Food & Drug

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FDA Orders Submission of Data Regarding Certain Class III Pre-Amendment Medical Devices

On April 9, 2009, the Food and Drug Administration (FDA) issued an order requiring manufacturers of 25 types of Class III medical devices originally marketed before 1976 to submit safety and effectiveness information regarding these devices.[1] The Agency will use the submitted data to evaluate the risk level of these device types and determine whether each type is properly classified as Class III or should be reclassified to a lower risk classification.

If Class III status is appropriate for a given category of devices, FDA plans to initiate a rulemaking to require submission of premarket approval applications (PMAs) or notices of completion of a product development protocol (PDP)[2] for these devices. If the submitted data instead demonstrate that the device is not appropriately classified as a Class III device, FDA plans to commence proceedings to reclassify the category of devices as Class I (low risk) or Class II (intermediate risk).

According to FDA's order, "all" manufacturers of the identified Class III devices must submit the enumerated data and information by August 7, 2009.[3] Failure to comply with this order could expose manufacturers to enforcement action.

I. Background

The Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Medical Device Amendments of 1976 (MDA)[4] and subsequent laws, provides for the classification of medical devices into one of three classes based on their risk levels. For Class I devices, only "general controls" — including good manufacturing practices and establishment registration — are needed to provide a reasonable assurance of safety and effectiveness.[5] Class I devices generally are exempt from premarket review.[6]

[1] 74 Fed. Reg. 16214 (April 9, 2009).
[2] Under section 515(f) of the Federal Food, Drug, and Cosmetic Act (FDCA), manufacturers of a Class III device may pursue a PDP as an alternative track to the PMA for consideration and approval of the device. Under this procedure, FDA and the manufacturer agree in advance on the device testing program. If the testing is completed with sufficient results, the manufacturer provides a notice of completion of testing, and FDA declares the protocol complete, the product will be considered as having PMA approval. FDCA § 515(f)(1)&(6).
[3] 74 Fed. Reg. at 16216.
[4] Pub. L. No. 94-295, 90 Stat. 539 (May 28, 1976).
[5] FDCA § 513(a)(1)(A).
[6] FDCA § 510(*l*).

Class II devices require "special controls" (such as postmarket surveillance, patient registries, and compliance with FDA special controls guidance) to provide this reasonable assurance.[7] Before marketing a Class II device, a manufacturer generally must submit and obtain clearance of a premarket notification under section 510(k) of the FDCA ("510(k) notification") showing the device is "substantially equivalent" to a legally marketed predicate device.[8] Finally, Class III devices generally require submission and approval of a PMA prior to marketing.[9]

In enacting this regulatory framework in 1976, Congress included transition provisions designed both to preserve availability of then-marketed Class III devices pending FDA approval of PMAs for them and to assure that manufacturers of pre- and post-amendments devices would be treated similarly. Congress provided that Class III devices that were commercially distributed before enactment of the MDA (preamendments devices), and postamendments devices deemed "substantially equivalent" to these preamendments devices pursuant to a 510(k) notification, would not require approved PMAs until FDA promulgated a regulation triggering the PMA requirement for all such devices of a certain type (*e.g.*, all automated external defibrillators devices).[10] This type of regulation is known as a "call for PMAs."

By the late 1980s, FDA had not called for PMAs for many categories of preamendments Class III devices. Consequently, as part of the Safe Medical Devices Act of 1990,[11] Congress added to the FDCA section 515(i), which required FDA to complete the following tasks before December 1, 1995: (1) issue an order mandating that manufacturers submit information regarding these Class III devices; and (2) publish a regulation for each type of device revising the devices' classification to Class I or II or else indicating the devices should remain in Class III.[12] FDA did not meet this deadline. A recent Government Accountability Office (GAO) report to Congress criticized the Agency because the review still remains incomplete.[13]

FDA's order is meant to "[a]ddress[] GAO['s] [r]ecommendation."[14] According to FDA, the Agency has already down-classified or issued a call for PMAs with respect to 122 of the 149 device types that the Agency initially classified or proposed for classification into Class III.[15] Of the 27 remaining devices, two are the subject of ongoing rulemakings — Herpes simplex virus serological assays and Topical oxygen chambers for extremities.[16] The April 9, 2009 order applies to the remaining 25 device types.

FDA will review the submitted information and issue regulations for each device type, either calling for PMAs or down-classifying them. In the meantime, FDA advises that: "New premarket notification submissions for devices of these 25 types will continue to receive an appropriate level of scrutiny to ensure safety and effectiveness." [17]

[7] FDCA § 513(a)(1)(B).
[8] FDCA § 510(m).
[9] FDCA §§ 513(a)(1)(C), 515(a).
[10] FDCA §§ 513(f)(1)(A), 515(b)(1).
[11] Pub. L. No. 101-629 (November 28, 1990).
[12] FDCA § 515(i).
[13] GAO, Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved Through the Most Stringent Premarket Review Process (Jan. 2009).
[14] Press Release, FDA, FDA to Review Medical Devices Marketed Prior to 1976 (Apr. 8, 2009).
[15] 74 Fed. Reg. at 16215.
[16] *Id.*; FDA Press Release, *supra* note 14.
[17] FDA Press Release, *supra* note 14.

II. Device Types Subject to FDA's Order

FDA's order applies to 25 categories of devices, namely:

- Membrane lungs for long-term pulmonary support
- Intra-aortic balloon and control systems
- Ventricular bypass (assist) devices
- External pacemaker pulse generators
- Implantable pacemaker pulse generators
- Cardiovascular permanent pacemaker electrodes
- Pacemaker programmers
- Pacemaker repair or replacement materials
- Nonroller-type cardiopulmonary bypass blood pumps
- External cardiac compressors
- External counterpulsating devices
- Automated external defibrillators
- Endosseous dental implants (blade form)
- Mandibular condyle prostheses (temporary implant)
- Implanted blood access devices
- Sorbent hemoperfusion systems
- Cranial electrotherapy stimulators
- Electroconvulsive therapy devices
- Female condoms
- Pedicle screw spinal systems (certain uses)
- Hip joint metal/metal semi-constrained, with a cemented acetabular component, prostheses
- Hip joint metal/metal semi-constrained, with an uncemented acetabular component, prostheses
- Shortwave diathermy (certain uses)
- Iontophoresis devices (certain uses)
- Transilluminators for breast evaluation

The order applies to "all manufacturers currently marketing the preamendments class III devices subject to this order."[18]

III. Terms of the Order

The Agency's order mandates submission of certain information regarding devices falling within the 25 above categories before August 7, 2009.[19] The order provides that "FDA does not anticipate extending the time for submitting the required information."[20]

[18] 74 Fed. Reg. at 16216.
[19] *Id.*
[20] *Id.*

A. Required Content of Submissions

The order requires manufacturers of the identified devices to provide a summary of and citation to "any information known or otherwise available to them respecting the device."[21] This encompasses all safety and effectiveness data, except for reports submitted under section 519 of the FDCA (regarding medical device reporting (MDR) and reports of correction/removal). FDA does recommend, however, that manufacturers summarize information submitted under section 519 "to facilitate FDA's decisionmaking."[22]

The order establishes two formats for manufacturers' submissions. The appropriate format depends on whether the manufacturer is "aware" of information supporting reclassification of the device into Class I or II.[23]

If the manufacturer is unaware of such information, it must submit information in the following format: (1) indications for use; (2) device description; (3) "[o]ther device labeling that includes contraindications, warnings and precautions and/or promotional materials;" (4) a "Risks" section, including a summary of all adverse safety and effectiveness information, identification of risks the device presents, and any mechanisms or procedures that control these risks; (5) a description of "alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended;" (6) a summary of preclinical and clinical data from studies supporting the device's safety and effectiveness and addressing the adverse health effects of the device, including brief descriptions of the study protocol, data collection and analysis, results, statistical analysis, inclusion/exclusion criteria, study population, and reasons for patient discontinuances; and (7) a bibliography, including reference copies, a summary of each reference and a brief discussion of the reference's relevance to evaluation of the device's safety or effectiveness.[24]

Manufacturers "aware" of information supporting reclassification may submit the required information in a formal reclassification petition under 21 C.F.R. §§ 860.120 and 860.123(a)(3)-(4). Alternatively, they may submit the information in the following format: (1) "[a] brief narrative identification of the device;" (2) an identification of the risks to health posed by the device, including a summary of all adverse safety and effectiveness information that has not been submitted under section 519 of the FDCA, descriptions of the mechanisms or procedures that will control these risks, a list of general hazards associated with the device, and a bibliography with reference copies; (3) the manufacturer's recommendation as to the device's appropriate Class; (4) a summary of the reasons for this recommendation, including an explanation of how the device meets the statutory criteria for reclassification, and a description of appropriate special controls if recommending placement in Class II; and (5) "[a] summary of valid scientific evidence on which the recommendation is based."[25]

B. Standard for Reclassification

The notice reviews the statutory and regulatory standards FDA will apply to determine whether a device should be reclassified pursuant to a formal reclassification petition. The order does not describe expressly the criteria FDA will apply in evaluating information submitted pursuant to the above alternative procedure or in assessing whether it will commence proceedings to require PMAs or reclassification for given devices.

[21] *Id.*
[22] *Id.*
[23] *Id.*
[24] *Id.*
[25] *Id.*

The Agency will rely only on "valid scientific evidence" to reclassify a device pursuant to a formal reclassification petition.[26] "Valid scientific evidence" is comprised of evidence from which it can "fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness" of the device for its intended use.[27] The evidence required may vary according to the device, its indications, the existence and adequacy of warnings and other restrictions, and the amount of experience with that device type. Valid scientific evidence may consist of "well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device."[28] However, this showing cannot be made with "isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions."[29]

The order provides no timetable for FDA's assessment of the data or action with respect to any particular device type. Under FDA's regulations, however, a petition for reclassification requires action by the Agency within 180 days.[30]

IV. Enforcement

In the notice, FDA states that failure to comply with the order renders the manufacturer's affected devices misbranded and constitutes a prohibited act under the FDCA.[31] The Agency intends to use its enforcement powers — including seizure and injunction, civil penalties, and criminal prosecution — to "deter noncompliance."[32]

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[26] *Id.* at 16216-16217.
[27] *Id.* at 16217.
[28] *Id.*; 21 C.F.R. § 860.7(c)(2).
[29] 74 Fed. Reg. at 16217.
[30] 21 C.F.R. § 860.130(e).
[31] 74 Fed. Reg. at 16215 (citing FDCA §§ 502(t), 301(a)&(q)).
[32] *Id.*