investigation in 2008, the number of surgeries to implant the device has dropped by about 28%, reaping a savings for Medicare of some $2 billion over the five years that followed."[102] Unnecessary and potentially harmful ICD implantation surgery is less of a problem in Europe. "The implantation rates for all types of devices are lower in Europe than in the United States; thus, the need for [lead] extraction can be expected to be higher in the United States than in Europe."[103]

Humanitarian Device Exemption (HDE)

The Safe Medical Devices Act of 1990 (SMDA, P.L. 101-629) authorized the Humanitarian Device Exemption (HDE) to encourage the development of devices that aid in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. An HDE application is similar to a PMA, but it is exempt from the effectiveness requirements to encourage manufacturers to develop devices for these small markets.

However, there are some important restrictions: there is a 4,000-unit limit per year on the number of devices shipped, and use of an HDE device requires approval by an institutional review board (IRB) at the institution where the device is to be used.[104] The IRB process may involve "substantial costs for meticulous record keeping, application production, and IRB fees (which could involve hundreds of sites)."[105] Also, there is "the potential for insurers not to cover the device (for lack of evidence of efficacy)."[106]

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[99] Ibid.

[100] Trudy Lieberman, "With clout growing, hospitals avoid negative coverage of huge fines, safety violations," *HealthNewsReview*, March 21, 2016, http://www.healthnewsreview.org/2016/03/with-clout-growing-hospitals-avoid-negative-coverage-of-huge-fines-safety-violations/.

[101] Ibid.

[102] Ibid.

[103] Charles Kennergren, "A European Perspective on Lead Extraction: Part 1," *Heart Rhythm*, vol. 5, no. 1 (January 2008), pp. 160-162.

[104] 21 C.F.R. §814.100, §814.104(b)(5), and §814.124.

[105] IOM, *Rare Diseases and Orphan Products: Accelerating Research and Development*, Washington, DC, 2010, p. 236, http://books.nap.edu/catalog.php?record_id=12953.

[106] Ibid.

In the past, the device sponsor was also not allowed to make a profit on the sale of the HDE device if its price was more than $250. FDAAA (P.L. 110-85) removed the restriction on profit for HDEs developed for pediatric use and required GAO to report by 2012 on the impact of removing this restriction.[107] FDASIA allows an HDE device to qualify for an exemption to the general ban on selling such devices for a profit if the HDE device is intended for the treatment or diagnosis of (1) a disease or condition that does not occur in pediatric patients, or (2) that occurs in pediatric patients in such numbers that device development is impossible, highly impracticable, or unsafe.[108] Also, a sponsor of a device granted an HDE prior to FDASIA's enactment may seek a determination as to whether it would qualify for an exemption to the profit ban.

In order for a device to receive HDE marketing approval, there cannot be another legally marketed device, either via the 510(k) process or the PMA process, available to treat or diagnose the disease or condition. Once a device with the same intended use as the humanitarian use device is approved or cleared, an HDE cannot be granted for the humanitarian use device.[109] However, the agency will "consider an HDE application if a comparable device has been approved under another HDE or if a comparable device is being studied under an IDE."[110]

Parallel Review: FDA Approval or Clearance and Medicare National Coverage Determinations (NCDs)[111]

CMS requires as a condition of coverage under the Medicare program, with certain exceptions, that devices (including IVDs) be FDA-approved or cleared where such approval or clearance is required. This approval does not guarantee coverage, as there are a number of other factors that CMS considers in its coverage decisions. CMS has stated that manufacturers will often focus their efforts on gaining FDA approval, without realizing that upon receiving such approval, Medicare coverage of the device is not automatic. Most private payer coverage decisions also require FDA approval where such approval is required by law. For example, BlueCross BlueShield's Technology Evaluation Center (TEC) requires that final FDA approval be received where required by law.

There are a few specific circumstances where a device may be covered under Medicare without FDA approval or clearance. These include cases where the FDA has (1) granted an investigational device exemption (IDE); (2) provided a classification of nonexperimental investigational device, for which underlying questions of safety and effectiveness have been resolved for that device type; and (3) required that clinical trials be conducted, with Medicare beneficiaries participating in the FDA-approved clinical trial.

Importantly, Medicare coverage determinations are often closely monitored by private health insurance plans, and many private plans will follow Medicare's decisions. Therefore, a decision by CMS to cover a device through a positive national coverage determination (NCD) will often result in more rapid diffusion and adoption of that device in the health care system. For this

[107] U.S. Government Accountability Office, *Pediatric Medical Devices: Provisions Support Development, but Better Data Needed for Required Reporting*, 12-225, December 20, 2011, http://gao.gov/assets/590/587164.pdf.

[108] Section 613 of FDASIA.

[109] For additional information, see *Guidance for Industry and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers*, July 18, 2006, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071473.htm.

[110] IOM, *Rare Diseases and Orphan Products: Accelerating Research and Development*, Washington, DC, 2010, p. 216, http://books.nap.edu/catalog.php?record_id=12953.

[111] This section was written by Amanda Sarata.

reason, from the perspective of the device manufacturer, CMS's coverage decision carries significant weight.

The statutory basis of and processes used for determining FDA approval (or clearance) of a device are distinct from the statutory basis of and processes used by CMS to make its NCDs. In each case, the purpose of the review differs, as do the contextual factors of the decision. FDA review and Medicare NCDs are usually carried out in a serial manner (i.e., one after the other). However, in order to try to shorten the timeframe for getting a device into clinical use, in October 2011 CMS and FDA launched a two-year pilot program for the parallel review of medical products.[112] The pilot program was extended for an additional two years, effective December 2013.[113]

Although the agency has not formally extended the pilot program beyond December of 2015, the original Memorandum of Understanding (MOU) between FDA and CMS from 2010 that was created to facilitate the parallel review pilot was amended in 2015 to have a termination date of "indefinite." The original MOU termination date was no later than five years after it was signed, in June 2010.[114] Congress has expressed interest in the ongoing status of the parallel review pilot. Both the House and Senate Appropriations Committee reports, accompanying the respective Agriculture appropriations bills, included language directing FDA to report on whether it plans to extend the pilot and how it anticipates encouraging more manufacturers to participate.[115] In addition, based partially on the experience with the parallel review pilot, FDA published a request for expressions of interest from coverage organizations who would like to share input on coverage decisions with medical device sponsors. The agency states that it has realized the value of earlier discussions between the agencies, payers and manufacturers with respect to which information and evidence may be needed to support a positive coverage decision.[116]

On August 11, 2014, FDA announced that it had approved a product for the first time through the CMS Parallel Review Program, resulting in the simultaneous FDA approval of the product (Exact Sciences' Cologuard) and CMS issuance of a proposed NCD for the product.[117] The agencies plan to evaluate the pilot once a representative group of products have gone through the process and to extend the program to both drugs and biologics.

510(k) Notification

In general, a 510(k) submission is required for a moderate-risk medical device that is not exempt from premarket review. A 510(k) could also be used for currently marketed devices for which the manufacturer seeks a new indication (e.g., a new population, such as pediatric use, or a new

[112] FDA, "FDA, CMS launch pilot program for voluntary parallel review of innovative devices," press release, October 7, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm274833.htm.

[113] FDA and CMS, "Pilot Program for Parallel Review of," 78 *Federal Register* 76628-76629, December 18, 2013.

[114] FDA and CMS, "Memorandum of Understanding Between United States Food and Drug Administration and Centers for Medicare & Medicaid Services," http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm217585.htm.

[115] U.S. Congress, Senate Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill,* 2017, report to accompany S. 2956, 114th Cong., 2d sess., S. Rept. 114-259, (Washington, DC: GPO, 2016), p. 90; and U.S. Congress, House Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill,* 2017, report to accompany H.R. 5054, 114th Cong., 2d sess., H. Rept 114-531, (Washington, DC: GPO, 2016), p. 70.

[116] 81 *Federal Register* 9203, February 24, 2016.

[117] FDA, "FDA approves first non-invasive DNA screening test for colorectal cancer," press release, August 11, 2014, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm409021.htm.

disease or condition), or for which the manufacturer has changed the design or technical characteristics such that the change may affect the performance characteristics of the device.

Between 1996 and 2009, more than 80% of the devices cleared by FDA using 510(k) notification were Class II devices, about 10% were Class I and less than 5% were Class III.[118] A 2009 GAO report found that 25% of the 10,670 Class II devices cleared by FDA in FY2003 through FY2007 were either implantable, life sustaining or presented significant risk to the health, safety, or welfare of the patient.[119] The agency cleared about 90% of 510(k) submissions reviewed during FY2003 through FY2007.[120]

According to FDA data, 85% of 510(k)s accepted for review in 2015 were determined to be substantially equivalent.[121] As noted previously, the standard for clearance of a traditional 510(k) is substantial equivalence with a predicate device. A predicate device can be one of two things. It can be a previously cleared Class I or II device that does not require a PMA. It can also be preamendment Class III for which the agency has not issued regulations requiring a PMA. (PMAs, which are more rigorous submissions than 510(k)s, are discussed in the "Premarket Approval (PMA)" section.)

A manufacturer may choose one of three types of 510(k) submissions for premarket clearance: traditional, special, or abbreviated.[122] A study of 510(k) submissions between 1996 and 2009 found that about 80% were traditional, 16% were special, and 3% were abbreviated.[123] For novel devices without a predicate, there is another alternative called the de novo 510(k) process.

Traditional 510(k)

A traditional 510(k) must include the name of the device, a description of the device, a comparison with a predicate device, the intended use of the device, and the proposed label, labeling, and advertisements for the device and directions for use.[124] Studies supporting a 510(k) submission are usually preclinical studies (laboratory testing), not clinical studies (in human beings). Substantial equivalence, in many cases, means only that the device performs in a similar fashion to the predicate under a similar set of circumstances. As a result, many devices never have to demonstrate safety and effectiveness through studies using human subjects.

In addition to not requiring clinical studies, three other characteristics of the 510(k) process make it much less rigorous than the PMA process: (1) premarket inspections of how devices were manufactured are generally not required by FDA; (2) postmarket studies are not required by FDA

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[118] IOM, *Public Health Effectiveness of the FDA 510(k) Clearance Process: Measuring Postmarket Performance and Other Select Topics*, Workshop Report, Washington, DC, 2011, pp. 12 and 78.

[119] U.S. Government Accountability Office, *Medical Devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process*, GAO-09-190, January 2009, p. 18.

[120] Ibid., p. 27.

[121] *1st Quarter FY2016 Package, MDUFA III (FY2013-2017) Performance*, February 18, 2015, p. 199, at http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM487953.pdf.

[122] FDA, Medical Devices, 510(k) Submission Methods, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm.

[123] IOM, *Public Health Effectiveness of the FDA 510(k) Clearance Process: Measuring Postmarket Performance and Other Select Topics*, Workshop Report, Washington, DC, 2011, pp. 12 and 79.

[124] FDA, Medical Devices, *How to Prepare a Traditional 510(k)*, Content and Format of a Traditional 510(k), 07/01/2015; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134572.htm#link_4.

as a condition of clearance; and (3) FDA has limited authority to rescind or withdraw clearance if a 510(k) device is found to be unsafe or ineffective.[125]

FDA may take any of the following actions on a 510(k) after conducting its review:

- find the device substantially equivalent to the predicate and issue a clearance letter;
- find the device not substantially equivalent (NSE) and issue an NSE letter prohibiting marketing;
- determine that the device is exempt from a 510(k) submission;
- request additional information (with the final clearance decision pending review of that information).[126]

A manufacturer generally has 30 days to provide any additional information, or FDA may issue a notice of withdrawal of the application.[127] The manufacturer may, at any time, withdraw its 510(k). FDA has 90 days to review a traditional 510(k).[128]

Abbreviated and Special 510(k)s

Abbreviated and special 510(k)s were new approaches to premarket notification that came from FDAMA. These approaches were intended to streamline and expedite FDA's review for routine submissions meeting certain qualifications, thus leaving reviewer time for more complicated submissions.

An abbreviated 510(k) uses guidance documents developed by FDA to communicate regulatory and scientific expectations to industry.[129] Guidance documents have been prepared for many different kinds of devices, and are available on FDA's website. All guidance documents are developed in accordance with Good Guidance Practices (GGP), and many with public participation or opportunities for public comment.[130] In addition to issuing guidance documents, FDA can either develop performance or consensus standards or 'recognize' those developed by outside parties.[131] In an abbreviated 510(k), the manufacturer describes what guidance document, special control, or performance standard was used, and how it was used to assess performance of their device. Other minimum required elements are the product description, representative labeling, and a summary of the performance characteristics. FDA typically reviews an abbreviated 510(k) in 60 days.

A special 510(k) may be used for a modification to a device that has already been cleared under the 510(k) process.[132] It typically uses the design control requirement of the Quality System (QS)

[125] Diana M. Zuckerman, Paul Brown, and Steven Nissen, "Medical device recalls and the FDA approval process," *Archives of Internal Medicine*, Online publication 2011, p. E4.

[126] 21 C.F.R. §807.100(a).

[127] 21 C.F.R. §807.87(l).

[128] The FDA time clock (i.e., review cycle) begins when FDA receives the 510(k) and ends with the date that FDA issues either a request for additional information or a decision. More than one cycle may occur before FDA issues its final decision.

[129] FDA, Medical Devices, *510(k) Submission Methods*, Abbreviated 510(k), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm#abbrev.

[130] 21 C.F.R. §10.115. FDA continually accepts public comment on any draft or final guidance document.

[131] 21 C.F.R. §861.

[132] FDA, Medical Devices, *510(k) Submission Methods*, Special 510(k), http://www.fda.gov/MedicalDevices/

regulation.[133] The QS regulation describes the good manufacturing practice (GMP) requirements for medical devices.[134] The special 510(k) allows the manufacturer to declare conformance to design controls without providing the data. This type of submission references the original 510(k) number, and contains information about the design control requirements. FDA aims to review most special 510(k)s in 30 days.

De Novo 510(k)

Under the FFDCA, novel devices lacking a legally marketed predicate are automatically designated Class III. FDAMA amended FFDCA Section 513(f) to allow FDA to establish a new, expedited mechanism for reclassifying these devices based on risk, thus reducing the regulatory burden on manufacturers. The de novo 510(k), though requiring more data than a traditional 510(k), often requires less information than a premarket approval (PMA) application.

Under the original de novo 510(k) process created in 1997 by FDAMA, the manufacturer submitted a traditional 510(k) for its device. Because there was no predicate device or classification, FDA would return a decision of not substantially equivalent. Within 30 days, the manufacturer would submit a petition requesting reclassification of its device into Class II or I, as appropriate. Within 60 days, FDA would render a decision classifying the device.

Section 607 of FDASIA modified FFDCA Section 513(f)(2), creating an alternative de novo pathway that does not require that a device be reviewed first under a 510(k) and found NSE prior to submission of a de novo. FDA has released draft guidance on the alternative de novo review process.[135] "Under the new de novo pathway, if a person believes their device is appropriate for classification into Class I or Class II and determines there is no legally marketed predicate device, they may submit a de novo without a preceding 510(k) and NSE."[136] This classification request may be declined by FDA if there exists a legally marketed device on which to base a substantial equivalence review, or if the new device is not a low-moderate risk device or general controls would be inadequate to control risks and special controls cannot be developed.

Assessments of the 510(k) Process

As mentioned earlier, several reports have examined aspects of the FDA device review process.[137] FDAAA (2007) required GAO to study and report on the appropriate use of the 510(k) process

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DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm#special.

[133] Design controls are a series of predetermined checks, verifications, and specifications that are built into the manufacturing process to validate the quality of the product throughout the process. These can include defining the personnel responsible for implementing steps in the development and manufacturing process, defining specifications and standards for assessing the quality of the materials that go into making the product, designing specifications for accepting and rejecting different batches or lots of final product, and requirements for maintaining appropriate records.

[134] 21 C.F.R. §820.30.

[135] FDA, Medical Devices, *De Novo Classification Process (Evaluation of Automatic Class III Designation) - Draft Guidance for Industry and Food and Drug Administration Staff*, August 13, 2014, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf and, "FDA Seeks Comment on Streamlined Review of Lower Risk, New Technology, Devices," press release, September 30, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm274008.htm.

[136] FDA, Medical Devices, *De Novo Classification Process (Evaluation of Automatic Class III Designation) - Draft Guidance for Industry and Food and Drug Administration Staff*, August 13, 2014, p. 4.

[137] For example, U.S. Government Accountability Office, *Medical Devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process*, GAO-09-190, January 2009; Daniel R. Levinson, *Adverse Event Reporting for Medical Devices*, Department of Health and Human Services, Office

"to determine whether a new device is as safe and effective as a classified device."[138] The report, released in January 2009, found that a number of Class III devices—including device types that are implantable, life sustaining, or posing a significant risk to the health, safety, or welfare of a patient—were cleared for the U.S. market through FDA's less stringent 510(k) review process.[139] GAO recommended that "FDA expeditiously take steps to issue regulations for Class III device types currently allowed to enter the market via the 510(k) process by requiring PMAs or reclassifying them to a lower class."[140]

In December 2008 an orthopedic device made by ReGen, a New Jersey company, was cleared for marketing via the 510(k) process. In April 2009, Acting FDA Commissioner Joshua Sharfstein initiated an internal review of the decision to clear the ReGen Menaflex device.[141] In September 2009, FDA released a preliminary report on the review of ReGen Menaflex device.[142] The report provided a list of 22 instances in which the agency did not follow established processes, procedures, or practices.[143] The report provides a possible reason for this, noting "the presence of widespread internal disagreement and confusion about the legal standard for 510(k) review."[144] Acting Commissioner Sharfstein said that the report made "a series of recommendations, all of which will be adopted."[145]

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of Inspector General, Washington, DC, October 2009; and, IOM (Institute of Medicine), *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011. In addition, GAO regularly reports on government operations that it identifies as high risk due to their greater vulnerability to fraud, waste, abuse, mismanagement or the need for transformation to address economy, efficiency or effectiveness challenges. FDA review of medical products has been included in these reports. See GAO, High-Risk Series: An Update, GAO-09-271, January 2009; GAO, High-Risk Series: An Update, GAO-11-278, February 2011; and, GAO, High-Risk Series: An Update, GAO-13-283, February 2013.

[138] P.L. 110-85, Section 225.

[139] See last four paragraphs of "Device Classification" section in this report. FDASIA changed the process for the reclassification of a device from rulemaking to an administrative order.

[140] U.S. Government Accountability Office, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process*, GAO-09-190, January 2009, http://www.gao.gov/new.items/d09190.pdf.

[141] In January 2009 CDRH scientists sent letters to Congressional Committees and to the Obama transition team regarding the ReGen Menaflex device. See Alicia Mundy, "Political Lobbying Drove FDA Process," *The Wall Street Journal*, March 6, 2009. A May 11, 2009, letter to Acting Commissioner Sharfstein from Members of the House Committee on Energy and Commerce indicated that the process used by FDA to clear the ReGen Menaflex device was under investigation by the Committee and the letter outlined concerns with the process. See http://democrats.energycommerce.house.gov/Press_111/20090511/fdaregen.pdf. The ReGen Menaflex device was under investigation on the Senate side as well; Senator Charles Grassley "wrote to FDA and ReGen in March 2006 regarding allegations that ReGen influenced FDA's actions on the device." http://www.grassley.senate.gov/news/Article.cfm?customel_dataPageID_1502=23269.

[142] FDA, *Review of the ReGen Menaflex: Departures from Processes, Procedures and Practices Leave the Basics for a Review Decision in Question*, September 2009, p. 8, http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM183642.pdf. See also: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm183745.htm; and, Transcript for FDA's Media Briefing on the FDA's Review of the ReGen Menaflex, September 24, 2009, http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM184027.pdf.

[143] See Attachment 3B at http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm183745.htm.

[144] FDA, *Review of the ReGen Menaflex: Departures from Processes, Procedures and Practices Leave the Basics for a Review Decision in Question*, September 2009, p. 2, http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM183642.pdf.

[145] Transcript for FDA's Media Briefing on the FDA's Review of the ReGen Menaflex, September 24, 2009, p. 2, http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM184027.pdf. On October 14, 2010, FDA announced that Menaflex "should not have been cleared for marketing in the United States. … To correct this error, the agency will begin the process to rescind the product's marketing clearance." http://www.fda.gov/

In September 2009, FDA announced that it had requested an independent evaluation of the 510(k) process by IOM.[146] The agency also stated it would convene its own internal comprehensive assessment of the 510(k) process by forming two FDA staff working groups. One group would review the 510(k) program and make recommendations to enhance the decisionmaking process. The second group would review how the agency incorporates new science into its decisionmaking and make recommendations on incorporating new science while maintaining predictability in the process for industry. During the development of the two internal reports, FDA sought public input via two public meetings, three town hall meetings, three public dockets, and many smaller meetings with various stakeholder groups.[147]

FDA released the two final reports of the agency's internal review in August 2010.[148] The reports contained a total of 55 recommendations; the agency again sought public comment on the reports and their recommendations. In January 2011, FDA released its "Plan of Action," based on some of the recommendations in the August 2010 internal review reports.[149] Further information about FDA's "Plan of Action" and list of accomplishments for its implementation is provided on the agency's website.[150]

In July 2011, IOM released a report on the 510(k) process.[151] The IOM Committee recommended that the current 510(k) process be "replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle."[152] In response to the 2011 IOM 510(k) report, CDRH Director Jeffrey Shuren stated in July 2011 that "FDA believes that the 510(k) process should not be eliminated but we are open to additional proposals and approaches for continued improvement of our device review programs.... Many of the IOM findings parallel changes already underway at the FDA to improve how we regulate devices. These actions, plus a sufficiently funded device review program, will contribute to a stronger program. Any major modifications made to the agency's premarket review programs should be based on sound science and through thoughtful and transparent discussion"[153]

NewsEvents/Newsroom/PressAnnouncements/ucm229384.htm.

[146] FDA, "Institute of Medicine to Study Premarket Clearance Process for Medical Devices," press release, September 23, 2009, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm183497.htm.

[147] U.S. Congress, Senate Special Committee on Aging, *A Delicate Balance: FDA and the Reform of the Medical Device Approval Process*, Testimony of William Maisel, Deputy Center Director for Science, FDA/CDRH, 112th Cong., 1st sess., April 13, 2011.

[148] FDA, "FDA Issues Assessments of the 501(k) Program and Use of Science in Decision-Making," press release, August 4, 2010, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm221166.htm.

[149] FDA, "FDA to improve most common review path for medical devices," press release, January 19, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm240418.htm.

[150] See, FDA, About FDA, CDRH Plan of Action for 510(k) and Science, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm239448.htm.

[151] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011.

[152] Ibid., Recommendation 7-1.

[153] FDA, "FDA to seek public comment on IOM recommendations," press release, July 29, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm265908.htm.

2011 IOM Report on 510(k) Substantial Equivalence

"In practice, the assessment of substantial equivalence generally does not require evidence of safety or effectiveness of a device. Unlike the premarket approval (PMA) process, by law the 510(k) process, with some exceptions [see SMDA 1990], focuses solely on the determination of a device's substantial equivalence to a predicate device. According to the FDA and the Supreme Court, when the FDA finds a device substantially equivalent to a predicate device, it has done no more than find that the new device is as safe and effective as the predicate. It is important to note that devices on the market before the enactment of the 1976 Medical Device Amendments (MDA)—the origin of all predicate devices for the 510(k) process—have never been systematically assessed to determine their safety and effectiveness. Because the preamendment device to which equivalence was established was not itself reviewed for safety or effectiveness, the committee found that clearance of a 510(k) submission was not a determination that the cleared device was safe or effective." See p. 154.

It is interesting to note that the 510(k) clearance process has not been adopted elsewhere, in contrast to the FDA approach to drug regulation, which has been adopted by many other countries. Although the U.S. system of medical device regulation has been in place much longer than systems elsewhere, such as the European Union, and FDA has greater experience than most countries in regulating medical devices, the IOM report found that "other countries that tightly regulate medical devices do not rely solely on substantial equivalence to a predicate for premarket review of medium-risk devices."[154] In addition, the IOM report notes that the "Global Harmonization Task Force also does not offer as part of its guidance a predicate-based system for premarket review of medical devices."[155]

The Medical Device Review Process: Post-Market Requirements

Once approved or cleared for marketing, manufacturers of medical devices must comply with various regulations on labeling and advertising, manufacturing, and postmarketing surveillance. This section describes such requirements as well as efforts under development—the Sentinel Initiative and the Unique Device Identification (UDI) system—and CDRH compliance and enforcement actions.

[154] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Finding 6-8, p. 146.

[155] Ibid., p. 145. The Global Harmonization Task Force (GHTF) was formed in 1992 by the regulatory bodies and industry of the leading medical-device producer and consumer nations—Canada, the European Union/European Free Trade Association, Japan, Australia, and the United States. Its purpose was to improve public health and safety, promote international trade, and provide guidance to countries with developing medical-device regulatory systems. The GHTF was an attempt to bring nations that tightly regulate medical devices into line with one another to ease the flow of devices between countries, manufacturers, and consumers while ensuring safety. GHTF no longer exists, and it has been permanently replaced by the International Medical Device Regulators Forum (IMDRF), which is continuing the work of the GHTF. For further information, see http://www.imdrf.org/index.asp.

Postmarketing Surveillance and the National Evaluation System for Health Technology (NEST)

Because the premarket review process cannot be designed to completely ensure the safety of all devices before they enter the market, it is essential to have a strong surveillance system that monitors the safety of medical devices. When a problem is identified with a particular medical device, various corrective actions can then be implemented. Corrective actions might include changing the device labeling and instructions for use, improving user training, continued study of the device problem via postmarket surveillance, or removal of the device from the market if appropriate.

However, the iterative nature of medical device development adds a layer of complication to devising postmarket requirements for a product that may be replaced by the next-generation product before the start of, for example, a postmarket surveillance study. As noted earlier in this report, for high-risk cardiac implantable electronic devices that entered the market between 1979 and 2012, there was a median of 50 supplements per original PMA approved by FDA; clinical data are rarely collected as part of PMA supplement applications prior to marketing.[156] The 2011 IOM report recommended that FDA "develop and implement a comprehensive strategy to collect, analyze, and act on medical-device postmarket performance information."[157]

In response to the 2011 IOM report and its recommendation to replace the 510(k) process, CDRH released its own report in September 2012. The 2012 CDRH report stated that "several high-profile medical device performance concerns have led some to question whether the current United States postmarket surveillance system is optimally structured to meet the challenges of rapidly evolving medical devices and the changing nature of health care delivery and information technology."[158]

In some cases, foreign surveillance systems have identified serious device safety concerns sooner than in the United States.[159] For example, a Swedish registry found that drug-eluting stents were associated with an increased risk of death compared with bare-metal stents.[160] An Australian registry was the first to identify the increased failure rates of metal-on-metal hip joints and found that many other new hip replacement products did not improve health outcomes compared with older devices.[161] Patients and taxpayer-financed health care programs were receiving limited or no benefit from expensive new devices with a higher risk of adverse events.[162] Postmarket data can be used to not only monitor device safety, but also to better understand and measure device innovation and cost-effectiveness.

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[156] See "Evaluations of the PMA and PMA Supplement Process"

[157] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, Recommendation 7-2.

[158] FDA Center for Devices and Radiological Health, *Strengthening Our National System for Medical Device Postmarket Surveillance*, Silver Spring, MD, September 2012, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM301924.pdf.

[159] The Brookings Institution, Engelberg Center for Health Care Reform, *Strengthening Patient Care: Building an Effective National Medical Device Surveillance System*, Washington, DC, February 2015, p. 12, http://www.brookings.edu/~/media/research/files/papers/2015/02/23-medical-device-policy-surveillance/med-device-report-web.pdf.

[160] Bo Lagerqvist, Stefan K. James, Ulf Stenestrand, et al., "Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden," *The New England Journal of Medicine*, vol. 356 (February 12, 2007), pp. 1009-1019.

[161] Rajan Anand, Stephen E. Graves, Richard N. de Steiger, et al., "What is the Benefit of Introducing New Hip and Knee Prostheses?," *The Journal of Bone and Joint Surgery*, vol. 93 Suppl. 3(E) (2011), pp. 51-54.

[162] Ibid.

According to the CDRH report, the "current United States medical device postmarket surveillance system depends primarily upon" the following sources for detecting potential problems with medical devices:

- **Medical Device Reporting (MDR).** FDA annually receives several hundred thousand reports of confirmed or possible medical device related malfunctions, serious injuries, and deaths. Limitations of this passive surveillance system include incomplete, inaccurate, and/or delayed data reporting; underreporting of events; and lack of information on the total number of devices on the market in clinical use.
- **Medical Product Safety Network (MedSun).** FDA receives about 5,000 higher quality reports each year on device use and adverse outcomes from a network of 280 U.S. hospitals. The network "can be used for targeted surveys and clinical research" and has specialty subnetworks that focus on particular device types (HeartNet), laboratories (LabNet), or patients (KidNet).
- **Post-Approval Studies.** Such studies may be ordered by FDA as a condition of approval for a PMA device. These studies are typically "used to assess device safety, effectiveness, and/or reliability including longer-term, real-world device performance."
- **Postmarket Surveillance Studies.** FDA may order a manufacturer of a Class II or Class III device to conduct a 522 study (FFDCA Section 522) if failure of the device is reasonably likely to have serious adverse health consequences, if it is expected to have significant use in pediatric populations, or if it (1) is intended to be implanted for longer than one year or (2) has life-supporting or life-sustaining use outside a device user facility. Approaches used in 522 studies "vary widely and may include nonclinical device testing, analysis of existing clinical databases, observational studies, and, rarely, randomized controlled trials."
- **FDA Discretionary Studies.** In addition to those mentioned above, FDA "conducts its own research to monitor device performance, investigate adverse event signals and characterize device-associated benefits and risks to patient sub-populations." Sources of privacy-protected data for these studies include "national registries, Medicare and Medicaid administrative and claims data, data from integrated health systems, electronic health records, and published scientific literature."
- **Other Tools.** Identified in the appendix of the September 2012 FDA report.[163]

There are limitations associated with the above sources of information on postmarket problems caused by medical devices. "Currently, medical device data arise from disparate data sources with variable data elements, data definitions, data quality, and frequently from only limited subsets of patient exposures."[164] Because of these limitations, FDA is attempting to create a new resource for all stakeholders—patients, physicians, hospitals, payers, manufacturers, regulators, and other federal entities—involved in the use of medical devices.

The September 2012 CDRH report described "FDA's vision" for the creation of a national system focused on medical devices that "would augment, not replace, other mechanisms of surveillance

[163] Ibid., pp. 5-6.

[164] The Medical Device Registry Task Force and the Medical Devices Epidemiology Network, *Recommendations for a National Medical Device Evaluation System, Draft for Public Comment*, August 20, 2015, p. 9.

such as FDA's MDR and MedSun."[165] The new national system would conduct "active surveillance in near real-time using routinely collected electronic health information containing unique device identifiers [UDIs], quickly [identify] poorly performing devices, accurately [characterize] the real-world clinical benefits and risks of marketed devices, and [facilitate] the development of new devices and new uses of existing devices through evidence generation, synthesis and appraisal."[166]

The September 2012 CDRH report proposed four specific actions to strengthen the U.S. medical device postmarket surveillance system:

1. establish a UDI system and promote its incorporation into electronic health information;
2. promote the development of national and international device registries for selected products;
3. modernize adverse event reporting and analysis; and
4. develop and use new methods for evidence generation, synthesis, and appraisal.[167]

The agency held a series of meetings in September 2012 in order to solicit public comments regarding the U.S. medical device postmarket surveillance system.[168]

In a series of subsequent reports, FDA and its partners have further refined this vision and provided updates on efforts to move toward the creation of a new National Evaluation System for health Technology (NEST).[169] Two reports focus on providing medical devices with a UDI that corresponds to the product's manufacturer and model. Incorporation of UDI into patient electronic health records, health insurance claims, and registries would eventually allow for assessment of medical device performance in large patient populations. The remaining reports discuss recommendations for implementing the system as a whole, including a coordinating center, a seven-year implementation plan and several pilot programs. The cost to implement and maintain the system over the first five years is estimated to be $200 million to $250 million, or about $50 million annually, $25 million from appropriations, and $25 million from user fees.[170]

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[165] FDA, *Strengthening Our National System for Medical Device Postmarket Surveillance*, p. 8.

[166] Ibid.

[167] Ibid., pp. 4 and 8.

[168] Public Meeting - Strengthening the National Medical Device Postmarket Surveillance System, September 10, 2012, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm300721.htm; Public Workshop - MDEpiNet 2012 Annual Meeting: The Medical Device Epidemiology Network as a Partnership for Building Global Medical Device Epidemiology and Surveillance Capabilities, September 11, 2012, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm300722.htm; Public Workshop - Leveraging Registries With Medical Device Data for Postmarket Surveillance and Evidence Appraisal Throughout the Total Product Life Cycle, September 12-13, 2012, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm300724.htm.

[169] For additional information see FDA, Remarks by Robert Califf to the Medical Device Manufacturers Association, May 5, 2016, at http://www.fda.gov/NewsEvents/Speeches/ucm499546.htm, National Evaluation System, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm, and Jeffrey Shuren and Robert M. Califf, "Need for a National Evaluation System for Health Technology," *JAMA*, published online July 11, 2016.

[170] The Brookings Institution, Engelberg Center for Health Care Reform, *Strengthening Patient Care: Building an Effective National Medical Device Surveillance System*, Washington, DC, February 2015, p. 49, http://www.brookings.edu/~/media/research/files/papers/2015/02/23-medical-device-policy-surveillance/med-device-report-web.pdf, and Ferdous Al-Faruque, "Shuren: FDA Willing to Kick-Start Device Evaluation Program, but Funding Guarantee Needed," *The Gray Sheet*, May 16, 2016, p. 7. The Obama Administration requested $1.8 million in the FDA FY2017 budget to start establishing the National Medical Device Evaluation System as part of the Precision

The reports by FDA and its partners on the medical device postmarket surveillance system are listed in the text box below.

Reports on the National Evaluation System for Health Technology (NEST)

- FDA, Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps, April 2013.
- The Brookings Institution, Unique Device Identifiers (UDIs): A Roadmap for Effective Implementation, December 2014.
- The Brookings Institution, Strengthening Patient Care: Building an Effective National Medical Device Surveillance System, February 2015.
- FDA, FDA's Role in Ensuring American Patients Have Access to Safe and Effective Medical Device Technology, March 2015.
- The Medical Device Registry Task Force and the Medical Devices Epidemiology Network, Recommendations for a National Medical Device Evaluation System, August 2015.
- The Pew Charitable Trusts, Implementing Unique Device Identification, September 2015.
- Duke-Margolis Center for Health Policy, Better Evidence on Medical Devices: A Coordinating Center for a 21st Century National Medical Device Evaluation System, April 2016.

A January 2016 Senate Health, Education, Labor and Pensions Committee minority staff report on antibiotic-resistant infections associated with the use of duodenoscope devices recommends that Congress fully fund the National Medical Device Evaluation System.[171] A public workshop, sponsored by the FDA and the University of Maryland/Center of Excellence in Regulatory Science and Innovation, on the National Evaluation System for Medical Devices was held on March 24, 2016.[172]

On July 27, 2016, FDA released draft guidance on how the agency plans to use real-world data (RWD) in making premarket and post market regulatory decisions regarding medical devices.[173] RWD is defined as "data collected from sources outside of traditional clinical trials." Such sources may include, for example, "administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries."[174]

Postmarket Surveillance Studies ("522 Studies")

While the term postmarketing surveillance refers to a wide range of programs, the term postmarket surveillance refers to a specific activity defined in law.[175] For certain class II and class III devices, FDA may order a manufacturer to conduct a postmarket surveillance study—also

Medicine Initiative. FDA, *FY2017 Justification of Estimates for Appropriations Committees*, p. 150, at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM485237.pdf.

[171] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Preventable Tragedies: Superbugs and How Ineffective Monitoring of Medical Device Safety Fails Patients*, Minority Staff Report, 114th Cong., 2nd sess., January 13, 2016.

[172] For further information, see http://www.pharmacy.umaryland.edu/centers/cersievents/deviceeval/.

[173] FDA, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," July 27, 2016, at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf.

[174] Ibid., p. 4.

[175] FFDCA §522.

called a 522 study—once the device is approved or cleared for marketing in order to gather safety and efficacy data. A postmarket surveillance study may be ordered if

- device failure would be reasonably likely to have serious adverse health consequences;
- the device is expected to have significant use in pediatric populations;
- the device is intended to be implanted in the body for more than one year; or
- the device is intended to be a life-sustaining or life-supporting device used outside a device user facility.[176]

The primary objective of postmarket surveillance is to study the performance of the device after clearance or approval as it is used in the population for which it is intended—and to discover cases of device failure and its attendant impact on the patient. Manufacturers may receive notification that their device is subject to postmarket surveillance when FDA files (i.e., accepts) the submission, and again when a final decision is made. If notified, manufacturers must submit a plan for postmarket surveillance to FDA for approval within 30 days of introducing their device into interstate commerce.[177]

FDASIA specifies that the Secretary's authority to order the conduct of postmarket surveillance is at the time of approval or clearance of a device or at any time thereafter.[178] It also requires the manufacturer to commence any required postmarket surveillance not later than 15 months after being so ordered.

Researchers have found that 522 studies "have often been difficult to implement and complete reliably."[179] For example, a "key challenge in conducting these studies is a lack of incentives for clinicians and patients to participate, because they represent already marketed devices and an additional reporting burden and other requirements on top of their usual practice."[180] In addition, "522 studies have been criticized for inconsistencies in design, the lack of oversight, timeliness of reporting findings, and how the information is eventually used."[181] On May 16, 2016, FDA issued final guidance on postmarket surveillance under FFDCA Section 522.[182]

A September 2015 GAO study described "(1) the types of devices for which FDA has ordered a *postapproval* study and the status of these studies, and (2) the types of devices for which FDA has ordered a *postmarket surveillance* study and the status of these studies."[183]

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[176] FFDCA §522; a device user facility means a hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician's office.

[177] Further information, and a listing of 522 studies, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostmarketSurveillance/ucm134497.htm.

[178] Section 616 of FDASIA.

[179] The Brookings Institution, Engelberg Center for Health Care Reform, *Strengthening Patient Care: Building an Effective National Medical Device Surveillance System*, Washington, DC, February 2015, p. 12, http://www.brookings.edu/~/media/research/files/papers/2015/02/23-medical-device-policy-surveillance/med-device-report-web.pdf.

[180] Ibid.

[181] Jeanne Lenzer and Shannon Brownlee, "Why the FDA can't protect the public," *BMJ*, vol. 341 (November 3, 2010).

[182] FDA, *Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry and Food and Drug Administration Staff*, May 16, 2016, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268141.pdf.

[183] U.S. Government Accountability Office, *Medical Devices: FDA Ordered Postmarket Studies to Better Understand*

GAO analyzed FDA data on 313 *postapproval* studies that FDA ordered between January 1, 2007, and February 23, 2015. GAO found that 56% of the postapproval studies were for cardiovascular devices, 11% were for orthopedic devices, 9% were for general and plastic surgery devices, and 24% were for devices used by other medical specialties, such as anesthesiology, neurology, obstetrics and gynecology, and gastroenterology-urology.[184] Nearly all (94%) of the postapproval studies were for devices approved through the PMA process, the remainder (6%) were for devices approved through the HDE process.[185] Of the 313 postapproval studies, GAO found that 225 (72%) were ongoing, 62 (20%) were completed, and 26 (8%) were inactive.[186] Of the 225 ongoing studies, 81% were making adequate progress and 19% were delayed due to, for example, limited patient enrollment.[187]

GAO analyzed FDA data on 392 *postmarket surveillance* studies that FDA ordered between May 1, 2008, and February 24, 2015. GAO found that 196 (50%) of the postmarket surveillance studies were for orthopedic medical devices.[188] "In 2011 alone, FDA ordered 176 studies for orthopedic devices following safety concerns about metal-on-metal hip implants, including potential bone or tissue damage from metal particles."[189] Another 121 postmarket surveillance studies were ordered by FDA in 2012 "following safety concerns about the use of implanted surgical mesh used for urogynecological procedures."[190] Of the 392 studies, most (94%) were for devices cleared through the 510(k) process (primarily metal-on-metal hips and surgical mesh), 2% were approved through the PMA process, and 4% were approved through the HDE process.[191] GAO found that 88% of the 392 postmarket surveillance studies were inactive, 10% were ongoing, and 2% were completed.[192]

Adverse Event Reporting

The Safe Medical Devices Act of 1990 (SMDA, P.L. 101-629) required FDA to establish a system for monitoring and tracking serious adverse events that resulted from the use or misuse of medical devices.[193] Medical Device Reporting (MDR) is one mechanism that FDA uses to identify and monitor significant adverse events involving medical devices.[194]

Device manufacturers are required to report to FDA (1) within 30 calendar days of acquiring information that reasonably suggests one of their devices may have caused or contributed to a death, serious injury, or malfunction and (2) within 5 working days if an event requires action other than routine maintenance or service to prevent a public health issue.[195] User facilities, such as hospitals and nursing homes, are also required to report deaths to both the manufacturer, if

Safety Issues, and Many Studies Are Ongoing, GAO-15-815, September 2015.

[184] Ibid., p. 8.

[185] Ibid., pp. 10-11.

[186] Ibid., p. 14.

[187] Ibid., p. 15.

[188] Ibid., p. 17.

[189] Ibid.

[190] Ibid.

[191] Ibid., p. 18.

[192] Ibid., p. 20.

[193] FFDCA §519(a)

[194] The searchable MDR database for devices is publically accessible at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmdr/search.CFM.

[195] 21 C.F.R. §803.10(c)(1) and §803.10(c)(2).

known, and FDA within 10 working days.[196] User facilities must report serious injuries to the manufacturers (or FDA if the manufacturer is unknown) within 10 working days.[197] User facilities must also submit annual reports to FDA of all adverse event reports sent to manufacturers or FDA in the past year.[198]

In August 2009, FDA published notice of a proposed rule, and a related draft guidance document, that would require manufacturers to submit MDRs to the agency in an electronic format.[199] According to FDA, the proposed regulatory changes would provide the agency with a more efficient data entry process that would allow for timely access to medical device adverse event information and identification of emerging public health issues. The device industry requested a longer timeframe to implement the changes. A report by the HHS Office of Inspector General released in October 2009 raised a number of questions about adverse event reporting for medical devices.[200] The report found that CDRH does not consistently use adverse event reporting and made several recommendations about how it could better do so.

On February 13, 2014, FDA published a final rule on Electronic Medical Device Reporting (eMDR) requiring manufacturers to submit MDRs to the agency in an electronic format. User facilities may also submit eMDR reports, but the final rule allows user facilities to continue to submit paper MDR reports.[201]

Medical Device Tracking

"Manufacturers are required to track certain devices from their manufacture through the distribution chain when they receive an order from [FDA] to implement a tracking system for a certain type of device."[202] Device tracking ensures that manufacturers of these devices can locate them quickly, if needed once in commercial distribution, to facilitate notifications and recalls if serious risks to health are associated with a particular device. FDA may issue a tracking order for any Class II or Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences;
- which is intended to be implanted in the human body for more than one year; or
- which is intended to be a life-sustaining or life-supporting device used outside a device user facility.[203]

[196] 21 C.F.R. §803.10(a)(1)(i).

[197] 21 C.F.R. §803.10(a)(1)(ii).

[198] 21 C.F.R. §803.10(a)(2) and §803.33.

[199] FDA, "Proposed Rule, Medical Device Reporting: Electronic Submission Requirements," 74 *Federal Register* 42203-42217, August 21, 2009; and FDA, "Draft Guidance for Industry, User Facilities, and Food and Drug Administration Staff; eMDR—Electronic Medical Device Reporting; Availability," 74 *Federal Register* Page 42310, August 21, 2009.

[200] Daniel R. Levinson, *Adverse Event Reporting for Medical Devices*, HHS Office of Inspector General, OEI-01-08-00110, October 2009, http://oig.hhs.gov/oei/reports/oei-01-08-00110.pdf.

[201] For further information, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/eMDR–ElectronicMedicalDeviceReporting/default.htm.

[202] FDA, *Medical Device Tracking*, May 13, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/MedicalDeviceTracking/default.htm#link_2.

[203] 21 C.F.R. §821.1(a)

FDA has issued orders to track a number of implantable devices (including silicone-gel filled breast implants, certain joint prostheses, implantable pacemakers, implantable defibrillator, mechanical heart valves, and implantable infusion pumps) and various other devices that are used outside a device user facility.[204]

The Sentinel Initiative

Section 905 of FDAAA mandated that FDA create an active postmarket risk identification system.[205] Although the FDAAA language is focused on monitoring drugs, FDA is using its general authority to monitor all FDA-regulated products, including medical devices, after they have reached the market.[206] FDASIA required the Secretary to modify the postmarket risk identification and analysis system, now called Sentinel, to include medical devices and to engage stakeholders during this expansion.[207]

FDA launched the Sentinel Initiative in May 2008; once completed, it will be called the Sentinel System. FDAAA set goals that the new system must be able to access data on 25 million people by July 2010, a goal which FDA has met, and 100 million people by July 2012.[208] FDA met the 100 million people goal in December 2011, and as of June 2012 "has secure access to data concerning approximately 126 million patients nationwide derived from 17 different data partners."[209] According to FDA, Sentinel aims to develop and implement a proactive system that will complement existing systems that the agency has in place to track reports of adverse events linked to the use of its regulated products.[210]

FDA is collaborating with institutions throughout the United States, including academic medical centers, health care systems and health insurance companies, who act as data partners in the system. Additional collaborators will include patient and health care professional advocacy groups, academic institutions and the medical products industry. As an example of data applicable to medical devices, "one Sentinel-related project identified, described, and evaluated potential US orthopedic-implant registries that could participate in the creation of a national network of such registries as part of the Sentinel Initiative. Data related to medical devices include rates of selected outcomes (for example, myocardial infarction and stroke), rates of infection, and rates of implant revision and reintervention."[211] According to FDA and other stakeholders, including a

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[204] A device user facility means a hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician's office. A current list of the devices for which tracking is required can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/MedicalDeviceTracking/default.htm#link_2.

[205] FFDCA §505(k); 21 U.S.C. §355

[206] FFDCA §1003(b)(2)(c)

[207] FDASIA §615.

[208] U.S. Food and Drug Administration, *The Sentinel Initiative: Access to Electronic Healthcare Data for More Than 25 Million Lives*, July 2010, http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf.

[209] FDA, FDAVoice, *FDA's Mini-Sentinel exceeds 100 million lives (and counting)… A major milestone in developing a nationwide rapid-response electronic medical product safety surveillance program*, CDR Melissa Robb, June 29, 2012, http://blogs.fda.gov/fdavoice/index.php/2012/06/fdas-mini-sentinel-exceeds-100-million-lives-and-counting-a-major-milestone-in-developing-a-nationwide-rapid-response-electronic-medical-product-safety-surveillance-program/.

The Sentinel Initiative is focused on electronic claims data held by health plans. Importantly, the plans retain control over the patient-level data within their own data firewalls and provide only aggregated information to FDA.

[210] Information on the current status of the Sentinel Initiative is available at http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm.

[211] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 106.

Unique Device Identification (UDI) on CMS claims forms is "the best way to expand the agency's Sentinel system to include medical devices."[212]

Unique Device Identification (UDI) System

FDAAA required the HHS Secretary to promulgate regulations establishing a UDI system.[213] FDASIA required the Secretary to issue proposed regulations for the UDI system not later than December 31, 2012.[214] The proposed rule was published in July 2012, and the final rule was published in September 2013.[215] When fully implemented, the label of most devices will include a UDI in human- and machine-readable (bar code) form.[216] A UDI is an alphanumeric code composed of two parts: the device identifier (DI) indicating the device's manufacturer and model number, and the production identifier (PI) identifying the device serial number, lot number, manufacture date, and in some cases expiration date. According to FDA, the UDI system offers "a range of benefits to industry, FDA, consumers, health care providers and health care systems," such as

> • Allowing more accurate reporting, reviewing and analyzing of adverse event reports so that problem devices can be identified and corrected more quickly.
>
> • Reducing medical errors by enabling health care professionals and others to more rapidly and precisely identify a device and obtain important information concerning the characteristics of the device.
>
> • Enhancing analysis of devices on the market by providing a standard and clear way to document device use in electronic health records, clinical information systems, claim data sources and registries. A more robust postmarket surveillance system can also be leveraged to support premarket approval or clearance of new devices and new uses of currently marketed devices.
>
> • Providing a standardized identifier that will allow manufacturers, distributors and healthcare facilities to more effectively manage medical device recalls.
>
> • Providing a foundation for a global, secure distribution chain, helping to address counterfeiting and diversion and prepare for medical emergencies.
>
> • Leading to the development of a medical device identification system that is recognized around the world.[217]

UDI is being implemented in phases. In general, the Class III device compliance date was September 2014 (one year after the final rule was published), Class II is September 2016 (three years after the final rule), and Class I is September 2018 (five years after the final rule).[218] FDA

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[212] Todd Allen Wilson, "Pascrell To Burwell: Press CMS To Put UDIs In Claims Forms," *Inside CMS*, February 25, 2016.

[213] FFDCA §519(f); 21 U.S.C. §360i

[214] FDASIA §614.

[215] Food and Drug Administration, "Unique Device Identification System," 77 *Federal Register* 40735-40778, July 10, 2012; and, "Unique Device Identification System—Final Rule," 78 *Federal Register* 58786-58828, September 24, 2013. An amendment to the proposed rule was published in the *Federal Register* on November 19, 2012, 69393-69399.

[216] For further information, see: The Brookings Institution, *Unique Device Identifiers (UDIs): A Roadmap for Effective Implementation*, December 2014; and, The Pew Charitable Trusts, *Implementing Unique Device Identification*, September 2015.

[217] FDA, Medical Devices, Benefits of a UDI system, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/BenefitsofaUDIsystem/default.htm.

[218] FDA, Medical Devices, Compliance Dates for UDI Requirements, http://www.fda.gov/MedicalDevices/

has held a number of public meetings and workshops with stakeholders to discuss the adoption, implementation, and use of a UDI system and has posted further information about the use of UDI for medical devices on its website.[219]

Members of Congress, FDA, and other organizations, such as the Brookings Institute and the Pew Charitable Trusts, have called for the inclusion of the UDIs in Medicare claims forms. For example, in a January 2016 Senate Health, Education, Labor and Pensions Committee minority staff report on outbreaks of antibiotic-resistant infections associated with the use of duodenoscope devices, the first recommendation is that Congress should require and promote that UDIs be included in insurance claims.[220]

In a September 2015 letter to Senators Elizabeth Warren and Charles E. Grassley, the HHS Inspector General, Daniel Levinson, indicates the benefits of incorporating UDI into "claims data, both to protect beneficiaries from adverse events and the Medicare trust funds from significant losses."[221] Research performed by two independent groups estimates that following the recall of the Medtronic Sprint Fidelis defibrillator lead (wire) in October 2007, "Medicare incurred costs exceeding $1 billion due to this recall alone."[222] According to the HHS Inspector General, at the present time,

> Medicare claims forms insufficiently identify Medicare beneficiaries who received a recalled or defective device. Therefore, we cannot readily determine the number of Medicare beneficiaries affected by medical device recalls and failures or assess the financial impact on Medicare. However, we have identified over 200 FDA recalls for cardiac devices alone since early 2010 that we believe have significantly increased Medicare costs. There have also been numerous orthopedic-related recalls within the last 5 years that we believe have significantly increased Medicare costs.[223]

In the past, CMS has been opposed to the inclusion of UDIs in claims.[224] Former Medicare Administrator Marilyn Tavenner stated in a February 2015 letter that "including UDIs on claims would entail significant technological challenges, costs and risks" for the agency.[225] The February

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DeviceRegulationandGuidance/UniqueDeviceIdentification/CompliancedatesforUDIRequirements/default.htm.

[219] Further information about UDI is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/default.htm.

[220] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Preventable Tragedies: Superbugs and How Ineffective Monitoring of Medical Device Safety Fails Patients*, Minority Staff Report, 114th Cong., 2nd sess., January 13, 2016.

[221] Letter from Daniel Levinson, Inspector General, Department of Health and Human Services, to Senator Elizabeth Warren and Senator Charles H. Grassley, September 1, 2015, http://www.grassley.senate.gov/sites/default/files/news/upload/IG%20Levinson%20Response%20to%20Senator%20Grassley%20and%20Senator%20Warren%20re%20UDI%20-%209.01.2015.pdf.

[222] Ibid. "Examining the Sprint Fidelis Effect on Medicare Costs," H. Dennis Tolley, Ph.D., ASA; and, "Medtronic Sprint Fidelis lead recall: Determining the Initial 5-year management cost to Medicare," Heart Rhythm Center in the Section of Cardiology, Department of Internal Medicine, University of Chicago, Chicago, Illinois, and Electrophysiology Section, Northwestern University, Chicago, Illinois.

[223] Letter from Daniel Levinson, Inspector General, Department of Health and Human Services, to Senator Elizabeth Warren and Senator Charles H. Grassley, September 1, 2015, http://www.grassley.senate.gov/sites/default/files/news/upload/IG%20Levinson%20Response%20to%20Senator%20Grassley%20and%20Senator%20Warren%20re%20UDI%20-%209.01.2015.pdf.

[224] Michael D. Williamson, "Pulled Measure Would Lead to Faster Info on Bad Devices," *Health Care Daily Report*, March 15, 2016.

[225] Thomas M. Burton, "Medical Device ID Effort Hits Snag," *The Wall Street Journal*, March 10, 2015,

2015 letter estimated the costs at $700 million.[226] However, in a July 13, 2016, letter, CMS Acting Administrator Andrew Slavitt and FDA Commissioner Robert Califf stated support for including UDI on claims and urged the Accredited Standards Committee X12 to permit the device identifier portion of UDI for implantable devices to be included in the next version of the claims form.[227]

Labeling

Like drugs and biological products, all FDA approved or cleared medical devices are required to be labeled in a way that informs a user of how to use the device. The FFDCA defines a "label" as a "display of written, printed, or graphic matter upon the immediate container of any article."[228] "Labeling" is defined as "all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article" at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.[229]

The term "accompanying" is interpreted to mean more than physical association with the product; it extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, web pages, etc. Accompanying can also include labeling that is connected with the device after shipment or delivery for shipment in interstate commerce. According to an appellate court decision, "most, if not all advertising, is labeling. The term 'labeling' is defined in the FFDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."[230]

All devices must conform to the general labeling requirements.[231] Certain devices require specific labeling, which may include not only package labeling, but informational literature, patient release forms, performance testing, and/or specific tolerances or prohibitions on certain ingredients.[232]

A section of the Quality System (QS) regulation also has an impact on various aspects of labeling.[233] The QS regulation applies to the application of labeling to ensure legibility under normal conditions of use over the expected life of the device and also applies to inspection, handling, storage, and distribution of labeling. FDA considers a device to be adulterated if these requirements are not met. These requirements do not apply to the adequacy of labeling content, except to make sure the content meets labeling specifications contained in the device master record. However, failure to comply with GMP requirements, such as proofreading and change

http://www.wsj.com/articles/medical-device-id-effort-is-stalled-1426027440.

[226] Todd Allen Wilson, "Pascrell To Burwell: Press CMS To Put UDIs In Claims Forms," *Inside CMS*, February 25, 2016.

[227] ASC X12 is a committee of government officials and industry stakeholders that are tasked with developing operational and data transfer standards. The committee will propose a revised claim form that will be approved or rejected by CMS in 2017. Nicholas Florko, "CMS Cautiously Throws Support Behind UDI In Claims Forms, But It May Be Too Late," *InsideHealthPolicy*, July 14, 2016.

[228] FFDCA §201(k).

[229] FFDCA §201(m).

[230] United States v. Research Laboratories, Inc., 126 F.2d 42 (9th Cir. 1942).

[231] 21 C.F.R. §801.

[232] 21 C.F.R. §§801.405 - 801.437. These devices included denture repair kits, impact resistant lenses in sunglasses and eyeglasses, ozone emission levels, chlorofluorocarbon propellants, hearing aids, menstrual tampons, chlorofluorocarbons or other ozone depleting substances, latex condoms, and devices containing natural rubber.

[233] 21 C.F.R. §820.120.

control, could result in labeling content errors. In such cases, the device could be misbranded and/or adulterated.

Manufacturing

Like drug manufacturers, medical device manufacturers must produce their devices in accordance with Good Manufacturing Practice (GMP). The GMP requirements for devices are described in the QS regulation.[234] The QS regulation requires that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of nonexempt finished medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed and manufactured under a quality system to meet these specifications; that finished devices meet these specifications; that devices be correctly installed, checked, and serviced; that quality data are analyzed to identify and correct quality problems; and that complaints are processed. FDA monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements.[235] Though FDA has identified in QS regulation the essential elements that a quality system should have, manufacturers have a great deal of leeway to design quality systems that best cover nuances of their devices and the means of producing them.

Compliance and Enforcement

Compliance requirements apply to both the premarket approval process and postmarket surveillance. When a problem arises with a product regulated by FDA, the agency can take a number of actions to protect the public health. Initially, the agency tries to work with the manufacturer to correct the problem on a voluntary basis. If that fails, legal remedies may be taken, such as asking the manufacturer to recall a product, having federal marshals seize products, or refusing imported products that are in violation of the FFDCA. If warranted, FDA can ask the courts to issue injunctions or prosecute individual company officers that deliberately violate the law. When warranted, criminal penalties, including prison sentences, may be sought.

Section 516 of the FFDCA gives FDA the authority to ban devices that present substantial deception or unreasonable and substantial risk of illness or injury. Section 518 enables FDA to require manufacturers or other appropriate individuals to notify all health professionals who prescribe or use the device and any other person (including manufacturers, importers, distributors, retailers, and device users) of any health risks resulting from the use of a violative device, so that these risks may be reduced or eliminated. This section also gives consumers a procedure for economic redress when they have been sold defective medical devices that present unreasonable risks. Section 519 of the act authorized FDA to promulgate regulations requiring manufacturers, importers, and distributors of devices to maintain records and reports to assure that devices are not adulterated or misbranded. Section 520(e) authorizes FDA to restrict the sale, distribution, or use of a device if there cannot otherwise be reasonable assurance of its safety and effectiveness. A restricted device can only be sold on oral or written authorization by a licensed practitioner or under conditions specified by regulation.

[234] FFDCA §520; 21 C.F.R. §820.

[235] FDA, *Medical Devices: 1. The Quality System Regulation*, June 18, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/ucm122391.htm.

Inspection

Each FDA center has an Office of Compliance (OC) that ensures compliance with regulations while pre- or postmarket studies are being undertaken, with manufacturing requirements, and with labeling requirements. The objectives of CDRH's OC's Bioresearch Monitoring (BIMO) program are to ensure the quality and integrity of data and information submitted in support of IDE, PMA, and 510(k) submissions and to ensure that human subjects taking part in investigations are protected from undue hazard or risk. This is achieved through audits of clinical data contained in PMAs prior to approval, data audits of IDE and 510(k) submissions, inspections of IRBs and nonclinical laboratories, and enforcement of the prohibitions against promotion, marketing, or commercialization of investigational devices. Any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept, can be subject to inspection. (See **Table 3**.)

The OC also reviews the quality system design and manufacturing information in the PMA submission to determine whether the manufacturer has described the processes in sufficient detail and to make a preliminary determination of whether the manufacturer meets the QS regulation. If the manufacturer has provided an adequate description of the design and manufacturing process, a preapproval inspection can be initiated. Inspection is to include an assessment of the manufacturer's capability to design and manufacture the device as claimed in the PMA and confirm that the quality system is in compliance with the QS regulation. Postapproval inspections can be conducted within 8 to 12 months of approval of the PMA submission. The inspection is to primarily focus on any changes that may have been made in the device design, manufacturing process, or quality systems.

Table 3. CDRH, FDA Domestic and Foreign Device Establishment Inspections, FY2009–FY2015

	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015
Domestic	1,711	2,115	2,125	2,183	2,209	2,024	1,942
Foreign	267	333	398	454	550	595	721
Total Inspections	1,978	2,448	2,523	2,637	2,759	2,619	2,663

Sources: FDA, *Justification of Estimates for Appropriations Committees*, Center for Devices and Radiological Health, Field Devices and Radiological Health Program Activity Data (PAD) table. Data above was found in the "Actual" column of the PAD table from the FDA *Justification* documents for FY2011 through FY2017. Domestic and Foreign data consist of Bioresearch Monitoring Program Inspections, Pre-Market Inspections, Post-Market Audit Inspections, and GMP Inspections.

The compliance offices work closely with the Office of Regulatory Affairs (ORA),[236] which operates in the field to regulate almost 124,000 business establishments that annually produce, warehouse, import and transport $1 trillion worth of medical products. ORA field inspectors typically have conducted about 22,000 domestic and foreign inspections a year to ensure that regulated products meet the agency's standards. CSOs also monitor clinical trials. Scientists in ORA's 13 laboratories typically have analyzed more than 41,000 product samples each year to determine their adherence to FDA's standards.

[236] See ORA at http://www.fda.gov/AboutFDA/CentersOffices/ORA/default.htm.

Warning Letter

A Warning Letter is a written communication from FDA notifying a responsible individual, manufacturer, or facility that the agency considers one or more products, practices, processes, or other activities to be in violation of the laws that FDA enforces. The Warning Letter informs the recipient that failure to take appropriate and prompt action to correct and prevent any future repeat of the violations could result in an administrative or judicial action. Although serious noncompliance is often a catalyst for issuance of a Warning Letter, the Warning Letter is informal and advisory[237] (see **Table 4**).

Table 4. CDRH Warning Letters Issued, FY2009–FY2015

	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015
Number of Letters	136	204	175	210	217	114	168

Source: FDA Enforcement Statistics Summary, reports for fiscal years FY2009-FY2015, at http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm.

Product Recall

A recall is a method of removing or correcting products that FDA considers are in violation of the law.[238] Medical device recalls are usually conducted voluntarily by the manufacturer after negotiation with FDA.[239] Manufacturers (including refurbishers and reconditioners) and importers are required to report to FDA any correction or removal of a medical device that is undertaken to reduce a health risk posed by the device.[240] A recall may involve the removal of all or a portion of the product on the market (such as a single lot). In rare instances, where the manufacturer or importer fails to voluntarily recall a device that is a risk to health, FDA may issue a recall order to the manufacturer.[241]

When a recall is initiated, FDA performs an evaluation of the health hazard presented taking into account the following factors, among others:

- Whether any disease or injuries have occurred from the use of the product;
- Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard;
- Assessment of hazard to various populations (e.g., children, surgical patients, pets, livestock) who would be exposed to the product;
- Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed;

[237] Warning letters are publically available on FDA's website at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

[238] Recall does not include market withdrawal or a stock recovery. A market withdrawal is a firm's removal or correction of a distributed product for a minor violation that does not violate the law and would not be subject to legal action by FDA (e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc.). Stock recovery involves correction of a problem before product is shipped (i.e., is still in the manufacturer's control).

[239] 21 C.F.R. §7

[240] 21 C.F.R. §806.

[241] 21 C.F.R. §810. See out-of-print CRS Report RL34167, *The FDA's Authority to Recall Products*, by Vanessa K. Burrows (available to congressional clients from the author upon request).

- Assessment of the likelihood of occurrence of the hazard;
- Assessment of the consequences (immediate or long-range) of the hazard.

Following the health hazard assessment, FDA assigns the recall a classification according to the relative degree of health hazard. *Class I* recalls are the most serious, reserved for situations where there is a reasonable probability that the use of, or exposure to, a product will cause serious adverse health consequences or death. *Class II* recalls are for situations where the use of, or exposure to, a product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. In a *Class III* recall situation, the use of, or exposure to, a product is not likely to cause adverse health consequences (see **Table 5**). In addition to a warning letter or recall, FDA may issue a public notification or safety alert (e.g., "Dear Doctor" letter), to warn health care providers and consumers of the risk of the device.[242]

FDASIA requires the Secretary to establish a program to improve the device recall system.[243] Among other things, it requires an assessment of information on device recalls, an assessment of the effectiveness of corrections or action plans for recalls, and documentation of the basis for terminations of recalls.

Table 5. CDRH Class I, II, and III Product Recalls, FY2009–FY2015

	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015
Class I	129	334	427	124	185	360	287
Class II	N/A	2,208	2,665	2,210	1,988	N/A	2,494
Class III	N/A	92	246	141	131	N/A	69
Total	2,306	2,634	3,211	2,475	2,304	2,706	2,850

Source: FDA Enforcement Statistics Summary, reports for fiscal years FY2009-FY2015, at http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm.

[242] The main page for recalls, market withdrawals, and safety alerts for all FDA-regulated products is http://www.fda.gov/opacom/7alerts.html.

[243] Section 605 of FDASIA.

Appendix A. A Comparison of FDA Premarket Review of Prescription Drugs and Medical Devices

Table A-1. FDA Premarket Review for Prescription Drugs and Medical Devices

	Prescription drugs	High-risk devices (Class III)	Moderate-risk devices (Class II)
Year proof of safety and effectiveness began	1932 (safety) 1962 (effectiveness)	1976	N/A
Premarket review process	New drug application (NDA)	Premarket approval application (PMA)	510(k) notification
Form of permission to market medical product	Approval	Approval	Clearance
Standard of evidence	Substantial evidence that the drug is safe effective for the purpose in the application[a]	Reasonable assurance of safety and effectiveness	Substantial equivalence to a predicate device
Supporting data	Clinical trials and pre-clinical studies	Clinical trials and pre-clinical studies	Pre-clinical studies[b]
Process for introducing postmarket changes	None[c]	PMA supplements	New 510(k) notification
Tort liability claims against manufacturer mostly preempted?[d]	No	Yes	No

Source: Based on Table 1 in Benjamin N. Rome, Daniel B. Kramer, and Aaron S. Kesselheim, "Approval of High-Risk Medical Devices in the US: Implications for Clinical Cardiology," *Current Cardiology Reports*, vol. 16, no. 6 (June 2014), pp. 489-502.

a. Substantial evidence is defined as "adequate and well-controlled investigations, including clinical investigations." FFDCA §505(d).

b. Clinical trials are rarely required as part of the 510(k) process.

c. A change to the molecular structure of an active ingredient requires its own New Drug Application. In some instances, the FDA may approve formulations of an approved drug based on bioequivalence studies.

d. The question of whether an individual can bring a state-law tort claim after suffering an injury caused by a medical device can be a complex inquiry with varied results. While the Supreme Court has generally found that under the MDA preemption provision, the ability of an individual to bring a state-law tort suit alleging certain defects with a medical device can turn on how that device received marketing approval from the FDA, (i.e., through either the §510(k) process or premarket approval), the inquiry is not this straightforward and questions remain about which state-law tort claims brought against medical device manufacturers are preempted by federal law. See, e.g., Gross v. Stryker Corp., 858 F. Supp.2d 466 (W.D. Pa. 2012) (motion to dismiss granted against claims involving artificial hip prosthesis that had received premarket approval with components that received FDA approval through §510(k) process; court finds preemption extended to all components of the device, even those originally receiving §510(k) clearance). For further information, see CRS Report R43218, *Preemption of Drug and Medical Device Claims: A Legal Overview*, by Andrew Nolan and Jennifer A. Staman.

Appendix B. History of Laws Governing Medical Device Regulation

The Federal Food, Drug and Cosmetics Act of 1938

The first general federal food and drug law, the *Food and Drugs Act of 1906*, did not contain any provisions to regulate medical device safety or claims made regarding such devices. Strong support for reform developed during the 1930s due to "false therapeutic claims for medical devices [that] were being presented to the public through radio and newspaper advertising."[244] Medical devices came under federal scrutiny when Congress passed the *Federal Food, Drug and Cosmetic Act (FFDCA) of 1938* (P.L. 75-717). The regulatory authority provided to FDA by the 1938 law was "limited to action after a medical device has been offered for introduction into interstate commerce" and only when the device was deemed to be "adulterated or misbranded."[245]

Most of the legitimate devices on the market at the time the 1938 act became law "were relatively simple items which applied basic science concepts such that experts using them could readily recognize whether the device was functioning properly; the major concern with respect to these devices was assuring truthful labeling."[246] During the first 20 years following enactment of the 1938 law, FDA's activity with respect to medical devices involved protecting the American public from *fraudulent* devices; FDA began to turn its attention to the hazards from *legitimate* devices around 1960.[247]

> The post-war revolution in biomedical technology had resulted in the introduction of a wide variety of sophisticated devices. New developments in the electronic, plastic, metallurgy, and ceramics industries, coupled with progress in design engineering, led to invention of the heart pacemaker, the kidney dialysis machine, defibrillators, cardiac and renal catheters, surgical implants, artificial vessels and heart valves, intensive care monitoring units, and a wide spectrum of other diagnostic and therapeutic devices. Although many lives have been saved or improved by the new discoveries, the potential for harm to consumers has been heightened by the critical medical conditions in which sophisticated modern devices are used and by the complicated technology involved in their manufacture and use. In the search to expand medical knowledge, new experimental approaches have sometimes been tried without adequate premarket clinical testing, quality control in materials selected, or patient consent.[248]

The Dalkon Shield, a contraceptive device introduced in November 1970, is "an example of a legitimate device which was marketed without adequate premarket testing."[249] Other examples

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[244] U.S. Congress, House Committee on Interstate and Foreign Commerce, *Medical Device Amendments of 1976*, to accompany H.R. 11124, 94th Cong., 2nd sess., February 29, 1976, H. Rept. 94-853, p. 6.

[245] Ibid. "A device is adulterated if it includes any filthy, putrid, or decomposed substance, or if it is prepared, packed, or held under unsanitary conditions. A device is misbranded if its labeling is false or misleading; unless it identifies the manufacturer, packer, or distributor and quantity of contents; if required labeling statements are not conspicuous; if it fails to bear adequate directions for use or adequate warnings; or if it is dangerous to health when used as indicated."

[246] Ibid.

[247] Ibid., p. 7.

[248] Ibid., p. 7-8.

[249] Ibid., p. 8. By 1975, the Dalkon Shield had been linked to at least 16 deaths and 25 miscarriages, numerous cases of pelvic perforation and pelvic infection, removal of the IUD for medical reasons, and pregnancies due to IUD failure. As of February 1976, more than 500 lawsuits seeking compensatory and punitive damages totaling more than $400 million were pending against the manufacturer of the Dalkon Shield. IOM, *Medical Devices and the Public's Health: The FDA*

include defective cardiac pacemakers and intraocular lenses which, following implantation, caused unusual eye infections resulting in serious vision impairment or the need for removal of the eye.

Congress amended the FFDCA in 1962 to require FDA approval of a new drug application prior to marketing and to require that a new drug be shown to be effective as well as safe. Following these changes, FDA began "to impose rigorous premarket approval of some products that today would be deemed devices." Court decisions in the late 1960s upheld FDA's authority to regulate some medical devices as drugs due in part to the overlapping definitions of drug and device in the 1938 law. FDA classified a number of devices as drugs (contact lenses, injectable silicone, pregnancy-test kits, bone cement), and only such devices were subject to premarket review (prior to 1976). However the approach of classifying devices as a drug was unsuccessful in other court decisions and the need for more comprehensive authority to regulate devices was recognized by the Kennedy, Johnson, and Nixon Administrations.[250]

The Medical Device Amendments of 1976

The *Medical Device Amendments of 1976* (MDA; P.L. 94-295) was the first major legislation passed to address the review of medical devices. The MDA provided a definition for the term device.[251] It established a number of requirements referred to as *general controls* that applied to all devices.[252] Examples include provisions on adulteration and misbranding, prohibitions on false or misleading advertising, and a requirement to register all medical device manufacturers with FDA. One such provision required manufacturers to notify FDA 90 days prior to the marketing of any new device; if the agency failed to act, marketing could begin. Because this provision is outlined in section 510(k) of the FFDCA, it is often referred to as a "510(k) notification."

The MDA directed FDA to classify, into one of three classes, all medical devices that were on the market at the time of enactment; these are the *preamendment* devices.[253] Congress provided definitions for the three classes—Class I, Class II, Class III—based on the risks to patients posed by the devices. In contrast to the approach taken with pharmaceuticals (all, except generic agents, undergo rigorous premarket review and approval), Congress limited premarket approval to only a small number of devices. "Only the highest-risk category [Class III] would require agency review

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510(k) Clearance Process at 35 Years, Washington, DC, July 2011, p. 172, http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx.

[250] U.S. Congress, House Committee on Interstate and Foreign Commerce, *Medical Device Amendments of 1976*, to accompany H.R. 11124, 94th Cong., 2nd sess., February 29, 1976, H. Rept. 94-853, p. 8-9.

[251] 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 any of its principal 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. The definition was changed in 1992 from "any of its principal intended purposes" to "its primary intended purposes." Current definition at FFDCA §201(h), (21 U.S.C. 321).

[252] The law has since been amended to exempt many (Class I) products from some general controls or to limit the application of general controls to subsets of (Class II or Class III) products that pose higher risks. IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 175.

[253] Preamendment devices were presumed to be marketable. They did not undergo premarket review and could be legally marketed unless FDA required their removal. After classifying the preamendment devices, FDA used them as the first cadre of "predicate" devices in order to demonstrate substantial equivalence.

and approval as a precondition for commercial sale and routine medical use. The other two categories would be subject not to a rigorous review but merely a requirement [510(k)] that the manufacturer of a device notify FDA, at least 90 days before commencing marketing, of its intent to distribute the product commercially."[254] For Class I devices, no additional review was needed once the status of Class I was confirmed; general controls were considered to be sufficient to protect public health. For Class II devices, limited supplemental review would be needed to verify conformity with performance standards if such standards had been established by the agency.[255]

Under MDA, all devices coming to market after enactment were automatically placed in Class III until reclassified; these are the *postamendment* devices. As stated above, Class III medical devices receive more intense scrutiny and require an application for premarket approval (PMA) before the device can be marketed. However, the MDA allowed for the reclassification of a device from one class to another. According to a 2011 IOM report on medical devices:

> The classification and reclassification process did not include any evaluation of the safety or effectiveness of the device types being categorized. Once a device type was assigned to Class III, the FDA was directed to promulgate a regulation calling for manufacturers of devices of that type to submit a [PMA] application. The agency would then (and only then) undertake a review of the safety and effectiveness of the devices. For device types placed into Class I or Class II, there was no mechanism for the systematic review of safety and effectiveness. Congress envisioned instead that the agency would use its postmarketing tools to identify and address issues of lack of safety or lack of effectiveness case by case. Thus, preamendment devices in Class I and II were never subjected to a comprehensive FDA evaluation for safety or effectiveness. The classification process was not completed until 1988.[256]

For postamendment devices, which were automatically placed into Class III, there were two important exceptions:

> The primary exception involved a postamendment device that was substantially equivalent to another device of the same type that either as a preamendment device that had not been classified into any class or was not a preamendment device but had already been classified into Class I or Class II. The FDA permitted manufacturers of postamendment devices to demonstrate substantial equivalence to a preamendment device in Class I or II as part of the 510(k) submission. An alternative exception provided that the postamendment device would not be in Class III if the FDA, in response to a petition, classified it into Class I or Class II.[257]

The MDA did not provide a definition for the term *substantially equivalent.* The MDA also did not itemize the required contents of a 510(k). Such a notification "need only set forth its proposed intended use or indications for use, the device to which substantial equivalence is claimed, and evidence demonstrating that equivalence."[258]

The Safe Medical Devices Act of 1990

The *Safe Medical Devices Act of 1990* (SMDA; P.L. 101-629) made a number of changes to the law such as providing a definition for the term *substantial equivalence* and revising the definition for Class II. FDA had not promulgated performance standards for most Class II devices. The new

[254] Ibid., p. 24.

[255] Ibid., p. 177.

[256] Ibid., p. 25.

[257] Ibid., p. 179.

[258] Ibid. p. 180.

law authorized the use of alternative restrictions, called special controls, at the agency's discretion and simplified the process of establishing performance standards for Class II devices. Examples of special controls include special labeling requirements, mandatory performance standards, patient registries and postmarket surveillance.

FDA also had experienced difficulty in promulgating regulations needed to require submission of PMA applications for Class III devices. SMDA authorized FDA to reconsider all the preamendment devices that had been placed in Class III and reclassify some of these devices into Class I or Class II.[259] The purpose was "to reduce the number of device types that needed PMA review."[260] For those devices remaining in Class III, the agency was directed to establish a schedule for promulgation of regulations calling for PMAs of devices that still used the 510(k) notification as an entry to the marketplace.

Under SMDA, FDA must issue a response to a 510(k) submission before marketing of a new device can begin. SMDA allowed for the evaluation of safety and effectiveness data in 510(k) notifications, but only in certain situations. These were limited to cases in which a new device offered different technologic characteristics from the already marketed *preamendment or postamendment* (predicate) device.[261] "Because the assessment of substantial equivalence generally did not require evidence of safety or effectiveness of a device and because a preamendment device to which equivalence was established was not itself reviewed for safety or effectiveness, the FDA made clear from the outset that clearance of a 510(k) notification was not a determination that the cleared device was safe or effective. That position was reiterated by the agency numerous times. The US Supreme Court accepted this interpretation in a 1996 opinion."[262]

U.S. Supreme Court 1996 Opinion Medtronic v. Lohr

"Substantial equivalence determinations provide little protection to the public. These determinations simply compare a post-1976 device to a pre-1976 device to ascertain whether the latter is no more dangerous and no less effective than the earlier device. If the earlier device poses a severe risk or is ineffective, then the latter device may also be risky or ineffective." Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996).

SMDA established postmarket requirements for medical devices. SMDA required facilities that use medical devices to report to FDA any incident that suggested that a medical device could have caused or contributed to the death, serious illness, or injury of a patient. Manufacturers of certain permanently implanted devices were required to establish methods for tracking the patients who received them and to conduct postmarket surveillance to identify adverse events. The act authorized FDA to carry out certain enforcement actions, such as device product recalls, for products that did not comply with the law.

The Food and Drug Administration Modernization Act of 1997

The *Food and Drug Administration Modernization Act of 1997* (FDAMA; P.L. 105-115) mandated wide-ranging reforms in the regulation of foods, drugs, and medical devices by FDA. In general, provisions involving medical devices "were designed to reduce FDA's workload and

[259] FFDCA §515(i).

[260] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 205.

[261] FFDCA §513(i).

[262] IOM, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, Washington, DC, July 2011, p. 28.

permit concentration of resources on devices that presented greater potential for harm" and "to limit the FDA's discretion and authority in regulating the device industry" in order to "accelerate the pace of technology transfer."[263]

FDAMA eliminated the 510(k) notification requirement for most Class I devices and some Class II devices. It authorized the creation of a third-party review system of 510(k) submissions for Class I and most Class II devices that still required 510(k) review. It allowed certain new devices (those not substantially equivalent to another device and automatically placed in Class III) to be evaluated for immediate placement in Class I or Class II. This process, called the de novo 510(k), avoids PMA review, must be completed in 60 days, and may be requested by the sponsor.

For substantial equivalence determinations in which the new device has a different technological characteristic, FDAMA requires that FDA "consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."[264] For a medical device using an important breakthrough technology, or which does not have an approved alternative device, priority review of the PMA must be provided by FDA.[265]

FDAMA limited the use of some postmarket controls (device tracking and postmarket surveillance) to Class II and Class III devices, eased reporting requirements of adverse events for device user facilities, eliminated mandatory reporting of adverse events by medical device distributors, and directed FDA to establish a sentinel reporting system to collect information on deaths and serious injuries or illnesses associated with the use of a medical device.[266]

Medical Device User Fee Acts

The *Medical Device User Fee and Modernization Act of 2002* (MDUFMA; P.L. 107-250) established a user fee program for premarket reviews of 510(k) submissions and PMA applications; user fees may not be used for other FDA or CDRH activities. MDUFMA also made targeted changes that would reduce regulatory burdens and agency workload, such as allowing establishment inspections to be conducted by accredited persons (third parties). MDUFMA was amended and clarified by two laws: the *Medical Device Technical Corrections Act of 2004* (MDTCA, P.L. 108-214), and the *Medical Device User Fee Stabilization Act of 2005* (MDUFSA, P.L. 109-43), and had its user fee provisions reauthorized by the *Medical Device User Fee Act of 2007* (MDUFA; Title II of FDAAA, see below).

FDA Amendments Act of 2007

The *Food and Drug Administration Amendments Act of 2007* (FDAAA; P.L. 110-85) amended the FFDCA and the Public Health Service Act (PHSA) to reauthorize several expiring programs (including the medical device user fee act) and to make agency-wide changes, several of which have implications for the regulation of medical devices.[267] FDAAA created incentives as well as reporting and safety requirements for manufacturers of medical devices for children; required that certain clinical trials for medical devices and some other products be publicly registered and have

[263] Ibid., p. 213.

[264] FFDCA §513(i)(1)(D).

[265] FFDCA §515(d)(5).

[266] FFDCA §519 and §522. A device user facility means a hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician's office.

[267] See CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Susan Thaul.

their results posted;[268] created requirements to reduce conflicts of interest in advisory committees for medical devices and other products;[269] and made certain other amendments to the regulation of devices.

FDA Safety and Innovation Act

The *Food and Drug Administration Safety and Innovation Act of 2012* (FDASIA, P.L. 112-144) amended the FFDCA and the PHSA to reauthorize the prescription drug and medical device user fee programs, created new user fee programs for generic and biosimilar drug approvals, and modified FDA authority to regulate medical products. Several provisions in FDASIA made modifications to various aspects of premarket and postmarket device regulation. Examples of premarket changes include those which affect the efficiency, transparency, and data requirements of the 510(k) and PMA processes; and alter or make clarifications to certain types of exempt devices, for example, custom devices and humanitarian use devices. Provisions affecting postmarket regulation include those which focus on expanding active postmarket surveillance; altering requirements related to postmarket studies for devices; and strengthening both device recall and tracking capabilities through a recall program and the unique device identifier system. Miscellaneous reforms include those aimed at increasing transparency of FDA's approval and clearance decisions and processes for issuing industry guidance documents; improving health information technology for the agency; and harmonizing device regulation with FDA's international counterparts.

[268] See the Clinical Trials Databases section of CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Susan Thaul.

[269] FDA uses advisory committees to gain independent advice from outside experts. See CRS Report RS22691, *FDA Advisory Committee Conflict of Interest*, by Erin D. Williams.

Appendix C. Acronyms Used in this Report

BIMO	Bioresearch Monitoring
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMS	Centers for Medicare & Medicaid Services
CSOs	Consumer safety officers
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997
FDASIA	Food and Drug Administration Safety and Innovation Act of 2012
FFDCA	Federal Food, Drug, and Cosmetic Act
GAO	Government Accountability Office
GGP	Good Guidance Practices
GHTF	Global Harmonization Task Force
GMP	Good manufacturing practices
HHS	Health and Human Services
IDE	Investigational Device Exemption
IOM	Institute of Medicine
IRB	Institutional review board
IVD	In Vitro Diagnostic
MDA	Medical Device Amendments of 1976
MDR	Medical Device Reporting
MDTCA	Medical Device Technical Corrections Act of 2004
MDUFA	Medical Device User Fee Act of 2007
MDUFMA	Medical Device User Fee and Modernization Act of 2002
MDUFSA	Medical Device User Fee Stabilization Act of 2005
NSE	Not substantially equivalent
OC	Office of Compliance
ORA	Office of Regulatory Affairs
PMA	Premarket Approval
QS	Quality System regulation
SMDA	Safe Medical Devices Act of 1990
UDI	Unique device identification

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