

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 870 and 882

DDM

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D. Hawkins

[Docket No. 2003N-0567]

Cardiovascular and Neurological Devices; Reclassification of Two Embolization Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify two embolization devices to change the names of the devices, revise the identification of the devices, and reclassify the two devices from class III (premarket approval) into class II (special controls). The vascular embolization device (previously the arterial embolization device) is intended to control hemorrhaging due to aneurysms, certain tumors, and arteriovenous malformations. The neurovascular embolization device (previously the artificial embolization device) is intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations. These reclassifications are being proposed under the agency's own initiative under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments), the Safe Medical Devices Act of 1990 (the SMDA), the Food and Drug Administration Modernization Act of 1997 (FDAMA), and the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) based on new information. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of the draft

guidance document that the agency proposes to use as a special control for these devices.

DATES: Submit written or electronic comments on the proposed rule by *[insert date 90 days after date of publication in the **Federal Register**]*.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to: *http://www.fda.gov/dockets/ecomments*.

FOR FURTHER INFORMATION CONTACT: Peter L. Hudson, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-3090.

SUPPLEMENTARY INFORMATION:

I. Regulatory Authorities

The act, as amended by the 1976 amendments (Public Law 94-295), the SMDA (Public Law 101-629), the FDAMA (Public Law 105-115), and MDUFMA (Public Law 107-250) established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment,

along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Postamendments devices require premarket approval, unless FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the act, to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and 21 CFR part 807 of the regulations.

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

In 1990, the SMDA added section 515(i) to the act. This section requires FDA to issue an order to manufacturers of preamendments class III devices for which no final regulation requiring the submission of PMAs has been issued to submit to the agency a summary of, and a citation to, any information known or otherwise available to them respecting such devices, including adverse safety and effectiveness information that has not been submitted under section 519 of the act (21 U.S.C. 360i). Section 519 of the act requires manufacturers, importers, and device user facilities to submit adverse event

reports of certain device-related events and reports of certain corrective actions taken. Section 515(i) of the act also directs FDA to either revise the classification of the device into class I or class II or require the device to remain in class III and establish a schedule for the issuance of a rule requiring the submission of PMAs for those devices.

In the **Federal Register** of May 6, 1994 (59 FR 23731), FDA announced the availability of a document setting forth its strategy for implementing the provisions of the SMDA that require FDA to review the classification of preamendments class III devices. Under this plan, the agency divided preamendments class III devices into the following three groups: Group 1 devices are devices that FDA believes raise significant questions of safety and/or effectiveness, but are no longer used or are in very limited use; group 2 devices are devices that FDA believes have a high potential for being reclassified into class II; and group 3 devices are devices that FDA believes are currently in commercial distribution and are not likely candidates for reclassification.

In the **Federal Register** of August 14, 1995 (60 FR 41984 and 41986), FDA published two orders for certain class III devices requiring the submission of safety and effectiveness information in accordance with the preamendments class III strategy for implementing section 515(i) of the act. FDA published two updated orders in the **Federal Register** of June 13, 1997 (62 FR 32352 and 32355). The orders describe in detail the format for submitting the type of information required by section 515(i) of the act so that the information submitted would clearly support reclassification or indicate that a device should be retained in class III. The orders also scheduled the required submissions in groups, at 6-month intervals, beginning with August 14, 1996.

The devices proposed in this regulation for reclassification are included in group 3.

Reclassification of classified preamendments devices is governed by section 513(e) of the act. This section provides that FDA may, by rulemaking, reclassify a device (in a proceeding that parallels the initial classification proceeding) based upon “new information.” The reclassification can be initiated by FDA or by the petition of an interested person. The term “new information,” as used in section 513(e) of the act, includes information developed as a result of a re-evaluation of the data before the agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., *Holland Rantos v. United States Department of Health, Education, and Welfare*, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); *Upjohn v. Finch*, 422 F.2d 944 (6th Cir. 1970); *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966).)

Re-evaluation of the data previously before the agency is an appropriate basis for subsequent regulatory action where the re-evaluation is made in light of changes in “medical science.” (See *Upjohn v. Finch, supra*, 422 F.2d at 951.) However, regardless of whether data before the agency are past or new data, the “new information” upon which reclassification under section 513(3) of the act is based must consist of “valid scientific evidence” as defined in section 513(a)(3) of the act and 21 CFR 860.7(c)(2). FDA relies upon “valid scientific evidence” in the classification process to determine the level of regulation for devices. For the purpose of reclassification, the valid scientific evidence upon which the agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information,

and other information that may be protected. (See section 520(c) of the act (21 U.S.C. 360j(c)).)

11. Regulatory History of the Devices

A. Vascular (Arterial) Embolization Device

In the **Federal Register** of February 5, 1980 (45 FR 7937), FDA issued a final rule classifying the arterial embolization device, into class III (§ 870.3300 (21 CFR 870.3300)). The preamble to the proposed rule to classify the device (44 FR 13363, March 9, 1979) included the recommendations of the Cardiovascular Device Classification Panel (the Cardiovascular Panel) regarding the classification of the device. The Cardiovascular Panel recommended that the device be classified into class III and identified the following risks to health associated with the device: Thromboembolization, inadvertent embolization and infarction, vessel perforation, progressive granulomatous inflammation, and infection. FDA agreed with the Cardiovascular Panel's recommendation.

B. Neurovascular (Artificial) Embolization Device

In the **Federal Register** of September 4, 1979 (44 FR 51777), FDA issued a final rule classifying the artificial embolization device into class III (§ 882.5950 (21 CFR 882.5950)). The preamble to the proposed rule to classify the device (43 FR 55730, November 28, 1978) included the recommendations of the Neurological Devices Classification Panel (the Neurological Panel), an FDA advisory committee regarding the classification of the device. The Neurological Panel recommended that the device be classified into class III and identified tissue infarction and tissue toxicity as risks to health associated with use of the device. FDA agreed with the Neurological Panel's recommendation.

III. Device Descriptions

FDA is proposing the following revised device names and identifications based on the agency's review:

FDA is proposing to rename the arterial embolization device as "vascular embolization device" and the artificial embolization device as the "neurovascular embolization device."

A vascular embolization device is an intravascular implant intended to control hemorrhaging due to aneurysms, certain types of tumors (e.g., nephroma, hepatoma, uterine fibroids), and arteriovenous malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in neurovascular applications are also not included in this classification. (See § 882.5950.)

A neurovascular embolization device is an intravascular implant intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in other vascular applications are also not included in this classification. (See § 870.3300.)

The proposed names of vascular embolization device and neurovascular embolization device and the proposed device identifications more accurately reflect the intended uses of the legally marketed arterial and artificial embolization devices, respectively. Postamendments class III vascular and neurovascular embolization devices, such as cyanoacrylates and other embolization devices, which act by polymerization and precipitation, continue to require premarket approval.

IV. Recommendation of the Neurological Panel

At a public meeting on June 12, 1998, the Neurological Panel recommended that the neurovascular (artificial) embolization device be reclassified from class III into class II (Ref. 1). The Neurological Panel believed that class II with the special controls, in addition to the general controls, would reasonably assure the safety and effectiveness of the device. The Neurological Panel also recommended that the special controls for the device be labeling, sterilization, and biocompatibility.

At another public meeting on September 16 and 17, 1999 (Ref. 2), the Neurological Panel made recommendations on FDA's draft guidance document entitled "Guidance Document for Neurological Embolization Devices." The draft guidance document addressed the Neurological Panel's June 12, 1998, special controls recommendations for the device. Based on the Neurological Panel's recommendations and public comments on the draft guidance document, FDA revised the draft guidance document and issued it on November 1, 2000.

While the Panel's recommendation was specifically for the neurovascular (artificial) embolization device, because of the similarity of the vascular (arterial) embolization device to the neurovascular embolization device, in its intended use, design, risks to health, controls to mitigate the risks to health, and benefits, FDA has determined that the Neurological Panel's reclassification recommendation for the neurovascular embolization device is also relevant to the vascular embolization device.

V. Risks to Health

After considering the information in one 515(i) submission that addressed both device classifications (Ref. 3) and two other 515(i) submissions that

addressed the neurovascular embolization device (Refs. 4 and 5), the Neurological Panel's 1998 and 1999 recommendations, as well as the published literature and Medical Device Reports, FDA has evaluated the risks to health associated with use of the vascular and the neurovascular embolization devices. FDA believes that the following are risks to health associated with use of both device types: Vessel perforation or rupture, unintended thrombosis, adverse tissue reaction, infection, and hematoma formation. These risks to health are due to a combination of factors relating to the severely diseased, damaged, or malformed blood vessel; clinician experience; and the device.

A. Blood Vessel Perforation or Rupture

Blood vessel perforation or rupture may cause life-threatening hemorrhage. Blood vessel perforation may result from improper use of the delivery catheter, device-induced mechanical injury to the endothelial cells lining the blood vessel, or vasospasm. Blood vessel perforation or rupture may require surgery to correct this damage.

B. Unintended Thrombosis

Unintended thrombosis from implantation of an embolization device may cause distal tissue injury (i.e., ischemia and necrosis), which for the cerebral embolization may cause neurological deficits leading to cranial nerve palsy, visual impairment, stroke, infarct, unintended injury to organs, pulmonary embolization, or death. Incorrect device selection, device misplacement, device migration, device fracture, inadequate visualization of the device, or use of an inappropriate catheter delivery system may cause unintended thrombosis.

C. Adverse Tissue Reaction

Adverse tissue reaction is a risk to health common to all implanted devices. The implantation of embolization devices will elicit a mild inflammatory reaction typical of a normal foreign body response. Incompatible materials or impurities in the materials may increase the severity of a local tissue reaction or cause a systemic tissue reaction.

D. Infection

Infection of the soft tissue and fever are potential risks to health associated with all surgical procedures and implanted devices. Incompatible or impure material composition may irritate the vasculature, which could increase the risk of infection. Improper sterilization or packaging may also increase the risk of infection. Use of a device that is not pyrogen-free may elicit a fever response.

E. Hematoma Formation

Hematoma formation at the delivery catheter entry site, usually groin access to the femoral artery, is the result of internal bleeding.

VI. Summary of the Reasons for the Reclassification

FDA believes that the vascular embolization device and the neurovascular embolization device should be reclassified into class II because special controls, in addition to general controls, provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls to provide such assurance.

VII. Summary of the Data Upon Which the Reclassification is Based

In addition to the potential risks to health associated with implantation of the vascular and neurovascular embolization devices described in section V of this document, there is reasonable knowledge of the benefits of the devices. Specifically, the vascular and neurovascular embolization devices may

prevent life-threatening hemorrhage, reduce surgical morbidity and blood loss, and may reduce or relieve symptoms when surgical resection is not possible.

VIII. Special Controls

FDA believes that the guidance document entitled “Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices” (the class II special controls guidance document) in addition to general controls, can address the risks to health described in section V of this document. Because of the similarity of the two devices in intended use, design, risks to health, controls to mitigate the risks to health, and benefits, FDA has determined that the Neurological Panel’s special controls recommendation for the neurovascular embolization device is also relevant to the vascular embolization device. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of this draft class II special controls guidance document that the agency is proposing to use as the special control for these devices.

The draft guidance document contains specific recommendations with regard to device performance testing and other information in a premarket notification (510(k)) submission. Particular sections of the guidance document address the following topics for both embolization devices: Preclinical testing (including biocompatibility), sterility, animal testing, clinical testing, and labeling. In the table 1 of this document, FDA has identified the risks to health associated with the use of these devices in the first column and the recommended mitigation measures identified in the class II special controls guidance document in the second column. These recommendations will also help ensure that the device has appropriate performance characteristics and labeling for its use. Following the effective date of any final reclassification

rule based on this proposal, any firm submitting a 510(k) submission for these embolization devices will need to address the issues covered in the class II special controls guidance document. However, the firm need only show that its device meets the recommendations of the class II special controls guidance document or in some other way provides equivalent assurances of safety and effectiveness.

TABLE 1.—RISKS TO HEALTH AND RECOMMENDED MITIGATION MEASURES

Risk to health	Recommended mitigation measures
Blood vessel perforation or rupture	Preclinical testing, Animal testing, Clinical testing, Labeling
Unintended thrombosis	Preclinical testing, Animal testing, Clinical testing, Labeling
Adverse tissue reaction	Preclinical testing, Animal testing, Clinical testing
Infection	Sterility
Hematoma formation	Animal testing, Clinical testing, Labeling

IX. FDA's Tentative Findings

FDA believes the vascular and the neurovascular embolization devices should be reclassified into class II because special controls, in addition to general controls, can provide reasonable assurance of the safety and effectiveness of the devices and there is sufficient information to establish special controls to provide such assurance. FDA, therefore, is proposing to reclassify these devices into class II and establish the class II special controls guidance document as a special control for the devices.

For the convenience of the reader, FDA is also adding new § 870.1(e) and § 882.1(e) to inform the reader where to find guidance documents referenced in parts 870 and 882.

X. Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective **30** days after its date of publication in the **Federal Register**.

XI. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this proposed reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of these devices from class III to class II will relieve all manufacturers of the device types of the costs of complying with the premarket approval requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The agency

therefore certifies that this proposed rule, if finalized, would not have a significant economic impact on a substantial number of small entities. In addition, this proposed rule, if finalized, would not impose costs of \$100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement or analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

XIII. Paperwork Reduction Act of 1995

This proposed rule does not contain information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520).

XIV. Submission of Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XV. References

The following references are on display at the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday:

1. Neurological Devices Panel, transcript, June 12, 1998, pp. 1–124.
2. Neurological Devices Panel, transcript, September 17, 1999, pp. 9–11 and 101–152.

3. 515(i) submission submitted by Target Therapeutics, Inc., Fremont, CA, February 12, 1998.

4. 515(i) submission submitted by Cordis Endovascular Corp., Miami Lakes, FL, February 13, 1998.

5. 515 (i) submission submitted by Cook, Inc., Bloomington, IN, February 28, 1998.

List of Subjects in 21 CFR Parts 870 and 882

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 870 and 882 be amended as follows:

PART 870—CARDIOVASCULAR DEVICES

1. The authority citation for 21 CFR part 870 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 870.1 is amended by adding paragraph (e) to read as follows:

§ 870.1 Scope.

* * * * *

(e) Guidance documents referenced in this part are available on the Internet at <http://www.fda.gov/cdrh/guidance.html>.

3. Section 870.3300 is revised in subpart D to read as follows:

§ 870.3300 Vascular embolization device.

(a) *Identification.* A vascular embolization device is an intravascular implant intended to control hemorrhaging due to aneurysms, certain types of tumors (e.g., nephroma, hepatoma, uterine fibroids), and arteriovenous malformations. This does not include cyanoacrylates and other embolic agents,

which act by polymerization or precipitation. Embolization devices used in neurovascular applications are also not included in this classification. (See 21 CFR 882.5950.)

(b)*Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled “Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices.” For availability of this guidance document, see § 870.1(e).

PART 882—NEUROLOGICAL DEVICES

4. The authority citation for 21 CFR part 882 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

5. Section 882.5950 is revised to read as follows:

§ 882.5950 Neurovascular embolization device.

(a)*Identification.* A neurovascular embolization device is an intravascular implant intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in other vascular applications are also not included in this classification, see § 870.3300.

(b)*Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled “Class II Special Controls Guidance Document: Vascular Embolization Devices and Neurovascular

Embolization Devices.” For availability of this guidance document, see § 882.1(e).

Dated: 2/11/04
February 11, 2004.

Beverly Chernaik Rothstein
Beverly Chernaik Rothstein,
Acting Deputy Director for Policy and Regulations,
Center for Devices and Radiological Health.

[FR Doc. 04-????? Filed ??-??-04;8:45 am]

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Dawn P. Hawkins