neither an environmental assessment nor an environmental impact statement is required.

III. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments 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.

Dated: February 13, 2012.

Dennis M. Keefe,

Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition.

[FR Doc. 2012–3744 Filed 2–16–12; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 876

[Docket No. FDA–2012–M–0076]

Gastroenterology-Urology Devices; Reclassification of Sorbent Hemoperfusion Devices for the Treatment of Poisoning and Drug Overdose; Effective Date of Requirement for Premarket Approval for Sorbent Hemoperfusion Devices To Treat Hepatic Coma and Metabolic Disturbances

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify the sorbent hemoperfusion system, a preamendments class III device, into class II (special controls) for the treatment of poisoning and drug overdose, and to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the treatment of hepatic coma and metabolic disturbances. FDA is identifying the proposed special controls that the Agency believes will reasonably ensure the safety and effectiveness of the device for the treatment of poisoning and drug overdose. The Agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the devices to meet the statute's approval requirements and the benefits to the public from the use of the devices. In addition, FDA is announcing the opportunity for interested persons to request that the Agency change the classification of any of the devices mentioned in this document based on new information. This action implements certain statutory requirements.

DATES: Submit either electronic or written comments by May 17, 2012. Submit requests for a change in classification by March 5, 2012. See section XVIII of this document for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments, identified by Docket No. FDA–2012–M–0076, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Fax: 301–827–6870.
- Mail/Hand delivery/Courier (for paper or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2012–M–0076 for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Melissa Burns, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 1646, Silver Spring, MD 20993, 301–796–5616, *melissa.burns@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background—Regulatory Authorities

A. Requirement for Premarket Approval Application

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Medical Device Amendments (the 1976 amendments) (Pub. L. 94–295), the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. 101–629), Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107–250), the Medical Devices Technical Corrections Act (Pub. L. 108–214), and the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110–85) establish a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting 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 FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (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 automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and 21 CFR part 807.

A preamendments device that has been classified into class III may be

marketed by means of premarket notification procedures (510(k) process) without submission of a PMA until FDA issues a final regulation under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval. Section 515(b)(1) of the FD&C Act establishes the requirement that a preamendments device that FDA has classified into class III is subject to premarket approval. A preamendments class III device may be commercially distributed without an approved PMA or a notice of completion of a PDP until 90 days after FDA issues a final rule requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. Also, a preamendments device subject to the rulemaking procedure under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final rule requiring the submission of a PMA for the device. At that time, an IDE is required only if a PMA has not been submitted or a PDP completed.

Section 515(b)(2)(A) of the FD&C Act provides that a proceeding to issue a final rule to require premarket approval shall be initiated by publication of a notice of proposed rulemaking containing: (1) The regulation; (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or a declared completed PDP and the benefit to the public from the use of the device; (3) an opportunity for the submission of comments on the proposed rule and the proposed findings; and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(2)(B) of the FD&C Act provides that if FDA receives a request for a change in the classification of the device within 15 days of the publication of the notice, FDA shall, within 60 days of the publication of the notice, consult with the appropriate FDA advisory committee and publish a notice denying the request for change in reclassification or announcing its intent to initiate a proceeding to reclassify the device under section 513(e) of the FD&C Act. Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed rule and consideration of any comments received, issue a final rule to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

If a proposed rule to require premarket approval for a preamendments device is finalized, section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B)) requires that a PMA or notice of completion of a PDP for any such device be filed within 90 days of the date of issuance of the final rule or 30 months after the final classification of the device under section 513 of the FD&C Act, whichever is later. If a PMA or 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 since the device would be deemed adulterated under section 501(f) of the FD&C Act.

The device may, however, be distributed for investigational use if the manufacturer, importer, or other sponsor of the device complies with the IDE regulations. If a PMA or notice of completion of a PDP is not filed by the later of the two dates, and the device does not comply with IDE regulations, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). In the past, FDA has requested that manufacturers take action to prevent the further use of devices for which no PMA or PDP has been filed and may determine that such a request is appropriate for the class III devices that are the subjects of this regulation.

The FD&C Act does not permit an extension of the 90-day period after issuance of a final rule within which an application or a notice is required to be filed. The House Report on the 1976 amendments states that ''[t]he thirty month grace period afforded after classification of a device into class III * * * is sufficient time for manufacturers and importers to develop the data and conduct the investigations necessary to support an application for premarket approval (H. Rept. 94–853, 94th Cong., 2d sess. 42 (1976)).''

The SMDA added section 515(i) to the FD&C Act requiring FDA to review the classification of preamendments class III devices for which no final rule requiring the submission of PMAs has been issued and to determine whether or not each device should be reclassified into class I or class II or remain in class III. For devices remaining in class III, the SMDA directed FDA to develop a schedule for issuing regulations to require premarket approval. The SMDA does not, however, prevent FDA from proceeding immediately to rulemaking under section 515(b) of the FD&C Act on specific devices, in the interest of public health, independent of the procedures of section 515(i). Proceeding directly to rulemaking under section 515(b) of the FD&C Act is consistent with Congress' objective in enacting section 515(i), i.e., that preamendments class III devices for which PMAs have not been previously required either be reclassified to class I or class II or be subject to the requirements of premarket approval. Moreover, in this proposed rule, interested persons are being offered the opportunity to request reclassification of any of the devices.

B. Reclassification

Section 513(e) of the FD&C Act governs reclassification of classified preamendments devices. This section provides that FDA may, by rulemaking, reclassify a device (in a proceeding that parallels the initial classification proceeding) based upon ''new information.'' FDA can initiate a reclassification under section 513(e) or an interested person may petition FDA to reclassify a preamendments device. The term ''new information,'' as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation 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).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see *Bell* v. *Goddard,* supra, 366 F.2d at 181; *Ethicon, Inc.* v. *FDA,* 762 F. Supp. 382, 388–389 (D.D.C. 1991)) or in light of changes in ''medical science.'' (See *Upjohn* v. *Finch,* supra, 422 F.2d at 951.). Whether data before the Agency are past or new data, the ''new

information'' to support reclassification under section 513(e) must be ''valid scientific evidence,'' as defined in section 513(a)(3) of the FD&C Act and § 860.7(c)(2) (21 CFR 860.7(c)(2)). (See, e.g., *General Medical Co.* v. *FDA,* 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Assoc.* v. *FDA,* 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985).)

FDA relies upon ''valid scientific evidence'' in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the valid scientific evidence upon which the Agency relies must be publicly available. Publicly available information excludes trade secrets and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).) Section 520(h)(4) of the FD&C Act, added by FDAMA, provides that FDA may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This includes information from clinical and preclinical tests or studies that demonstrate the safety or effectiveness of the device but does not include descriptions of methods of manufacture or product composition and other trade secrets.

FDAMA added a new section 510(m) to the FD&C Act. New section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act, if the Agency determines that premarket notification is not necessary to assure the safety and effectiveness of the device.

II. Regulatory History of the Device

In the preamble to the proposed rule (46 FR 7562, January 23, 1981, and 46 FR 7630, January 23, 1981), the Gastroenterology-Urology Device Classification Panel (the Panel) recommended that sorbent hemoperfusion systems be classified into class III because the device is life sustaining and life supporting and because there was a lack of data on the absorption characteristics of this device regarding the possibility that it may, while removing toxic substances, also remove essential substances from the blood or cause loss or platelets and white cells. The Panel indicated that general controls alone would not be sufficient and that there was not enough information to establish a performance standard. Consequently, the Panel believed that premarket approval was necessary to assure the safety and effectiveness of the device. In 1983, FDA classified sorbent hemoperfusion systems into class III after receiving no comments on the proposed rule (48 FR 53012, November 23, 1983). In 1987, FDA published a clarification by inserting language in the codified language stating that no effective date had been established for the requirement for premarket approval for sorbent hemoperfusion system devices (52 FR 17732 at 17738, May 11, 1987).

In 2009, FDA published an order for the submission of information on sorbent hemoperfusion systems by August 7, 2009 (74 FR 16214, April 9, 2009). In response to that order, FDA received one reclassification petition from a device manufacturer recommending that sorbent hemoperfusion systems be reclassified to class II. The manufacturers stated that safety and effectiveness of these devices may be assured by device design, performance testing, and labeling (special controls).

III. Device Description

A sorbent hemoperfusion system is a device that consists of an extracorporeal blood system and a container filled with adsorbent material that removes a wide range of substances, both toxic and normal, from blood flowing through it. The adsorbent materials are usually activated-carbon or resins, which may be coated or immobilized to prevent fine particles entering the patient's blood. The generic type of device may include lines and filters specifically designed to connect the device to the extracorporeal blood system. Sorbent hemoperfusion systems may also include the machine or instrument used to drive and manage blood and fluid flow within the extracorporeal circuit, as well as any accompanying controllers, monitors, or sensors.

IV. Proposed Reclassification

FDA is proposing that sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose be reclassified from class III to class II. FDA believes that the identified special controls would provide reasonable assurance of safety and effectiveness. Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and § 860.130 (21 CFR 860.130), based on new information with respect to the devices, FDA, on its own initiative, is proposing to reclassify this preamendments class III device intended for the treatment of poisoning and drug overdose into class II. The Agency has identified special controls that would provide reasonable assurance of their safety and effectiveness. The Agency does not intend to exempt this proposed class II device from premarket notification (510(k)) submission as provided for under section 510(m) of the FD&C Act.

V. Risks to Health

After considering the information from the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted in response to the 515(i) order and any additional information that FDA has encountered, FDA has evaluated the risks to health associated with the use of sorbent hemoperfusion systems and determined that the following risks to health are associated with its use:

- *Extracorporeal leaks (blood loss)*—Rupture of the extracorporeal circuit, cartridge, filters, and/or tubing, as well as disconnections, may lead to blood leaks and blood loss.
- *Platelet loss and thrombocytopenia*—The adsorption characteristics of the device may cause large losses of platelets during hemoperfusion.
- *Leukopenia*—The materials used, or the design of the device, may cause absorption of leukocytes, leading to the transient loss of leukocytes in a patient.
- *Hemolysis*—The materials used, or the design of the blood pathways in the device, may cause the lysis of red blood cells.
- *Leak of adsorbent agent into fluid path (release of emboli)*—Fine particles leached from the sorbent column of the device may be deposited in the arterioles of the lungs and other organ as particulate emboli.
- *Lack of sterility*—Improper sterilization or compromise of the device packaging may lead to the introduction of microorganisms, which may be transmitted to a patient during use.
- *Toxic and/or pyrogenic reactions*—Toxic substances may be leached from the device, causing a patient to have a pyrogenic reaction (sudden fever with collapse and chills).
- *Infection*—Defects in the design or construction of the device preventing adequate cleaning and/or sterilization may allow pathogenic organisms to be introduced and may cause an infection in a patient.
- *Hypotension*—Sudden fluid shifts within the patient, due to pressures exerted by the device, or to fluid being removed by the device, may cause sudden decreases in a patient's blood pressure.
- *Lack of biocompatibility in materials or solutions contacting blood*—The patient-contacting materials of the device may cause an adverse

immunological or allergic reaction in a patient.

• *Clotting (blood loss)*—The materials used, or the design of the device, may cause a patient's blood to form clots, which may obstruct the device's extracorporeal circuit, interrupting or terminating treatments, and also leading to blood loss, because the blood entrapped in the clotted blood circuit often cannot be returned to the patient.

• *Removal or depletion of vital nutrients, hormones, vitamins, substances. and drugs (e.g., adsorption of glucose, unspecific removal characteristics, drop in patients' hematocrit), due to device's lack of specificity*—The adsorption characteristics of the device may cause removal or depletions of nutrients, hormones, and other necessary substances.

• *Metabolic disturbances*—The removal of normal metabolites along with undesirable substances may lead to metabolic disturbances.

• *Lack of effectiveness*—The adsorption characteristics of the device may lead to the failure to remove drugs in the treatment of poisoning or drug overdose, or to bring on clinical improvement in hepatic coma and metabolic disturbances.

• *Treatment interruptions or discontinuations*—Inadequate safeguards in the device may lead to treatment interruptions or discontinuations in the case of power failures.

• *Electrical shock due to lack of electrical safety*—Inadequate safeguards in the device may lead to electrical shocks in patients using them.

• *Electromagnetic interference, which may lead to adverse interactions with other patient systems*—Inadequate safeguards in the device may lead to its interference with other patient systems, causing adverse events in the patient, as well as adversely affecting the performance of the other patient systems.

VI. Summary of Reasons for Reclassification

FDA believes that sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose should be reclassified into class II because special controls, in addition to general controls, can be established to provide reasonable assurance of the safety and effectiveness of the device. In addition, there is now adequate effectiveness information sufficient to establish special controls to provide such assurance.

VII. Summary of Data Upon Which the Reclassification Is Based

Since the time of the original Panel recommendation, sufficient evidence has been developed to support a reclassification of sorbent hemoperfusion system to class II with special controls for the treatment of poisoning and hepatic coma. Evidence including reports of clinical evaluations and case studies of the use of these devices in the treatment of poisoning and drug overdose, and bench studies in which the devices' abilities to remove certain drugs have been well characterized.

VIII. Proposed Special Controls

FDA believes that the following special controls are sufficient to mitigate the risks to health described in section IV in this document for the treatment of poisoning and drug overdose:

• The device should be demonstrated to be biocompatible;

• Performance data to demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength), including testing for the possibility of leaks, ruptures, release of particles and/or disconnections;

• Performance data to demonstrate device sterility and shelf life;

• Bench performance data to demonstrate device functionality in terms of substances, toxins, and drugs removed by the device, and the extent that these are removed when the device is used according to its labeling;

• Summary of clinical experience with the device that discusses and analyzes device safety and performance, including a list of adverse events observed during the testing;

• Labeling controls, including appropriate warnings, precautions, cautions, and contraindications statements to alert and inform users of proper device use and potential clinical adverse effects, including blood loss, platelet loss, leukopenia, hemolysis, hypotension, clotting, metabolic disturbances, and loss of vital nutrients and substances. Labeling recommendations must be consistent with the performance data obtained for the device, and must include a list of the drugs the device has been demonstrated to remove, and the extent of removal/depletion; and

• For those devices that incorporate electrical components, appropriate analysis and testing to validate electrical safety and electromagnetic compatibility.

IX. Dates New Requirements Apply

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA or a notice of completion of a PDP be filed with the Agency for class III devices within 90 days after issuance of any final rule based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, will be permitted to continue marketing such class III devices during FDA's review of the PMA or notice of completion of the PDP. FDA intends to review any PMA for the device within 180 days and any notice of completion of a PDP for the device within 90 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that ''the continued availability of the device is necessary for the public health.''

FDA intends that under § 812.2(d), the preamble to any final rule based on this proposal will state that, as of the date on which the filing of a PMA or a notice of completion of a PDP is required to be filed, the exemptions from the requirements of the IDE regulations for preamendments class III devices in § 812.2(c)(1) and (c)(2) will cease to apply to any device that is: (1) Not legally on the market on or before that date or (2) legally on the market on or before that date but for which a PMA or notice of completion of a PDP is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA or notice of completion of a PDP for a class III device is not filed with FDA within 90 days after the date of issuance of any final rule requiring premarket approval for the device, commercial distribution of the device must cease. The device may be distributed for investigational use only if the requirements of the IDE regulations are met. The requirements for significant risk devices include submitting an IDE application to FDA for its review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before the end of the 90-day period after the issuance of the final rule to avoid interrupting investigations.

X. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury

designed to be eliminated or reduced by requiring that this device have an approved PMA or a declared completed PDP when indicated for the treatment of hepatic coma and metabolic disturbances and (2) the benefits to the public from the use of the sorbent hemoperfusion system for treatment of hepatic coma and metabolic disturbances.

These findings are based on the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted in response to the 515(i) Order, (74 FR 16214) and any additional information that FDA has encountered. Additional information regarding the risks as well as classification associated with this device type can be found in 46 FR 7630, 46 FR 7562, and 48 FR 53023.

For the treatment of hepatic coma and metabolic disturbances, FDA concludes that the safety and effectiveness of these devices have not been established by adequate scientific evidence, and the Agency continues to agree with the Panel's recommendation. The review of the published scientific literature revealed mostly observational studies performed with sorbent hemoperfusion devices. Only a few randomized, controlled trials were found, but sample sizes were small and not adequately powered, and etiologies and control group criteria were varied. Furthermore, based on FDA's experience reviewing these devices for use in the treatment of hepatic coma and metabolic disturbances, bench testing is not adequate in establishing the devices' safety and effectiveness, particularly since characterizing a sorbent hemoperfusion system's performance and adsorption capabilities has not correlated to patient outcomes, such as resolution of the patients' hepatic coma, or improvements in mortality. The scientific literature also revealed that there is no consensus on the clinical endpoints necessary to adequately evaluate sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances or on the patient populations who will benefit the most from the use of these devices.

XI. PMA Requirements

A PMA for sorbent hemoperfusion system indicated for the treatment of hepatic coma and metabolic disturbances must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see § 860.7(c)(2)). Valid scientific evidence is ''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. * * * 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. * * *'' (§ 860.7(c)(2)).

XII. PDP Requirements

A PDP for sorbent hemoperfusion system indicated for the treatment of hepatic coma and metabolic disturbances may be submitted in lieu of a PMA and must follow the procedures outlined in section 515(f) of the FD&C Act. A PDP must provide: (1) A description of the device, (2) preclinical trial information (if any), (3) clinical trial information (if any), (4) a description of the manufacturing and processing of the devices, (5) the labeling of the device, and (6) all other relevant information about the device. In addition, the PDP must include progress reports and records of the trials conducted under the protocol on the safety and effectiveness of the device for which the completed PDP is sought.

XIII. Opportunity To Request a Change in Classification

Before requiring the filing of a PMA or notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(A)(i) through (b)(2)(A)(iv) of the FD&C Act and § 860.132 to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of these devices is to be in the form of a reclassification petition containing the information required by § 860.123 (21 CFR 860.123), including new information relevant to the classification of the device.

The Agency advises that to ensure timely filing of any such petition, any request should be submitted to the Division of Dockets Management (see **ADDRESSES**) and not to the address provided in § 860.123(b)(1). If a timely request for a change in the classification of these devices is submitted, the Agency will, within 180 days after receipt of the petition, and after consultation with the appropriate FDA resources, publish an order in the **Federal Register** that either denies the request or gives notice of its intent to initiate a change in the classification of the device in accordance with section 513(e) of the FD&C Act and § 860.130 of the regulations.

XIV. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this 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.

XV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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 not a significant regulatory action defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The Agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires

that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Objective of the Proposed Rule

The objective of this proposed rule is to classify sorbent hemoperfusion devices, which are preamendments class III devices. These devices are used in the treatment of drug overdose, poisoning, hepatic coma, and metabolic disturbances. The classification of these devices will be split into two parts based on the indication of use. Devices indicated for treatment of poisoning and drug overdose will be reclassified into class II with special controls. Devices indicated for treatment in hepatic coma and metabolic disturbances will be maintained in class III with PMA or PDP requirements. Sorbent hemoperfusion systems were originally classified as class III because they are life sustaining and life supporting, and there was lack of data to establish an adequate performance standard for these devices. Since that time, sufficient evidence has been accumulated to develop special controls for the treatment of poisoning and drug overdose, and the risks to health are now well characterized and understood. However, there is insufficient scientific evidence to develop special controls for these devices when used for the treatment of hepatic coma and metabolic disturbances. The call for PMAs or PDPs will allow for adequate evaluation of the device, particularly with respect to the clinical data necessary to support the safety and effectiveness of these devices when used in the treatment of these conditions.

B. Sorbent Hemoperfusion Systems for the Treatment of Poisoning and Drug Overdose

This rule proposes to reclassify sorbent hemoperfusion devices for the treatment of drug overdose and poisoning into class II devices with special controls. Currently, manufacturers of sorbent hemoperfusion devices are subject to premarket notification requirements similar to most class II devices, with manufacturers receiving clearance to market via a 510(k) premarket notification submission with no premarket approval (PMA) requirement. FDA has concluded that special controls are sufficient for ensuring the safety and effectiveness of these devices and that these devices may be reclassified to class II (special controls).

FDA's Premarket Notification 510(k) database identifies five manufacturers of six sorbent hemoperfusion devices. All six of these devices have been cleared for use in the treatment of drug overdose and poisoning. According to the 2005–2009 annual reports of the American Association of Poison Control Centers' National Poison Data Systems, hemoperfusion was used in an average of 27 cases per year, which suggests limited use of this device for these indications.

The proposed rule would require that manufacturers who wish to market new sorbent hemoperfusion devices or implement changes to existing marketed devices indicated for the treatment of poisoning and drug overdose submit 510(k)s that comply with the proposed special controls. As current practice, the Agency already recommends that manufacturers adopt the risk mitigations that are being proposed as special controls, so this rule would essentially formalize current practice as a regulation for these devices. Hence, this reclassification will not result in any significant changes in how 510(k)s for the affected devices are prepared or in how they are reviewed, and compliance with the special controls proposed for this device will not yield significant new costs for affected manufacturers. Because the formal reclassification of the affected devices from class III to class II with special controls is consistent with current FDA and industry practice, the Agency concludes that the proposed rule would impose no additional regulatory burdens on the manufacturing and marketing of sorbent hemoperfusion devices for the treatment of drug overdose and poisoning.

C. Sorbent Hemoperfusion Systems for the Indications of Hepatic Coma and Metabolic Disturbances

1. Benefits

The proposed requirement for PMAs or PDPs for sorbent hemoperfusion systems for treatment of hepatic coma and metabolic disturbances would generate social benefits equal to the value of information generated by the safety and effectiveness tests that producers of the device would be required to conduct under the proposed call for PMAs or PDPs. Provided first to FDA, this information would assist physicians, patients, and insurance providers to make more informed decisions regarding the safe and proper use of these devices, which would also be expected to improve some patient outcomes. There are currently no actively marketed products that are cleared for the indication of hepatic coma and metabolic disturbances. However, FDA projects that two firms are likely to enter the market in the near future.

Hepatic coma is characterized as the final state of hepatic encephalopathy, a complication of liver failure in which the brain function progressively deteriorates. Hepatic encephalopathy is a condition in which toxic substances that are normally cleared from the body by the liver accumulate in the blood, eventually traveling to the brain. Hepatic coma marks the final stage of encephalopathy, at which the disturbance of the brain function leads to loss of consciousness. Sorbent hemoperfusion systems can be used as a treatment device to compensate for liver failure by removing toxins from the blood.

Data from the Healthcare Cost and Utilization Project, a nationally representative sample of hospital discharges, suggest that hepatic coma related hospitalizations are associated with prolonged and costly hospital stays. In 2009, there were approximately 43,500 patients hospitalized in the United States for a primary diagnosis of hepatic coma. The number of discharges rises to over 115,000 when accounting for all-listed diagnoses, which include all diagnoses that coexist at the time of admission or that develop during hospitalization. For patients admitted with a primary diagnosis of hepatic coma, the mean length of stay was 5.8 days, with a mean cost of $10,000 per stay. In-hospital mortality was nearly 8 percent in 2009, while the survival rate after 3 years among patients with hepatic encephalopathy is estimated to be 25 percent (Ref. 1).

There is limited scientific evidence regarding the effectiveness of sorbent hemoperfusion systems for the indication of hepatic coma, which could partially be due to the fragile nature of the patient population (i.e., individuals who are acutely ill due to liver disease, and thus face poor clinical prognosis and high mortality). Because the risks and benefits of these devices for this indication are unknown and therefore cannot be adequately characterized, it is impossible to estimate the direct effect of the devices on patient outcomes. However, if they are approved, the

devices have the potential to greatly improve patient outcomes relative to the current baseline, since there are no alternative devices currently on the market. The PMA requirement will provide clinical testing to establish the safety and efficacy of the devices, to characterize their performance, and to determine the patient populations who will benefit most from the use of these devices. Clinical trials may also identify design issues that would have gone unnoticed in a premarket notification process, thereby reducing the potential of device failures. Furthermore, PMA requirements allow for continuing postmarketing evaluation and periodic reporting to FDA on the safety, effectiveness, and reliability of the device for its intended use.

2. Costs

The proposed rule would require producers of sorbent hemoperfusion for treatment of hepatic coma and metabolic disturbances to obtain a PMA or PDP prior to marketing new products. Currently, producers of sorbent hemoperfusion systems receive clearance to market these devices through the less costly 510(k) premarket notification process. The incremental cost of this rule for those who are developing devices to treat hepatic coma and metabolic disturbance would be the difference between the cost of preparing and submitting a premarket approval application and the cost of preparing and submitting a 510(k) application. The cost of preparing an average 510(k) application has been estimated to be $21 per page, or $37 after adjusting for inflation (Ref. 2). According to FDA industry experts, the number of pages in 510(k) submissions can range from an average of 400 for simple devices to 4,000 pages for more complicated systems. Assuming that the devices for this indication of treatment are complex in nature due to the intricate health conditions of the intended patient population, we use 4,000 pages as our primary estimate. At a cost per page of $37, this yields an average cost of preparing and submitting a 510(k) of $148,000. FDA has estimated an upper bound on the cost of preparing and submitting a PMA at approximately $1,000,000 (see, for example, 73 FR 7498 at 7502, February 8, 2008), which rises to $1,019,000 after inflation. This yields a difference of $871,000 between the costs of PMA and 510(k) preparation. Manufacturers must also pay FDA user fees. For fiscal year 2012, the user fee for a 510(k) submission is $4,049 for large firms and $2,024 for small firms (76 FR 45826 at 45828, August 1, 2011). The user fee for a premarket application (PMA or PDP) is currently set at $220,050 for large firms and $55,013 for small firms (76 FR 45828). This yields a cost difference of PMA and 510(k) submission costs of $216,001 for large companies and $52,989 for small businesses. The total incremental upfront rule-induced cost to industry of preparing and submitting a PMA or PDP is $1,083,950 for large firms and $908,901 for small firms. Manufacturers also incur postmarketing annual fees for periodic reporting to FDA, with the standard fee for annual reports currently set at $7,702 for large firms and $1,925 for small firms.

In addition to the cost to industry of preparing and submitting PMAs or PDPs, the proposed rule would impose review costs on FDA. It has been estimated that, for devices reviewed by FDA's Center for Devices and Radiological Health in 2003 and 2004, review costs were $563,000 per PMA and $13,400 per 510(k) (Ref. 3). Updated for inflation to 2010 dollars, these review costs become $653,000 per PMA and $15,500 per 510(k). This yields an incremental cost to FDA of $637,500. A portion of this total will be paid by industry in the form of user fees, with the remainder borne by general revenues.

The social costs per PMA would be the sum of the difference between a PMA and a 510(k) and the additional FDA costs of reviewing the PMA, or $1,508,500 (= $871,000 + $637,500). The annual cost of the proposed rule would be the number of submissions multiplied by the cost per submission. Because we project that few entities will introduce this device, the number of submissions in most years will be zero. FDA requests comments on the methods and results of our estimation.

D. Impact on Small Entities

The Regulatory Flexibility Act requires Agencies to prepare an initial regulatory analysis if a proposed rule would have a significant effect on a substantial number of small businesses, nonprofit organizations, local jurisdictions, or other entities. The proposed rule will yield no new costs for the five producers of sorbent hemoperfusion devices for the treatment of drug overdose and poisoning, as the rule is essentially a formalization of current industry practice. There are currently no companies actively participating in the market for the indications of hepatic coma and metabolic disturbance, which will require PMAs or PDPs as a result of the proposed rule. FDA projects that very few entities will enter this market in the near future. If a small entity were to enter the market, the reduced user fees would provide some relief. FDA requests comments on the overall effect of the proposed classification on the potential entry of small entities.

Because this proposed rule would impose no additional regulatory burdens for manufacturers of sorbent hemoperfusion devices currently in the market and there is limited participation in the market for devices that will require PMAs or PDPs, FDA concludes that this proposed rule would not have a significant economic impact on a substantial number of small entities.

XVI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XVII. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR part 812 have been approved under OMB control number 0910–0078; the collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910–0120; the collections of information in 21 CFR part 814, subpart B, have been approved under OMB control number 0910–0231; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910–0485.

XVIII. Proposed Effective Date

FDA is proposing that any final rule based on this proposal become effective on the date of its publication in the **Federal Register** or at a later date if stated in the final rule.

XIX. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written

comments regarding this document. It is only necessary to submit one set of comments. Identify comments with the docket number found in the 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.

XX. References

The following references have been placed on display in 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. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. Schiano, T.D., ''Clinical Management of Hepatic Encephalopathy,'' vol. 30, pp. 10S–15S, *Pharmacotherapy,* 2010.
2. Blozan, C.F. and S.A. Tucker, ''Premarket Notifications: The First 24,000,'' pp. 59–69, *Medical Device & Diagnostic Industry,* 1986.
3. Geiger, D.R., ''FY 2003 and FY 2004 Unit Costs for the Process of Medical Device Review,'' (*http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109216.pdf*), September 2005.

List of Subjects in 21 CFR Part 876

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 part 876 be amended as follows:

PART 876—GASTROENTEROLOGY-UROLOGY DEVICES

1. The authority citation for 21 CFR part 876 continues to read as follows:

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

2. Section 876.5870 is amended by revising paragraphs (b) and (c) to read as follows:

§ 876.5870 Sorbent hemoperfusion system.

* * * * *

(b) *Classification.* (1) Class II (special controls) when the device is intended for the treatment of poisoning and drug overdose. The special controls for this device are:

(i) The device should be demonstrated to be biocompatible;

(ii) Performance data to demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength), including testing for the possibility of leaks, ruptures, release of particles, and/or disconnections;

(iii) Performance data to demonstrate device sterility and shelf life;

(iv) Bench performance data to demonstrate device functionality in terms of substances, toxins, and drugs removed by the device, and the extent that these are removed when the device is used according to its labeling;

(v) Summary of clinical experience with the device that discusses and analyzes device safety and performance, including a list of adverse events observed during the testing;

(vi) Labeling controls, including appropriate warnings, precautions, cautions, and contraindications statements to alert and inform users of proper device use and potential clinical adverse effects, including blood loss, platelet loss, leukopenia, hemolysis, hypotension, clotting, metabolic disturbances, and loss of vital nutrients and substances; Labeling recommendations must be consistent with the performance data obtained for the device, and must include a list of the drugs the device has been demonstrated to remove, and the extent for removal/depletion; and

(vii) For those devices that incorporate electrical components, appropriate analysis and testing to validate electrical safety and electromagnetic compatibility.

(2) Class III (premarket approval) when the device is intended for the treatment of hepatic coma and metabolic disturbances.

(c) *Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required.* A PMA or notice of completion of a PDP is required to be filed with FDA on or before [date 90 days after date of publication of the final rule in the **Federal Register**], for any sorbent hemoperfusion system indicated for treatment of hepatic coma or metabolic disturbances that was in commercial distribution before May 28, 1976, or that has, on or before [date 90 days after date of publication of the final rule in the **Federal Register**], been found to be substantially equivalent to any sorbent hemoperfusion device indicated for treatment of hepatic coma or metabolic disturbances that was in commercial distribution before May 28, 1976. Any other sorbent hemoperfusion system device indicated for treatment of hepatic coma or metabolic disturbances shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: February 14, 2012.

Nancy K. Stade,

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

[FR Doc. 2012–3810 Filed 2–16–12; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF DEFENSE

Defense Acquisition Regulations System

48 CFR Part 242

RIN 0750–AH52

Defense Federal Acquisition Regulation Supplement; DoD Voucher Processing (DFARS Case 2011–D054)

AGENCY: Defense Acquisition Regulations System, Department of Defense (DoD).

ACTION: Proposed rule; clarification.

SUMMARY: DoD is clarifying the rule published on January 19, 2012, proposing to amend the Defense Federal Acquisition Regulation Supplement (DFARS) to update DoD's voucher processing procedures and better accommodate the use of Wide Area WorkFlow to process vouchers.

DATES: *Comments* on the proposed rule published January 19, 2012, at 77 FR 2682, continue to be accepted until March 19, 2012.

FOR FURTHER INFORMATION CONTACT: Mr. Mark Gomersall, Defense Acquisition Regulations System, OUSD (AT&L) DPAP (DARS), Room 3B855, 3060 Defense Pentagon, Washington, DC 20301–3060. Telephone 703–602–0302; facsimile 703–602–0350.

SUPPLEMENTARY INFORMATION: DoD is clarifying the proposed rule published on January 19, 2012 (77 FR 2682), which proposes to revise requirements for approving interim vouchers. Interim vouchers that are selected using risk-based sampling methodologies will be reviewed and approved by the contract auditors for provisional payment and sent to the disbursing office after the pre-payment review. Interim vouchers not selected for a pre-payment review will be considered acceptable for payment and will be sent directly to the disbursing office. All interim vouchers are subject to an audit of actual costs incurred after payment. The sampling process will be accomplished largely within the Wide Area WorkFlow system.

The rule proposes to revise the requirements for approving interim vouchers by replacing the direct submission process currently referenced