

# Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Parts 876, 882, and 892

[Docket No. FDA-2013-N-0195]

#### Effective Date of Requirement for Premarket Approval for Three Class III Preamendments Devices; Reclassification of Sorbent Hemoperfusion Devices for the Treatment of Poisoning and Drug Overdose

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed order.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a proposed administrative order to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the following three class III preamendments devices: Sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation. FDA is also announcing the opportunity for interested persons to request that the Agency change the classification of any of the aforementioned devices based on new information. In addition, FDA is proposing to reclassify sorbent hemoperfusion devices for the treatment of poisoning and drug overdose, a preamendments class III device, into class II (special controls) based on new information respecting the device. This action implements certain statutory requirements.

**DATES:** Submit written or electronic comments on this proposed order by May 6, 2013. FDA intends that, if a final order based on this proposed order is issued, anyone who wishes to continue to market the sorbent hemoperfusion

devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; or transilluminator for breast evaluation will need to file a PMA or a notice of completion of a PDP within 90 days of the effective date of the final order. See section XIII of this document for the proposed effective date of any final order that may publish based on this proposed order.

**ADDRESSES:** You may submit comments, identified by Docket No. FDA-2013-N-0195 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 way:

- *Mail/Hand delivery/Courier [For paper, disk, 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 Number FDA-2013-N-0195 for this action. 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:** Michael Ryan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1615, Silver Spring, MD 20993, 301-796-6283.

**SUPPLEMENTARY INFORMATION:**

## I. Background-Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), among other amendments, established 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(d) 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 and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a PMA until FDA takes final action under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

Although, under the FD&C Act, the manufacturer of class III preamendments device may respond to the call for PMAs by filing a PMA or a notice of completion of a product development protocol (PDP), in practice, the option of filing a notice of completion of a PDP has not been used. For simplicity, although corresponding requirements for PDPs remain available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing and receiving approval of a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(b) of FDASIA (126 Stat. 1056) amended section 515(b) of the FD&C Act changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order. Prior to the enactment of FDASIA, FDA published four proposed rules under section 515(b) to require PMAs for the sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; shortwave diathermy for all uses other than the generation of deep heat within the body tissues for the treatment of selected medical conditions; and transilluminator for breast evaluation (76 FR 48062, August 8, 2011; 77 FR 9610, February 17, 2012; 77 FR 39953, July 6, 2012; 75 FR 52294, August 25, 2010). FDA is issuing this proposed administrative order to comply with the new procedural requirement created by FDASIA when requiring premarket approval for preamendments class III devices. Shortwave diathermy for all uses other than the generation of deep heat within the body tissues for the treatment of selected medical conditions is not included in this proposed administrative order due to an

approaching panel meeting on the classification of this device scheduled for April 5, 2013 (77 FR 71195, November 29, 2012). Because of the level of interest in the classification of shortwave diathermy for all uses other than the generation of deep heat within the body tissues for the treatment of selected medical conditions and because this technology was last considered by a panel December 13, 1979, FDA is electing to hold the panel meeting required by sections 513(e) and 515(b) of the FD&C Act before issuing a proposed order on this device. FDA believes a new panel meeting will be useful to consider significant new developments in the technology class III shortwave diathermy devices use since that time and the large volume of new information on the use of these devices. In addition, the 1979 Panel's deliberations focused on class II shortwave diathermy devices that achieve their affect through use of therapeutic deep heat instead of those class III shortwave diathermy devices that are the subject of FDA's July 6, 2012, proposed rule.

Comments submitted in response to the proposed rules on sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation will be considered under this proposed administrative order and do not need to be resubmitted. Similarly, FDA continues to review the merits of the requests for reclassification submitted in response to the proposed rules. Any preliminary decisions on those requests are not reflected in this proposed administrative order to require the filing of a PMA for sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation. This action is intended solely to fulfill the procedural requirements for reclassification implemented by FDASIA.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final administrative order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: Publication of a proposed order in the **Federal Register**; a meeting of a device classification panel described in section 513(b) of the FD&C Act; and consideration of comments from all affected stakeholders, including patients, payors,

and providers. FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia and transilluminator for breast evaluation, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (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 and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order 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)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order 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. 360(f)).

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA is considered to be a final order for purposes of section 501(f) of the FD&C Act (21 U.S.C. 351(f))) 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. For the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since the sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation were classified in 1983, 1979, and 1995, respectively, the 30-month period has

expired (48 FR 53028, November 23, 1983; 44 FR 51770, September 4, 1979; and 60 FR 36639, July 18, 1995, respectively). Therefore, if the proposal to require premarket approval for sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; or transilluminator for breast evaluation is finalized, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such device be filed within 90 days of the date of issuance of the final order. If a PMA is not filed for such device within 90 days after the issuance of a final order, the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process 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 order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, 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. Other enforcement actions include, but are not limited to, the following: 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 has been filed and may determine that such a request is appropriate for the class III devices that are the subject of this proposed order, if finalized.

In accordance with section 515(b)(2) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of

depression, anxiety, and insomnia; and transilluminator for breast evaluation that are the subject of this proposal. Requests for reclassification previously submitted in response to the proposed rules (76 FR 48062, August 8, 2011; 75 FR 52294, August 25, 2010; 77 FR 9610, February 17, 2012) will be considered under this proposed administrative order and do not need to be resubmitted.

Along with proposing to require PMAs for sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation, FDA is also publishing this document to propose the reclassification of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose from class III to class II. Section 513(e) of the FD&C Act governs reclassification of classified preamendments devices. This section provides that FDA may, by administrative order, reclassify a device 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 Co. 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 action where the reevaluation is made in light of newly available authority (see *Bell*, 366 F.2d at 181; *Ethicon, Inc. v. FDA*, 762 F. Supp. 382, 388–91 (D.D.C. 1991)), or in light of changes in "medical science" (*Upjohn*, 422 F.2d at 951). Whether data before the Agency are old 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 21 CFR 860.7(c)(2). (See, e.g., *General Medical Co. v. FDA*, 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Association v. FDA*, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

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 secret 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 (21 U.S.C. 360j(h)(4)), 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.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act changing the process for reclassifying a preamendments class III device from rulemaking to an administrative order. Prior to the enactment of FDASIA, FDA published a proposed rule under section 513(e) proposing the reclassification of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose. The same device is the subject of this proposed order so that FDA can comply with the new procedural requirement created by FDASIA when reclassifying a preamendments class III device.

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the **Federal Register**; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to a public docket.

FDAMA added section 510(m) to the FD&C Act. 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. Dates New Requirements Apply

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency for three preamendments class III devices, sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the

treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation, within 90 days after issuance of any final order 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 device during FDA's review of the PMA provided that the PMA is timely filed. FDA intends to review any PMA for the device within 180 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 publication in the **Federal Register** of any final order based on this proposal will include a statement that, as of the date on which a PMA 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 is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA for a class III device is not filed with FDA within 90 days after the date of issuance of any final order requiring premarket approval for the device, the device would be deemed adulterated under section 501(f) of the FD&C Act. 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 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, recommends that IDE applications be submitted to FDA at least 30 days before the end of the 90-day period after the issuance of the final order to avoid interrupting any ongoing investigations.

Because sorbent hemoperfusion devices for the treatment of poisoning and drug overdose can currently be marketed after receiving clearance of an application for premarket notification and FDA is proposing to reclassify these devices as class II requiring clearance of an application for premarket notification, this order, if finalized, will not impose any new requirements on

sorbent hemoperfusion devices for the treatment of poisoning and drug overdose.

### III. Proposed Findings With Respect to Risks and Benefits for Devices Subject to the Proposal To Require PMA

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 these devices have an approved PMA and (2) the benefits to the public from the use of the devices.

These findings are based on the reports and recommendations of the advisory committee (panel) for the classification of these devices along with information submitted in response to the 515(i) Order (74 FR 16214, April 9, 2009), and any additional information that FDA has obtained. Additional information regarding the risks as well as classification associated with these device types can be found in the following proposed and final rules and notices published in the **Federal Register**: Cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia, 43 FR 55716 (November 28, 1974), 44 FR 51770 (September 4, 1979), 54 FR 550 (January 6, 1989), 58 FR 45865 (August 31, 1993), 60 FR 43967 (August 24, 1995), 61 FR 59448 (November 22, 1996), 62 FR 4023 (January 28, 1997), 62 FR 30456 and 62 FR 30600 (June 4, 1997), and 76 FR 48062 (August 8, 2011); classification of transilluminators (Diaphanosopes or Lightscanners) for breast evaluation, 60 FR 3168 (January 13, 1995), 60 FR 36639 (July 18, 1995), and 75 FR 52294, (August 25, 2010); and sorbent hemoperfusion for the treatment of hepatic coma and metabolic disturbances (46 FR 7630, 46 FR 7562, and 48 FR 53023).

The proposed findings concerning the degree of risk of illness or injury for each of these devices is set out in section IV, as well as information concerning known benefits, if any for these devices. FDA notes, however, that there is limited scientific evidence regarding the effectiveness of the sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation devices. Because the benefits of these devices for the indications specified are unknown, it is impossible to estimate the direct effect of the devices on patient outcomes. However, claims for the devices state

the devices have the potential to benefit the public in the following ways:

- *Cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia.* CES devices are marketed as a treatment for insomnia, anxiety, or depression (either symptoms thereof or the underlying disorder).

- *Sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances.* Disorders that affect the liver can result in metabolic disturbances and a decrease in brain function due to the accumulation of toxins in the blood. This reduced brain function may eventually result in hepatic coma and death. Sorbent hemoperfusion systems are marketed as a treatment device to compensate for liver failure by removing toxins from the blood.

- *Transilluminator for breast evaluation.* Transilluminator for breast evaluation is marketed as an aid in breast self examination as an addition to normal breast health routine by visualizing translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.

### IV. Devices Subject to the Proposal To Require PMA

*A. Sorbent Hemoperfusion System for the Treatment of Hepatic Coma and Metabolic Disturbances (21 CFR 876.5870(c))*

#### 1. Identification

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.

#### 2. Summary of Data

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 Gastroenterology-Urology Device 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.

### 3. Risks to Health

• *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.

### B. Cranial Electrotherapy Stimulator (21 CFR 882.5800)

#### 1. Identification

A cranial electrotherapy stimulator is a device that applies electrical current to a patient's head to treat depression, anxiety, or insomnia.

#### 2. Summary of Data

The Neurological Devices Panel that discussed original classification for the cranial electrotherapy stimulator (CES) device in 1977 and 1978 ultimately recommended that the device be classified into class III because satisfactory device effectiveness had not been demonstrated. The panel considered information from the National Research Council, which reviewed 88 published studies on CES and concluded that the device has not been shown to be effective in treating any of the conditions for which it was prescribed. In addition, the panel indicated that it was not possible to establish an adequate performance standard for CES because the characteristics of the electrical current necessary for potential effectiveness were not known. The panel believed that general controls would not provide sufficient control over these characteristics, and that the device presented a potential unreasonable risk of illness or injury to the patient if the practitioner relied on the device, and it was ineffective in treating the patient's illness. Therefore, the panel recommended that premarket approval was necessary to assure the safety and effectiveness of CES devices.

In support of a subsequent proposed rule in 1993 for classification of CES into class III, FDA performed a literature review and identified additional studies that had been performed for CES. After a review of the scientific literature, FDA concluded that the effectiveness of CES had still not been established by adequate scientific evidence. While this rule was finalized in 1995 (60 FR 43969), it was withdrawn in 1997 (62 FR 30456). FDA performed additional literature searches for studies of CES published after the 1993 proposed rule in support of the proposed rule to retain CES devices in class III and a call for PMAs issued on August 8, 2011 (76 FR 48062), as well as in preparation for the panel meeting described in the paragraphs that follow.

FDA received three petitions requesting a change in the classification of CES devices in response to the August 8, 2011, proposed rule (76 FR 48062). FDA received a petition from Electromedical Products International, Inc., dated August 19, 2011 [FDA-2011-

N-0504-0029], requesting the Agency to reclassify from class III into class II the CES for the “treatment of insomnia, depression, or anxiety.” FDA received petitions from Fisher Wallace Laboratories, LLC, dated August 22, 2011 [FDA-2011-N-0504-0031], and Neuro-Fitness LLC, dated August 22, 2011 [FDA-2011-N-0504-0033], both requesting the Agency to reclassify from class III into class II the CES for the “treatment of depression, anxiety, and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication.” The petition from Neuro-Fitness also mentioned “general treatment of anxiety, depression, and insomnia as part of an approved program of medical care when conventional approaches have failed or are deemed inappropriate” and “treatment of the primary symptoms of substance abuse: Anxiety, depression, and insomnia when conventional approaches have failed or are deemed inappropriate.” FDA continues to review the merits of the previous requests for reclassification submitted in response to the proposed rules and any preliminary decisions on those requests are not reflected in this proposed administrative order proposing to require the filing of a PMA for the cranial electrotherapy stimulator device for the treatment of depression, anxiety, and insomnia.

Consistent with then-section 515(b)(2)(B) of the FD&C Act as it stood at the time and 21 CFR 860.125, FDA referred the petitions to the Panel for its recommendation on the requested change in classification in February 2012. FDA provided the panel members with the three reclassification petitions and FDA’s executive summary (Ref. 1). Based on its review of the data and information as well as information presented during its February 10, 2012, open meeting (Ref. 2), the Neurological Devices Panel recommended that the CES device for treatment of insomnia, depression, and anxiety should remain in class III requiring PMAs. The Panel consensus was that there was not adequate scientific evidence to provide a reasonable assurance of effectiveness for the CES device for any of the indications proposed by the petitioners. Although the panel expressed some reservations regarding several of the risks that FDA had identified as being associated with CES, the Panel consensus was that given the lack of adequate effectiveness data, the

probable benefits of the CES device did not outweigh the probable risks. The Panel also suggested that the list of risks in the proposed rule was not accurate. While there was consensus for including the risks of skin irritation, headaches, and dizziness, the panel did not agree that seizures and blurred vision were risks associated with CES as it is characterized today by the devices on the market and the comparable devices studied in clinical trials. The Panel also suggested that worsening of the condition being treated, though a risk, could be adequately addressed through patient supervision by a medical professional.

While the panel did not recommend a classification for the focused indication in the substance abuse population for which two petitioners requested class II, the panel concluded that the substance abuse population did adequately define a target population and that there were no significant additional risks associated with use of the device in the substance abuse population as compared to the population of patients who are not substance abusers. The panel also recommended there was not adequate scientific evidence to provide a reasonable assurance of effectiveness for the CES device for treatment of insomnia, depression, or anxiety in the substance abuse population.

### 3. Risks to Health

- *Worsening of the condition being treated*—If the device is not effective and the patient is not treated in a conventional manner, the patient’s psychological condition may worsen.
- *Skin irritation*—The electrodes or the conductive cream used with the electrodes may cause skin irritation.
- *Headaches*—Reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation.
- *Potential adverse effects from electrical stimulation of the brain*—The physiological effects associated with electrical stimulation of the brain by these devices have not been studied systematically; therefore, adverse effects which may be caused by these electrical stimuli remain unknown.

#### C. Transilluminator for Breast Evaluation (21 CFR 892.1990)

##### 1. Identification

A transilluminator, also known as a diaphanoscope or lightscanner, is an electrically powered device that uses low intensity emissions of visible light and near-infrared radiation (approximately 700–1050 nanometers

(nm)), transmitted through the breast, to visualize translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.

##### 2. Summary of Data

On January 11, 1991, the Obstetrics and Gynecology Devices Panel recommended that transilluminator devices for breast evaluation be classified into class III and subject to premarket approval to provide reasonable assurance of the safety and effectiveness of the device. The panel concluded that there were no published studies or clinical data demonstrating the safety and effectiveness of the device. The panel indicated that the device presents a potential unreasonable risk of illness or injury to the patient if the clinician relies on the device and that although the device’s illumination level, wavelength, and image quality can be controlled through tests and specifications, insufficient evidence exists to determine that special controls can be established to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

In addition, the Radiologic Devices Panel considered the classification of the device on April 12, 2012 (Ref. 3), and expressed concerns regarding the effectiveness of the device which may result in delayed diagnosis and determined that general controls and special controls are not sufficient to provide a reasonable assurance of safety and effectiveness of the device for the diagnosis of cancer, other conditions, diseases, or abnormalities. Accordingly, the panel concluded that the device should remain in class III. FDA agreed and continues to agree with the recommendations of both panels and is aware of no information submitted in response to the 515(i) Order (74 FR 16214, April 9, 2009) or otherwise available to FDA that would support a different classification. The Agency notes that the device has fallen into disuse and that the published data are not adequate to demonstrate the safety and effectiveness of the device.

##### 3. Risks to Health

a. *Missed or delayed diagnosis*—As a result of the questionable device performance of breast transilluminators, missed or delayed diagnosis are the most catastrophic risks to health for a woman. These devices depend on the users’ visual interpretation of their own breast illumination. One scenario may result when a woman incorrectly interprets her transillumination as a tumor and suffers the ensuing anxiety from her belief that she has a cancer. Another scenario may result when a

woman incorrectly dismisses the findings of her transillumination and then suffers from a missed diagnosis or delayed diagnosis and delayed treatment. Ultimately, missed or delayed diagnoses could result in the need for more aggressive treatment and a potentially higher risk of death.

b. *Electrical shock*—If a breast transilluminator is not designed properly, the user may receive an electrical shock.

c. *Optical radiation*—Prolonged gazing directly into the light of a breast illuminator while engaged in “bright light mode” may result in retinal damage.

#### V. PMA Requirements

A PMA for sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, or insomnia; and transilluminator for breast evaluation 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)(1) (21 CFR 860.7(c)(1))). 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.” (see § 860.7(c)(2)).

#### VI. Opportunity To Request a Change in Classification

Before requiring the filing of a PMA for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act 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 sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation devices is to be in the form of a reclassification petition containing the information required by 21 CFR 860.123, including new information relevant to the classification of the device.

Requests for reclassification submitted in response to the proposed rules will be considered under this proposed administrative order and do not need to be resubmitted. FDA continues to review the merits of the previous requests for reclassification submitted in response to the proposed rules and any preliminary decisions on those requests are not reflected in this proposed administrative order proposing to require the filing of a PMA for sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances; cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia; and transilluminator for breast evaluation.

#### VII. 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 is also proposing to create a separate classification for these devices to differentiate them from sorbent hemoperfusion systems for the treatment of hepatic coma and metabolic disturbances. FDA believes sorbent hemoperfusion devices for the treatment of poisoning and drug overdose can be useful in the treatment of emergent poisoning and drug overdose events by reducing the level of related toxic substances in the bloodstream, thereby reducing or preventing damage to the liver and resultant negative patient outcomes.

FDA has considered sorbent hemoperfusion systems intended for the treatment of poisoning and drug

overdose in accordance with the reserved criteria and determined that these devices require premarket notification. 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.

#### VIII. 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, are necessary to provide reasonable assurance of the safety and effectiveness of the device. In addition, there is now sufficient information to establish special controls to provide such assurance.

#### IX. Summary of Data Upon Which the Reclassification is Based

FDA believes that the identified special controls, in addition to general controls, are necessary to provide reasonable assurance of safety and effectiveness. Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and 21 CFR 860.130, based on new information with respect to the device, 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. Sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose are prescription devices restricted to patient use only upon the authorization of a practitioner licensed by law to administer or use the device. (Proposed § 876.5870(a); see section 520(e) of the FD&C Act and 21 CFR 801.109 (Prescription devices)). Prescription-use restrictions are a type of general controls authorized under section 520(e) and defined as a general control in section 513(a)(1)(A)(i) of the FD&C Act.

Sorbent hemoperfusion is used in a small number of poisoning and drug overdose cases each year. Due to the emergent nature of poisoning and drug overdose events, it is expected that the published clinical literature is limited and that randomized, controlled, clinical trials are not practical to conduct. Since the time of the original Gastroenterology-Urology Device Classification Panel recommendation in 1981, sufficient new 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. There is valid scientific evidence which demonstrate that these devices are of clinical value in treating poisoning and drug overdose patients (Refs. 4 to 11). In this patient population, which is often relatively healthy prior to the poisoning or overdose event, quick removal of the poison or drug can greatly impact clinical outcomes, whereas in the hepatic coma and encephalopathy population, which typically exhibit severe underlying disease, comorbidities, and high mortality there is no substantive evidence on what substances need to be removed or decreased to bring on patient improvements or change clinical outcomes.

Unlike sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances, appropriate bench testing methodologies have also been developed to provide assurance that the device can remove a particular poison or drug from the bloodstream. FDA has developed sufficient confidence in these bench tests via review of 510(k) submissions for these devices. In addition, a review of the available literature, FDA's MAUDE adverse event reporting database, and the manufacturer's submission to the 515(i) docket (74 FR 16214, April 9, 2009) did not present evidence of significant reports of adverse events associated with the use of the sorbent hemoperfusion despite the longstanding use of these devices.

Given the low occurrence of adverse events, the valid scientific evidence to support sorbent hemoperfusion for this use, and FDA's review experience with these devices, FDA believes that the identified special controls, including performance testing to ensure that the device is effective in removing particular poisons or drugs and is adequately designed and includes adequate safeguards, and labeling to inform users of inappropriate use conditions, in addition to general controls, provide reasonable assurance of effectiveness for this device for the treatment of poisoning and drug overdose.

#### X. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) and 25.34(b) 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.

#### XI. Paperwork Reduction Act of 1995

This proposed order refers to collections of information that 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 814 have been approved under OMB control number 0910–0231. The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910–0120. The effect of this order, if finalized, is to shift certain devices from the 510(k) premarket notification process to the PMA process. To account for this change, FDA intends to transfer some of the burden from OMB control number 0910–0120, which is the control number for the 510(k) premarket notification process, to OMB control number 0910–0231, which is the control number for the PMA process. FDA estimates that it will receive 16 new PMAs as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 4,842 hour burden increase. FDA also estimates that there will be 14 fewer 510(k) submissions as a result of this order, if finalized, because two manufacturers have not introduced their device to market yet. Based on FDA's most recent estimates, this will result in a 726 hour burden decrease. Therefore, on net, FDA expects a burden hour increase of 4,116 due to this proposed regulatory change.

The collections of information in part 812 have been approved under OMB control number 0910–0078.

#### XII. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices and section 515(b) of the FD&C Act provided for FDA to issue regulations to require approval of an application for premarket approval for preamendments devices or devices found to be substantially equivalent to preamendments devices. Because sections 513(e) and 515(b) as amended require FDA to issue final orders rather than regulations, FDA will continue to codify reclassifications and requirements for approval of an application for premarket approval, resulting from changes issued in final orders, in the Code of Federal Regulations. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this proposed order, we are proposing to revoke the requirements in 21 CFR 876.5870

related to the classification of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose as class III devices and to codify the reclassification of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose into class II.

#### XIII. Proposed Effective Date

FDA is proposing that any final order based on this proposed order become effective 90 days after date of publication of the final order in the **Federal Register**.

#### XIV. Comments

Comments submitted to the previous dockets for the relevant devices (cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia FDA–2011–N–0504; transilluminator for breast evaluation FDA–2010–N–0412; sorbent hemoperfusion devices to treat hepatic coma and metabolic disturbances; and sorbent hemoperfusion devices for the treatment FDA–2012–M–0076) have been officially noted and do not need to be resubmitted. FDA will consider previous docket comments in issuing any final orders for these devices. Interested persons may submit either written comments regarding this document to the Division of Dockets Management (see **ADDRESSES**) or electronic comments to <http://www.regulations.gov>. 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, and will be posted to the docket at <http://www.regulations.gov>.

#### XV. 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, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. FDA Executive Summary prepared for the February 10, 2012, meeting of the Neurologic Devices Panel—Petitions to Request Change in Classification for Cranial Electrotherapy Stimulators.
2. Transcript, Center for Devices and Radiological Health Medical Devices Advisory Committee, Neurological

- Devices Panel, February 10, 2012, 8 a.m., Hilton Washington DC North, 620 Perry Pkwy., Gaithersburg, MD. Available at <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm279941.htm>.
3. Transcript, Center for Devices and Radiological Health Medical Devices Advisory Committee, Radiological Devices Panel, April 12, 2012, 8 a.m., Hilton Washington DC North, 620 Perry Pkwy., Gaithersburg, MD. Available at <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm293275.htm>.
  4. Evenepoel, P., et al., "Detoxifying Capacity and Kinetics of the Molecular Adsorbent Recycling System. Contribution of the Different Inbuilt Filters." *Blood Purification*, 21(3): p. 244–52, 2003.
  5. Ash, S. R., et al., "Treatment of Acetaminophen-Induced Hepatitis and Fulminant Hepatic Failure With Extracorporeal Sorbent-Based Devices," *Advances in Renal Replacement Therapy*, 9(1): p. 42–53, 2002.
  6. Akdogan, M., et al., "Experience With Liver Dialysis in Acetaminophen Induced Fulminant Hepatic Failure: A Preliminary Report," *Turkish Journal of Gastroenterology*, 14(3): p. 164–7, 2003.
  7. Ash, S. R., et al., "Treatment of Severe Tricyclic Antidepressant Overdose With Extracorporeal Sorbent Detoxification." *Advances in Renal Replacement Therapy*, 9(1): p. 31–41, 2002.
  8. De Schoenmakere, G., et al., "Phenytoin Intoxication in Critically Ill Patients," *American Journal of Kidney Diseases*, 45(1): p. 189–92, 2005.
  9. Covic, A., et al., "Successful Use of Molecular Adsorbent Regenerating System (MARS) Dialysis for the Treatment of Fulminant Hepatic Failure in Children Accidentally Poisoned by Toxic Mushroom Ingestion," *Liver International*, 23 Suppl 3: p. 21–7, 2003.
  10. Shi, Y., et al., "MARS: Optimistic Therapy Method in Fulminant Hepatic Failure Secondary to Cytotoxic Mushroom Poisoning—A Case Report," *Liver*, 22 Suppl 2: p. 78–80, 2002.
  11. Wu, B. F. and M. M. Wang, Molecular Adsorbent Recirculating System In Dealing With Maternal *Amanita* Poisoning During the Second Pregnancy Trimester: A Case Report, *Hepatobiliary and Pancreatic Diseases International*, 3(1): p. 152–4, 2004.

#### List of Subjects

##### 21 CFR Part 876

Medical devices.

##### 21 CFR Part 882

Medical devices, Neurological devices.

##### 21 CFR Part 892

Medical devices, Radiation protection, X-rays.

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 876, 882, and 892 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 revised to read as follows:

##### § 876.5870 Sorbent hemoperfusion system.

(a) *Identification.* A sorbent hemoperfusion system is a prescription device that consists of an extracorporeal blood system similar to that identified in the hemodialysis system and accessories (§ 876.5820) 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. The device is used in the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances.

(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 must 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, and to validate the device's safeguards;

(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 and/or poisons 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 by [DATE 90 DAYS AFTER DATE OF PUBLICATION OF THE FINAL ORDER 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, by [DATE 90 DAYS AFTER DATE OF PUBLICATION OF THE FINAL ORDER 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.

#### PART 882—NEUROLOGICAL DEVICES

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

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

■ 4. Section 882.5800 is amended by revising paragraph (c) to read as follows:

##### § 882.5800 Cranial electrotherapy stimulator.

\* \* \* \* \*

(c) *Date PMA or notice of completion of PDP is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration by [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER],

for any cranial electrotherapy stimulator device that was in commercial distribution before May 28, 1976, or that has, by [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE **FEDERAL REGISTER**], been found to be substantially equivalent to any cranial electrotherapy stimulator device that was in commercial distribution before May 28, 1976. Any other cranial electrotherapy stimulator device shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

## PART 892—RADIOLOGY DEVICES

■ 5. The authority citation for 21 CFR part 892 continues to read as follows:

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

■ 6. Section 892.1990 is amended by revising paragraph (c) to read as follows:

### § 892.1990 Transilluminator for breast evaluation.

\* \* \* \* \*

(c) *Date PMA or notice of completion of PDP is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration by [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE **FEDERAL REGISTER**], for any transilluminator for breast evaluation that was in commercial distribution before May 28, 1976, or that has, by [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE **FEDERAL REGISTER**], been found to be substantially equivalent to any transilluminator for breast evaluation that was in commercial distribution before May 28, 1976. Any other transilluminator for breast evaluation shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: March 29, 2013.

**Peter Lurie,**

*Acting Associate Commissioner for Policy and Planning.*

[FR Doc. 2013-07730 Filed 4-3-13; 8:45 am]

**BILLING CODE 4160-01-P**

## DEPARTMENT OF HOMELAND SECURITY

### Coast Guard

#### 33 CFR Parts 100 and 165

[Docket No. USCG-2012-1036]

RIN 1625-AA00; 1625-AA08

#### Safety Zones & Special Local Regulations; Recurring Marine Events in Captain of the Port Long Island Sound Zone

**AGENCY:** Coast Guard, DHS.

**ACTION:** Notice of Proposed Rulemaking.

**SUMMARY:** The Coast Guard proposes to add, delete, and modify safety zones and special local regulations and add language to clarify time frames and notification requirements for annual marine events in the Sector Long Island Sound Captain of the Port (COTP) Zone. When these regulated areas are activated and subject to enforcement, this rule would restrict vessels from portions of water areas during these recurring events. The safety zones and special local regulations will facilitate public notification of events and provide protective measures for the maritime public and event participants from the hazards associated with these recurring events.

**DATES:** Comments and related material must be received by the Coast Guard on or before May 6, 2013.

Requests for public meetings must be received by the Coast Guard on or before April 25, 2013.

**ADDRESSES:** You may submit comments identified by docket number using any one of the following methods:

(1) *Federal eRulemaking Portal:*

<http://www.regulations.gov>.

(2) *Fax:* 202-493-2251.

(3) *Mail or Delivery:* Docket Management Facility (M-30), U.S. Department of Transportation, West Building Ground Floor, Room W12-140, 1200 New Jersey Avenue SE., Washington, DC 20590-0001. Deliveries accepted between 9 a.m. and 5 p.m., Monday through Friday, except federal holidays. The telephone number is 202-366-9329.

See the “Public Participation and Request for Comments” portion of the **SUPPLEMENTARY INFORMATION** section below for further instructions on submitting comments. To avoid duplication, please use only one of these three methods.

**FOR FURTHER INFORMATION CONTACT:** If you have questions on this rule, call or email Petty Officer Joseph Graun, Waterways Management Division at

Coast Guard Sector Long Island Sound, telephone 203-468-4544, email [joseph.l.graun@uscg.mil](mailto:joseph.l.graun@uscg.mil). If you have questions on viewing or submitting material to the docket, call Barbara Hairston, Program Manager, Docket Operations, telephone (202) 366-9826.

#### SUPPLEMENTARY INFORMATION:

##### Table of Acronyms

COTP Captain of the Port

DHS Department of Homeland Security

FR Federal Register

NPRM Notice of Proposed Rulemaking

#### A. Public Participation and Request for Comments

We encourage you to participate in this rulemaking by submitting comments and related materials. All comments received will be posted without change to <http://www.regulations.gov> and will include any personal information you have provided.

##### 1. Submitting comments

If you submit a comment, please include the docket number for this rulemaking, indicate the specific section of this document to which each comment applies, and provide a reason for each suggestion or recommendation. You may submit your comments and material online at <http://www.regulations.gov>, or by fax, mail, or hand delivery, but please use only one of these means. If you submit a comment online, it will be considered received by the Coast Guard when you successfully transmit the comment. If you fax, hand deliver, or mail your comment, it will be considered as having been received by the Coast Guard when it is received at the Docket Management Facility. We recommend that you include your name and a mailing address, an email address, or a telephone number in the body of your document so that we can contact you if we have questions regarding your submission.

To submit your comment online, go to <http://www.regulations.gov>, type the docket number [USCG-2012-1036] in the “SEARCH” box and click “SEARCH.” Click on “Submit a Comment” on the line associated with this rulemaking.

If you submit your comments by mail or hand delivery, submit them in an unbound format, no larger than 8½ by 11 inches, suitable for copying and electronic filing. If you submit comments by mail and would like to know that they reached the Facility, please enclose a stamped, self-addressed postcard or envelope. We will consider all comments and material received