

The FDA's Response to The Gao's Report: New Effort to Tighten The Pre-Market Review Process for Select Class III Medical Devices

By

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I. Introduction

The U.S. Food and Drug Administration (the "FDA") initiated a process to overhaul its pre-market approval process for medical devices in light of a January 2009 report (the "Report") published by the United States Government Accountability Office ("GAO").² The GAO Report suggested that the FDA has been too lax in its classification and oversight of approving certain Class II and III medical devices, and that it has failed "to subject some of the riskiest devices to a rigorous [pre-market approval] review mandated by Congress."³ More specifically, the GAO urged the FDA to reevaluate certain Class III devices that are eligible to obtain the FDA's clearance for commercial distribution through the 510(k) pre-market notification process instead of the more stringent pre-market approval process.

The FDA addressed the GAO's concerns by initiating a procedure to reconsider and possibly reclassify Class III devices that are still eligible to use the 510(k) pre-market notification process. Manufacturers of those devices were ordered by the FDA on April 9, 2009, to submit information on safety and efficacy of their devices to allow the agency to determine whether pre-market approval is necessary.

This article provides an overview of the FDA's current process for approving medical devices for

commercial distribution in the United States. It also discusses the GAO's criticism of the FDA's current pre-market approval process. Finally, in light of the recent pressures faced by the FDA, the article discusses the FDA's initiative to reexamine its approval process for certain Class III devices.

II. The FDA's Medical Device Classification System

A medical device manufacturer must register with the FDA and, depending on the FDA's classification of the manufacturer's new device, it must submit to the FDA either a 510(k) pre-market submission⁴ or a more stringent Premarket Approval ("PMA") before a device can be marketed in the United States. The Medical Device Amendments Act of 1976 (the "Act") established the multi-class device classification system currently used by the FDA.⁵ The Act established three categories of medical devices: Class I, Class II, and Class III devices.⁶ The Act and implementing regulations established approximately 1,700 generic device type categories for devices that existed prior to the Act.⁷ Each device type category provides a description of the device type, assigns a class to the device, and sets forth the process through which a manufacturer can introduce and market a new device fitting into the applicable category. The FDA uses product codes to further categorize devices. Each device type category contains multiple product codes. Devices developed after the Act with new indications for use or new

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² United States 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* (Jan. 2009).

³ *Id.*

⁴ Note that some devices are exempt from the 510(k) requirements of the Federal Food, Drug, and Cosmetic Act (e.g., 21 C.F.R. § 862.9; 21 C.F.R. § 864.9).

⁵ Pub. L. No. 94-295, 90 Stat. 539, codified at 21 U.S.C. § 360c(a)(1).

⁶ 21 C.F.R. § 860.1.

⁷ 21 C.F.R. pts. 862-892.

technologies are assigned a new product code that is placed under the device type category.

Class I devices pose minimal risk to users and include such devices as tongue depressors and reading glasses.⁸ Class I devices are generally exempt from the 510(k) pre-market submission and PMA processes unless a device is intended for a use of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class II devices pose moderate risks to users, and include devices such as powered bone drills and electrocardiographs.⁹ Class II devices typically obtain FDA clearance through the 510(k) pre-market submission process. Finally, Class III devices, like pacemakers and replacement heart valves, pose the most significant level of risk to users.¹⁰ A manufacturer of a Class III device must typically obtain PMA from the FDA before being marketed—although this is not always the case.

Class III device types that were marketed prior to passage of the Act (“Pre-Amendment Class III Device Types”) are not required to use the PMA pathway until a regulation requiring such pathway to be used is promulgated by the FDA. Prior to 1990, the FDA had not made significant progress in promulgating regulations requiring such Pre-Amendment Class III Device Types to use the PMA pathway to gain regulatory approval, and such devices were regularly cleared using the less onerous 510(k) pathway.

III. Medical Device Approval Pathways

a. 510(k) Pre-Market Notification

Most Class I, II, and III devices for which PMA is not required must submit 510(k) pre-market notification to the FDA.¹¹ A new 510(k) submission is required if a device is being introduced into commercial distribution for the first time by a new manufacturer who is required to register with the FDA.¹² A manufacturer must also submit a new 510(k) submission if a device

is being introduced for the first time and it is not, or is not substantially equivalent to, a pre-amendment device, or a device introduced for commercial distribution after May 28, 1976, that had been subsequently reclassified into Class I or II.¹³ Finally, a new submission is required if a device that is currently being marketed is significantly changed or modified.¹⁴ A significant change or modification can constitute either: (i) a major change or modification in the device’s intended use or (ii) a change or modification in design, materials, manufacturing processes, or components that significantly affect the safety and effectiveness of a device.¹⁵

A manufacturer must submit a 510(k) pre-market notification submission to the FDA at least 90 days before commercial distribution is scheduled to commence.¹⁶ A manufacturer must prepare either a 510(k) Summary or a 510(k) Statement. A 510(k) Summary provides a summary of information upon which a manufacturer bases its claim of substantial equivalence.¹⁷ A manufacturer must establish that its device is “substantially equivalent” to a legally marketed device. A legally marketed device—commonly known as a “predicate” device—is: (i) a device that was legally marketed prior to May 28, 1976, for which PMA is not required; (ii) a device which has been reclassified from Class III to Class I or II; or (iii) a device which has been found substantially equivalent through the 510(k) process.¹⁸

A manufacturer can demonstrate substantial equivalence if a new device has the same intended use and shares the same technological characteristics as the predicate. A statement of intended use must be submitted and should include a general description of the diseases or conditions that a device will diagnose, treat, prevent, cure, or mitigate, including the description of the patient population for which the device is intended.¹⁹ If a new device and its predicate are technologically different, a manufacturer must demonstrate that the new device: (i) has the same intended use as the predicate; (ii) is as safe and

⁸ 21 C.F.R. § 860.3(c)(1).

⁹ 21 C.F.R. § 860.3(c)(2).

¹⁰ 21 C.F.R. § 860.3(c)(3).

¹¹ Certain devices are exempt from the 510(k) pre-market notification requirement so long as they do not exceed certain exemption limitations delineated under 21 C.F.R. §§ 862.9 and 864.9.

¹² 21 C.F.R. § 807.81(a)(2).

¹³ 21 C.F.R. § 807.81(a)(1).

¹⁴ 21 C.F.R. § 807.81(a)(3).

¹⁵ 21 C.F.R. § 807.81(a)(3)(i) and (ii).

¹⁶ 21 C.F.R. § 807.81(a).

¹⁷ 21 C.F.R. § 807.92.

¹⁸ 21 C.F.R. § 807.92(a)(3).

¹⁹ 21 C.F.R. § 807.92(a)(5).

effective as the predicate; and (iii) does not raise different questions of safety or effectiveness.

The 510(k) Statement is a certification that a manufacturer will provide safety and effectiveness information supporting an FDA finding of substantial equivalence to any person within 30 days of written request.²⁰ Manufacturers choosing to submit a 510(k) Statement should note that anyone, including competitors, may request and review a copy of their 510(k) safety and effectiveness information. Trade secrets and certain other confidential information may be redacted, but safety and effectiveness data is required by law to be readily available. A 510(k) Summary, on the other hand, is only available to the public once a Freedom of Information Act request to examine the device information has been filed. While the 510(k) Statement may be convenient and less time-consuming to prepare, the 510(k) Summary better protects product information from exposure to competitors.

There are two alternative methods device manufacturers can use to establish substantial equivalence.²¹ First, the "Special 510(k): Device Modification" option is available for certain device modifications. A manufacturer may be able to submit a Special 510(k) if it modifies a device that has already been cleared through a 510(k) process and the modification conforms with the design controls set forth under the 21 C.F.R. part 820. To utilize a Special 510(k), however, a modification must not affect the intended use or alter the fundamental scientific technology of a device.²²

The second type of alternative method for establishing substantial equivalence is the "Abbreviated 510(k)," which relies upon the use of guidance documents, special controls, and recognized standards to facilitate the 510(k) review. Manufacturers may choose to submit an Abbreviated 510(k) when: (1) a guidance documents exists;²³ (2) a special control has been established; or (3) the FDA has recognized a relevant consensus standard.²⁴

²⁰ 21 C.F.R. § 807.93.

²¹ FDA Guidance, *The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications* (Mar. 20, 1998).

²² FDA Guidance, *How to Prepare a Special 510(k)* (last updated Nov. 13, 2007).

²³ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm> for a link to device guidance documents on FDA's website.

²⁴ 21 C.F.R. § 807.87.

Both alternative methods often result in a more rapid review by the FDA. Under the traditional 510(k) process, the FDA typically makes a substantial equivalence decision within 90 days after receiving a submission.²⁵ Under either alternative, however, the FDA maintains its ability to obtain any additional information it is authorized to request by the statute or regulations.

Regulations require that the FDA issue a substantial equivalence order within approximately 90 days after submission and receipt of a 510(k) pre-market submission. A manufacturer may not market a new device in the United States until it receives an order, in the form of a letter, from the FDA which finds the device to be substantially equivalent to the predicate and states that the device can be marketed in the U.S. If the FDA initially denies approval, a manufacturer may resubmit a 510(k) submission with new data, petition for de novo review, or choose to use the more time consuming and expensive PMA process.

b. Pre-Market Approval

Class III devices generally require FDA pre-market approval before they may be marketed in the United States.²⁶ The FDA imposes rigorous standards to provide reasonable assurances of safety and effectiveness for devices required to obtain PMA. The agency's scrutiny of a device under the PMA process is much stricter than under the 510(k) process. A PMA review may take the FDA an average of 1,200 hours to complete, while a review of a device subject to a 510(k) review generally takes about 20 hours.²⁷

A manufacturer using the PMA process must not only demonstrate that the probable benefits of its device outweigh potential risks, but also must submit scientific evidence demonstrating the absence of unreasonable risk of illness or injury. A device must be effective in a significant portion of the target population and, when used according to labeling, warnings, and indications, it must produce clinically significant results.²⁸ FDA regulations do

²⁵ U.S. Food and Drug Administration, Center for Devices and Radiological Health, *Device Advice on Premarket Notification 510(k)*.

²⁶ 21 U.S.C. § 360(e).

²⁷ *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 478-479 (1996).

²⁸ 21 C.F.R. § 860.7(e)(1).

not define “clinically significant results,” but an FDA official has said that such results indicate that the use of a device would have a positive effect on the disease being treated according to the standards of care for the related field.²⁹ Valid scientific evidence consisting primarily of well-controlled investigations also must be presented.

The amount of information a manufacturer must submit to the FDA is significantly greater under the PMA process than the 510(k) process. In addition to the summary of safety and effectiveness data, an applicant must submit its manufacturing methods and summaries of non-clinical and clinical studies.³⁰ A non-clinical laboratory summary should include the study purpose and rationale, protocol, results, and analysis and conclusion. The summary of clinical investigations should include a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, etc. The applicant must also describe both the positive and negative data obtained from both clinical and non-clinical studies. Unlike a 510(k) submission, which is reviewed only by a single reviewer who makes a determination of substantial equivalence, a PMA is reviewed by a multi-disciplinary team to ensure that the device that is the subject of the application is safe and effective.

Though the regulations require the FDA to review and make a determination regarding the sufficiency of a PMA submission within 180 days, the FDA rarely completes its review in this timeframe. The FDA’s fiscal year 2009 goal for PMAs is actually to review and decide upon 60 percent of original PMA submissions in 180 days and 90 percent of them within 295 days.³¹ An expedited review, however, is available for certain devices intended to treat or diagnose a life threatening or irreversibly debilitating disease or condition. These devices must: (i) utilize a breakthrough technology; (ii) have no existing approved alternative; (iii) offer significant

advantage over existing approved alternatives; or (iv) be such that its availability is in the best interest of patients.³²

The FDA may make one of four decisions when reviewing a PMA. First, the FDA may issue an approval order based on submission of final labeling before marketing.³³ The FDA may also issue an approval letter that contains certain conditions or information that is still required for approval.³⁴ The FDA may issue a no-approval letter in which the agency will notify the applicant of deficiencies that must be corrected for the agency to grant a device approval.³⁵ Finally, a denial order can be issued, in which case the applicant can petition the FDA for reconsideration.³⁶

IV. Combination Products

Manufacturers should note that the market approval pathway they must take to market a particular device in the United States depends upon the primary nature of the product to be marketed. For example, some companies manufacture “combination products”—products that consist of a combination of a device, drug, or biological product.³⁷ Combination products include items such as drug-eluting stents, antibiotic bone cement, and nasally administered influenza vaccine sprays. Depending on the combination product type, a manufacturer may submit a single marketing application or separate marketing applications for the individual components of the combination product.³⁸

A combination product’s primary mode of action (“PMOA”) determines which FDA center has primary jurisdiction over the product’s pre-market review. The FDA has defined a combination product’s PMOA as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode

²⁹ United States Government Accountability Office, *FDA’s Approval of TMJ Implants* (Sept. 2007).

³⁰ 21 C.F.R. § 814.20(b)(3).

³¹ United States 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* (Jan. 2009).

³² FDA Guidance, *Expedited Review of Premarket Submissions for Devices* (Feb. 29, 2008).

³³ 21 C.F.R. § 814.44(d).

³⁴ 21 C.F.R. § 814.44(e).

³⁵ 21 C.F.R. § 814.44(f).

³⁶ 21 C.F.R. § 814.45.

³⁷ 21 C.F.R. § 3.2(e).

³⁸ U.S. Food and Drug Administration, Office of Combination Products, Frequently Asked Questions.

of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”³⁹

The FDA’s Office of Combination Products (“OCP”) itself does not directly regulate products. Rather, it makes a determination as to the PMOA for a particular product and then transfers jurisdiction to the appropriate FDA center after such a determination is made. One of three FDA centers may assume primary jurisdiction over the review of a combination product based upon its PMOA: (i) the Center for Biologics Evaluation and Research; (ii) the Center for Devices and Radiological Health; or (iii) the Center for Drug Evaluation and Research. For example, if the PMOA of a device-biological combination product is attributable to the biological product, the Center for Biologics Evaluation and Research would likely assume responsibility for pre-market review of the combination product.

It is common for manufacturers to experience difficulty in determining a specific combination product’s PMOA. If neither the FDA nor the manufacturer can readily discern a combination product’s PMOA, a manufacturer may submit a Request for Designation (“RFD”) to the OCP. The RFD process can be formal or informal. In some circumstances OCP may have sufficient experience with similar products to make an informal determination over the telephone or through email.⁴⁰ Under the formal RFD process, an OCP scientific reviewer reviews a submission for administrative completeness and determines whether an RFD contains the information needed to make a jurisdictional determination.

The market for combination products has experienced significant growth. The number of original applications received by the OCP grew by 42 percent between fiscal years 2006 and 2007. The FDA has therefore made it a goal to raise the level of consistency in its classification and regulation of combination products. In fact, the FDA was scheduled to publish proposed rules addressing Good Manufacturing Practices and adverse reporting requirements for combination products by the end of 2008. While these proposed rules have not yet been published by the FDA, manufacturers should

anticipate potential changes in the agency’s governance of combination products by the end of 2009.

V. The GAO Report and the Medical Device Amendments of 1976

The FDA is under a Congressional mandate, through the Safe Medical Devices Act of 1990 (“SMDA”), to move towards requiring all Class III Device Types to undergo PMA review.⁴¹ Specifically, the SMDA required the FDA: (1) to collect data on and examine the Pre-Amendment Class III Device Types permitted to use the 510(k) process and determine whether such devices should be reclassified down to Class I or Class II; and (2) for all Pre-Amendment Class III Device Types that remain in Class III after the first step, to establish a schedule for requiring all Pre-Amendment Class III Device Types that remain Class III devices to be subject to the PMA process.⁴²

In 1994, the FDA, in response to the SMDA, developed and published a strategy for implementing the SMDA.⁴³ The FDA’s SMDA implementation strategy included a timeline for proposed implementing regulations. Completion dates, however, for implementation of the SMDA were not established.⁴⁴ The FDA has made some progress in its SMDA implementation. As of April 9, 2009, the FDA had either reclassified or issued regulations requiring PMA submission for 122 of the remaining 149 Pre-Amendment Class III Device Types.

This progress, however, does not mean that the FDA has fulfilled the SMDA mandate. Twenty-seven Pre-Amendment Class III Device Types have not been reclassified and are still permitted to rely upon the less stringent 510(k) process, despite the fact that the SMDA’s effective date occurred nearly two decades ago.⁴⁵

The Report released by the GAO supports the contention that the FDA has not satisfied the requirements of the SMDA. In the Report, the GAO urges the FDA to fulfill the SMDA mandate by requiring all Class III device types, regardless of their status as

³⁹ 70 Fed. Reg. 49,852 (Aug. 25, 2005).

⁴⁰ FDA Guidance, *How to Write a Request for Designation (RFD)* (Aug. 2005). 21 C.F.R. part 3 outlines the RFD process.

⁴¹ 21 U.S.C. § 360c(i).

⁴² 21 U.S.C. § 360c(i).

⁴³ 59 Fed. Reg. 23,731 (May 6, 1994).

⁴⁴ *Id.*

⁴⁵ 74 Fed. Reg. 16,215. (Apr. 9, 2009).

Pre-Amendment Class III Device Types, to either be reclassified or utilize the PMA pathway. In doing so, the GAO contends that the FDA would better protect the public by ensuring that all high-risk medical devices receive a thorough evaluation for safety and effectiveness.

The FDA spokeswoman, Karen Riley, responded to the GAO report on its release date. Ms. Riley stated that the agency generally agrees with the GAO's key conclusions. Further, she noted that the FDA has been continually striving to address the problems that exist with its current review processes, including efforts to either reclassify the Class III device types that are currently permitted to utilize the 510(k) process or require that they undergo PMA review.⁴⁶ She added that the agency is "considering legal and procedural options to accomplish this objective," but she did not specify a timeline for resolving the matter.⁴⁷

VI. A Step Towards Fulfilling the SMDA's Mandate: Initiation of Reexamination

On April 9, 2009, the FDA took an important and long-awaited step towards fulfilling the SMDA's mandate. A Federal Register notice published by the agency required manufacturers of 25 Pre-Amendment Class III Device Types to submit safety and efficacy information for their devices.⁴⁸ Among the 25 types are devices including external pacemaker pulse generators, hip joint metal, and implanted blood access devices. The FDA plans to examine the information submitted to it by manufacturers of these devices in order to determine whether each device should be re-categorized as Class I or II, or whether the risks associated with the device necessitate that it remain in Class III.

The type of information a manufacturer must submit depends upon whether the manufacturer is: (i) aware of information supporting the reclassification of the device into Class I or II; or (ii) aware of information that would support the device remaining in Class III. If a manufacturer is aware of any valid scientific

evidence supporting reclassification of a device into Class I or II, it may submit to the FDA either a petition for reclassification, as described in 21 C.F.R. § 860.123(a), or the following information:

- a. A brief narrative identification of the device;
- b. An identification of the risks to health;
- c. A statement whether a manufacturer believes the device should be reclassified into Class I or II;
- d. A summary of the reasons for requesting reclassification;
- e. An identification of the special controls the manufacturer believes is sufficient to provide reasonable assurance of safety and effectiveness of the device; and
- f. A summary of valid scientific evidence on which the recommendation is based.

If a manufacturer is not aware of information supporting reclassification of its device or is aware of valid scientific evidence that would support leaving the device in Class III, the manufacturer must submit the following information:

- a. Indications for use—a general description of the disease or condition to be diagnosed, treated, cured, mitigated, or prevented;
- b. Device description, including, among other things, basic scientific concepts that form the basis of the device;
- c. Other device labeling;
- d. A summary of risks;
- e. A description of alternative practices and procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended;
- f. A detailed summary of preclinical and clinical data; and
- g. Relevant references and their summaries.

Manufacturers have until August 7, 2009, to submit this above-described safety and efficacy information.⁴⁹

⁴⁶ Jared Favole, *GAO: FDA Medical Device Approval Process Needs Changes*, Dow Jones Newswires (Jan. 15, 2009).

⁴⁷ Ricardo Alonso-Zaldivar, *High Risk Medical Devices Escaped Close Review*, Denver Post (Jan. 15, 2009).

⁴⁸ 74 Fed. Reg. 16,214 (Apr. 9, 2009).

⁴⁹ For additional details on specific submission criteria and mechanics please refer to 74 Fed. Reg. 16,214 (Apr. 9, 2009).

VII. Conclusion

The FDA's renewed effort to update its pre-market review process will likely require unanticipated expenditure of resources for manufacturers of medical devices subject to the FDA's information request. Once the FDA has examined the data submitted for the remaining Pre-Amendment Class III Device Types, one of the following outcomes is likely to occur. First, the FDA could reclassify a device to Class I or II, in which case a manufacturer of such device would either be exempt from all pre-market review processes or be able to utilize the 510(k) pathway. Alternatively, the FDA could

determine that a given device should remain in Class III. In this case, the FDA would initiate procedures to require a PMA submission for such device.

Manufacturers whose devices are not reclassified will be required to file a PMA by an FDA-delineated effective date in order to continue marketing their product in the United States. Filing a PMA will require an even more significant financial and time investment on the part of these manufacturers. Further, any increase in the number of PMA submissions as a result of this initiative will likely result in substantial delays in the PMA submission process.