

the adverse effects of the device on health. The summary should include a brief description of the objective of the studies, the experimental design, how the data were collected and analyzed, and a brief description of the results of the studies, whether positive, negative, or inconclusive. The summary of the clinical study(ies) should also include a discussion of the subject inclusion and exclusion criteria, the study population, reasons for patient discontinuations, and results of statistical analyses.

7. *Bibliography.* A copy of the key references, a brief summary of the salient features of each key reference, and a brief discussion of why the reference is relevant to an evaluation of the safety and effectiveness evaluation of the device.

Manufacturers who believe that existing information would support the reclassification of their device into class I or class II may either submit information using the format described below or may submit a formal reclassification petition, which should include the information described below in addition to the information required under 21 CFR 860.123.

1. *Identification.* A brief narrative identification of the device. This identification should be specific enough to distinguish a particular device from a generic type of device. Where appropriate, this identification should include a listing of the materials, and the component parts, and a description of the intended use of the device.

2. *Risks to health.* An identification of the risks to health should be provided. This section should summarize all adverse safety and effectiveness information, which have not been submitted under section 519 of the act particularly the most significant. The mechanisms or procedures which will control the risk should be described. A list of the general hazards associated with the device and a bibliography with copies of the referenced material should be provided.

3. *Recommendation.* A statement whether the manufacturer believes the device should be reclassified into class I or class II.

4. *Summary of reasons for recommendation.* Each manufacturer should include a summary of the reasons for requesting reclassification of its device and an explanation why it believes the device meets the statutory criteria for reclassification into class I or class II. Each manufacturer should also identify the special controls that it believes would be sufficient to provide reasonable assurance of the safety and effectiveness of its device if it believes

the device should be reclassified into class II.

5. *Summary of valid scientific evidence on which the recommendation is based.* Manufacturers are advised that, when considering a formal reclassification petition, FDA will rely only upon valid scientific evidence to determine that there is a reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone (class I) or by general controls and special controls (class II). Valid scientific evidence consists of evidence from 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, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. (See § 860.7(c)(2).)

According to § 860.7(d)(1) there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions for use. Moreover, pursuant to § 860.7(e)(1), there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Manufacturers submitting a formal reclassification petition may wish to request two petitions as examples of successful reclassification petitions.

Magnetic resonance imaging devices, Docket Nos. 87P-0214/CP through 87P-0215/CP0013, and Nd:YAG Laser for posterior capsulotomy devices, Docket No. 86P-0083, were both reclassified from class III to class II subsequent to the submission of a reclassification petition. Both petitions are available upon submission of a Freedom of Information request to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20850.

IV. Submission of Required Information

The summary of, and citation to, any information required by the act must be submitted by the dates listed above to the Document Mail Center (address above).

Dated: July 13, 1995.

Joseph A. Levitt,

Deputy Director for Regulations Policy, Center for Devices and Radiological Health.

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[Docket No. 94N-0417]

Order for Certain Class III Devices; Submission of Safety and Effectiveness Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order requiring manufacturers of 31 class III devices to submit to FDA a summary of, and a citation to, all information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices which has not been submitted under the Federal Food, Drug, and Cosmetic Act (the act). FDA is requesting this information in order to determine, for each device, whether the classification of the device should be revised, or whether a regulation requiring the submission of premarket approval applications (PMA's) for the device should be promulgated. Based on preliminary information, FDA believes these 31 devices have a higher potential for reclassification.

DATES: Summaries and citations must be submitted by the dates listed below.

ADDRESSES: Submit summaries and citations to the Documents Mail Center (HFZ-401), Food and Drug Administration, Center for Devices and Radiological Health, 9200 Corporate Blvd., Rockville, MD 20850.

FOR FURTHER INFORMATION CONTACT:

Melpomeni K. Jeffries, Center for Devices and Radiological Health (HFZ-404), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-2186.

SUPPLEMENTARY INFORMATION:**I. Background**

Section 513 of the act (21 U.S.C. 360c) requires the classification of medical devices into one of three regulatory classes: Class I (general controls), class II (special controls), and class III (premarket approval). Generally, devices that were on the market before May 28, 1976, the date of enactment of the Medical Device Amendments of 1976 (the amendments) (Pub. L. 94-295), and devices marketed on or after that date that are substantially equivalent to such devices, have been classified by FDA. This notice refers to both the class III devices that were on the market before May 28, 1976, and the substantially equivalent devices that were marketed on or after that date, as "preamendments devices."

Section 515(b)(1) of the act (21 U.S.C. 360e(b)(1)) establishes the requirement that a preamendments device that FDA has classified into class III is subject to premarket approval. However, submission of a PMA, or a notice of completion of a product development protocol (PDP), is not required until 90 days after FDA promulgates a final rule requiring premarket approval for the device, or 30 months after final classification of the device, whichever is later. Also, such a device is exempt from the investigational device exemption (IDE) regulations of part 812 (21 CFR part 812) until the date stipulated by FDA in the final rule requiring premarket approval for that device. If a PMA or a notice of completion of a PDP is not filed by the later of the two dates, commercial distribution of the device is required to cease. The device may, however, be distributed only for investigational use if the manufacturer, importer, or other sponsor of the device complies with the IDE regulations.

To date, FDA has issued final rules requiring the submission of PMA's for nine preamendment class III devices. Additionally, FDA has issued proposed rules for 10 other devices. There are 116 remaining preamendment class III devices for which FDA has not yet initiated action requiring the submission of PMA's.

The Safe Medical Devices Act of 1990 (the SMDA) (Pub. L. 101-629) changed the definition of class II devices from those for which a performance standard is necessary to provide reasonable assurance of safety and effectiveness to

those for which there is sufficient information to establish special controls to provide such assurance. Special controls include performance standards, postmarket surveillance, patient registries, guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions the agency deems necessary to provide such assurance. Thus, the SMDA modified the definition of class II devices to permit reliance on special controls, rather than performance standards alone, to provide reasonable assurance of safety and effectiveness.

The SMDA also added new section 515(i) (21 U.S.C. 360e(i)) to the act. This section requires FDA to order manufacturers of preamendment class III devices for which no final regulation has been issued requiring the submission of PMA's 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 which has not been submitted under section 519 of the act (21 U.S.C. 360i). Section 519 of the act (21 U.S.C. 360i) requires manufacturers, importers, or distributors to maintain records and to report information that reasonably suggests that one of its marketed devices may have caused or contributed to a death or serious injury or that a malfunction of the device is likely to cause death or serious injury on recurrence. 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 for devices remaining in class III, to establish a schedule for the promulgation of a rule requiring the submission of PMA's for the device.

In the **Federal Register** of May 6, 1994 (59 FR 23731), FDA announced its strategy for addressing the remaining preamendment class III devices. In that notice, FDA made available a document setting forth its strategy for implementing the provisions of the SMDA which require FDA to review the classification of certain class III devices, and either reclassify them into class I or class II or retain them in class III. Pursuant to this plan, the agency divided the universe of preamendment class III devices into the following 3 groups. Group 1 devices are devices that FDA believes raise significant questions of safety and/or effectiveness, but are no longer used or are very limited in use. Group 2 devices are devices that FDA

believes have a high potential for being reclassified into class II. Group 3 devices are devices that FDA believes are currently in commercial distribution and are not likely candidates for reclassification. There are a total of 43, 31, and 42 (15 high priority) devices in Groups 1, 2, and 3, respectively.

In the May 6, 1994 notice, FDA announced its intent to call for the submission of PMA's for the 15 highest priority devices in Group 3 and for all Group 1 devices. The agency also announced its intent to issue an order under section 515(i) of the act for the remaining Group 3 devices and all of the Group 2 devices. Under section 515(i) of the act, FDA is authorized to require the submission of the adverse safety and effectiveness information identified in the summary and citation submitted in response to this order, if such information is available. Based upon the information submitted in response to this order, FDA will either propose reclassification of some or all of these devices into class I or class II, or propose retaining some or all of them in class III.

In this document, FDA is requiring manufacturers of all 31 devices in Group 2 to submit a summary of, and citation to, all safety and effectiveness information known or otherwise available to them respecting such devices, including adverse information concerning the devices which has not been submitted under section 519 of the act. As noted above, FDA believes that these devices have a higher potential for reclassification provided that manufacturers collect, analyze, and submit the necessary supporting information in response to this notice.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a similar notice with respect to the 27 remaining Group 3 devices.

II. Statutory Authority and Enforcement

In addition to the provisions of section 515(i) of the SMDA described above, this order is issued under section 519 of the act, as implemented by § 860.7(g)(2) (21 CFR 860.7(g)(2)). This regulation authorizes FDA to require reports or other information bearing on the classification of a device. Section 519 of the act also requires the reporting of any death or serious injury caused by a device or by its malfunction.

Failure to furnish the information required by this order results in the device being misbranded under section 502(t) of the act (21 U.S.C. 352 (t)) and is a prohibited act under sections 301(a) and (q) of the act (21 U.S.C. 331(a) and (q)). The agency will use its enforcement

powers to deter noncompliance. Violations of section 301 of the act may be subject to seizure or injunction under sections 304(a) and 302(a) of the act (21 U.S.C. 334(a) and 332(a) respectively). In addition, violations under section 301 of the act may be subject to civil penalties under section 303(f) of the act (21 U.S.C. 333(f)) and criminal prosecution under section 303(a) of the act (21 U.S.C. 333(a)).

III. Order

The agency is hereby issuing this order under sections 515(i) and 519 of the act and § 860.7(g)(1) of the regulations. Under the order, the required information shall be submitted by the dates listed below so that FDA may begin promptly the process established by section 515(i) of the act to either revise or sustain the current classification of these devices.

A. Deadlines for Submission of Information

For the following 8 devices, the required information shall be submitted by August 14, 1996.

1. § 864.7250 *Erythropoietin assay.*
 2. § 864.7300 *Fibrin monomer paracoagulation test.*
 3. § 876.3630 *Penile rigidity implant.*
 4. § 878.5360 *Tweezer-type epilator.*
 5. § 884.1060 *Endometrial aspirator.*
 6. § 884.1100 *Endometrial brush.*
 7. § 884.1185 *Endometrial washer.*
 8. § 886.3920 *Eye valve implant.*
- For the following 9 devices, the required information shall be submitted by February 14, 1997.
9. § 866.3305 *Herpes simplex virus serological reagents.*
 10. § 866.3510 *Rubella virus serological reagents.*
 11. § 870.3620 *Pacemaker lead adaptor.*
 12. § 872.6080 *Airbrush.*
 13. § 876.4480 *Electrohydraulic lithotripter.*
 14. § 878.3610 *Esophageal prosthesis.*
 15. § 878.3720 *Tracheal prosthesis.*
 16. § 884.4100 *Endoscopic electrocautery and accessories.*
 17. § 884.4150 *Bipolar endoscopic coagulator-cutter and accessories.*

For the following 10 devices, the required information shall be submitted by August 14, 1997.

18. § 868.1150 *Indwelling blood carbon dioxide partial pressure (Pco2) analyzer.*
19. § 868.1170 *Indwelling blood hydrogen ion concentration (pH) analyzer.*
20. § 868.1200 *Indwelling blood oxygen partial pressure (Pco2) analyzer.*
21. § 870.3680(b) *Cardiovascular permanent pacemaker electrode.*

22. § 870.4260 *Cardiopulmonary bypass arterial line blood filter.*

23. § 870.4350 *Cardiopulmonary bypass oxygenator.*

24. § 876.5860 *High permeability hemodialysis system.*

25. § 878.5650 *Topical oxygen chamber for extremities.*

26. § 882.5940 *Electroconvulsive therapy device.*

27. § 888.3660 *Shoulder joint metal/polymer semi-constrained cemented prosthesis.*

For the following 4 devices, the required information shall be submitted by August 14, 1998.

28. § 870.3710 *Pacemaker repair or replacement material.*

29. § 870.4320 *Cardiopulmonary bypass pulsatile flow generator.*

30. § 870.5200 *External cardiac compressor.*

31. § 876.5540(b)(1) *Implanted blood access device.*

B. Required Contents of Submissions

By the dates listed above, all manufacturers currently marketing preamendments class III devices subject to this order shall provide a summary of, and citation to, any information known or otherwise available to them respecting the devices, including adverse safety and effectiveness data which has not been submitted under section 519 of the act. FDA suggests that it may be in the best interest of submitters to summarize the information submitted under section 519 of the act to facilitate FDA's decision making, even though such information is not required.

The information should be submitted in one of the two following formats depending on whether the applicant is aware of any information which would support the reclassification of the device into class I (general controls) or class II (special controls). Information which would support the reclassification of the device must consist of adequate, valid scientific evidence showing that general controls alone (class I), or general controls and special controls (class II) will provide a reasonable assurance of the safety and effectiveness of the device.

For manufacturers who do *not* believe that existing information would support the reclassification of their device into class I or class II, the information provided should be submitted in the following format:

1. *Indications for use.* A general description of the disease or condition to be diagnosed, treated, cured, mitigated, or prevented, including a description of the patient population for which the device is intended.

2. *Device description.* An explanation of how the device functions, significant physical and performance characteristics of the device, and basic scientific concepts that form the basis for the device.

3. *Other device labeling.* Other device labeling that includes contraindications, warnings and precautions and/or promotional materials.

4. *Risks.* A summary of all adverse safety and effectiveness information and identification of the risks presented by the device as well as any mechanisms or procedures which will control the risk.

5. *Alternative practices and procedures.* 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. *Summary of preclinical and clinical data.* The summary of preclinical and clinical data should include the conclusions drawn from the studies which support the safety and effectiveness of the device as well as special controls, if any, which address the adverse effects of the device on health. The summary should include a brief description of the objective of the studies, the experimental design, how the data were collected and analyzed, and a brief description of the results of the studies, whether positive, negative, or inconclusive. The summary of the clinical study(ies) should also include a discussion of the subject inclusion and exclusion criteria, the study population, reasons for patient discontinuations, and results of statistical analyses.

7. *Bibliography.* A copy of the key references, a brief summary of the salient features of each key reference, and a brief discussion of why the reference is relevant to an evaluation of the safety and effectiveness evaluation of the device.

Manufacturers who believe that existing information would support the reclassification of their device into class I or class II may either submit information using the format described below or may submit a formal reclassification petition, which should include the information described below in addition to the information required under 21 CFR 860.123.

1. *Identification.* A brief narrative identification of the device. This identification should be specific enough to distinguish a particular device from a generic type of device. Where appropriate, this identification should include a listing of the materials, and the component parts, and a description of the intended use of the device.

2. *Risks to health.* An identification of the risks to health should be provided. This section should summarize all adverse safety and effectiveness information, which have not been submitted under section 519 of the act, particularly the most significant. The mechanisms or procedures which will control the risk should be described. A list of the general hazards associated with the device and a bibliography with copies of the referenced material should be provided.

3. *Recommendation.* A statement whether the manufacturer believes the device should be reclassified into class I or class II.

4. *Summary of reasons for recommendation.* Each manufacturer should include a summary of the reasons for requesting reclassification of its device and an explanation why it believes the device meets the statutory criteria for reclassification into class I or class II. Each manufacturer should also identify the special controls that it believes would be sufficient to provide reasonable assurance of the safety and effectiveness of its device if it believes the device should be reclassified into class II.

5. *Summary of valid scientific evidence on which the recommendation is based.* Manufacturers are advised that, when considering a formal reclassification petition, FDA will rely only upon valid scientific evidence to determine that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone (class I) or by general controls and special controls (class II).

Valid scientific evidence consists of evidence from 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, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. (See § 860.7(c)(2).)

According to § 860.7(d)(1) there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions for use. Moreover, pursuant

to § 860.7(e)(1), there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Manufacturers submitting a formal reclassification petition may wish to request two petitions as examples of successful reclassification petitions. Magnetic resonance imaging devices, Docket Nos. 87P-0214/CP through 87P-0215/CP0013, and Nd:YAG Laser for posterior capsulotomy devices, Docket No. 86P-0083, were both reclassified from class III to class II subsequent to the submission of a reclassification petition. Both petitions are available upon submission of a Freedom of Information request to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20850.

IV. Submission of Required Information

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Dated: July 13, 1995.

Joseph A. Levitt,

Deputy Director for Regulations Policy, Center for Devices and Radiological Health.

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