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May 6, 2013

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Jeffrey E. Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
Food and Drug Administration
Department of Health and Human Services
WO 66, Room 5442
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Effective date of requirement for premarket approval for three class III pre-amendment devices; reclassification of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose. Docket Number: FDA–2013–N–0195.

Dear Dr. Hamburg and Dr. Shuren:

Public Citizen, a consumer advocacy group representing more than 300,000 members and supporters nationwide, writes in response to the FDA proposed order issued Thursday, April 4, 2013 (Docket Number: FDA–2013–N–0195). We support the portion of the proposed order requiring the filing of premarket approval or a notice of completion of a product development protocol for the following III "preamendment" devices:

- Sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbance
- Cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia
- Transilluminator for breast evaluation

Public Citizen opposes the proposed order reclassifying sorbent hemoperfusion devices for the treatment of poisoning and drug overdose into Class II, because insufficient information exists to determine that general or special controls could provide reasonable assurance of safety and effectiveness for this device. Specifically, we are concerned that the device carry severe, life-threatening risks, and insufficient clinical evidence exists to determine whether sorbent hemoperfusion is effective at improving clinical outcomes for poisoning and drug overdose. We are also concerned that the device will be used off-label to treat hepatic coma and metabolic disturbance. Given the serious risks of the

device and uncertain efficacy, we urge the FDA to retain sorbent hemoperfusion devices in Class III and require PMAs for all indications.

I. Description of the Devices, Regulatory Background, and Proposed Actions

A. Description of the Devices

A sorbent hemoperfusion system is a prescription device that consists of an extracorporeal blood system similar to that used in hemodialysis, connected to a container filled with adsorbent material that removes a wide range of substances, both toxic and normal, from blood flowing through it.[1]

A cranial electrotherapy stimulator is a device that applies electrical current to a patient's head in order to treat depression, anxiety, or insomnia.[2]

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, transmitted through the breast, to visualize translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.[3]

B. Regulatory Background

The sorbent hemoperfusion system, cranial electrotherapy stimulator, and transilluminator for breast evaluation are all currently classified as Class III devices on the market prior to 1976 for which the FDA has never issued a final rule requiring pre-market approvals (PMAs).[4] As "Pre-amendment" Class III device types, these devices are subject to a unique regulatory history that has permitted them to be marketed without evidence of safety and efficacy from well-controlled clinical trials.

The 1976 Amendments established the current framework for device regulation by the FDA. This law grouped devices by type and sorted each device type into one of three regulatory classes, referred to as Classes I, II, and III. Under this regulatory framework, device types are subject to an increasingly rigorous set of regulatory requirements depending on their class.

Devices in Class I are subject to the least rigorous regulatory requirements. These devices include such low-risk devices as tongue depressors, elastic bandages, or reading glasses.[5, 6,7] Class I devices need not

[1] 78 F.R. 20268, 20276, Thursday April 4, 2013.
[2] *Ibid.*
[3] *Ibid.*
[4] *Ibid.*
[5] 21 C.F.R. § 880.6230.
[6] 21 C.F.R. § 880.5075.
[7] 21 C.F.R. § 886.5844.

be cleared or approved by the FDA prior to being sold in the U.S., although they are still subject to other regulatory requirements called general controls.[8]

Devices in Class II are subject to slightly more rigorous regulatory requirements. These devices include more complex or higher-risk items such as electrocardiographs, powered bone drills, and mercury thermometers.[9,10,11] New Class II devices generally must be cleared by the FDA prior to being sold in the U.S. To obtain premarket clearance, the manufacturer of a Class II device must submit a notification to the FDA under 510(k) of the FDCA and establish that the device is "substantially equivalent" to another Class II device already on the market in the U.S. (known as a "predicate device").[12,13] Such 510(k) clearances generally involve animal or bench testing to prove substantial equivalence, but they do not require that the sponsor test the safety and effectiveness of the device in well-controlled clinical investigations.[14] Thus, a new Class II device can be cleared based on a showing of substantial equivalence to a previously cleared predicate device that itself was not proven safe or effective in clinical trials.

The most stringent regulatory process is reserved for Class III devices, which include implantable, high-risk, or life-sustaining devices, such as silicone breast implants, implantable pacemakers, certain types of fetal monitors used in labor, and replacement heart valves.[15,16,17,18] In order to introduce a new device from a Class III device type into the U.S. market, a device manufacturer generally must submit a premarket approval application (PMA). Ordinarily, such an application will not be approved without evidence from at least one well-controlled clinical trial in humans providing reasonable assurance that the new device is effective.[19]

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[8] 21 U.S.C. § 360(*l*). However, Class I devices that are "of substantial importance in preventing impairment of human health," or that present "potential unreasonable risk of illness or injury" are also subject to 510(k) notice requirements. *Ibid.*

[9] 21 C.F.R. § 870.2340.

[10] 21 C.F.R. § 872.4120.

[11] 21 C.F.R. § 880.2920.

[12] 21 U.S.C. § 360(k).

[13] 21 U.S.C. § 360c(f).

[14] Department of Health and Human Services, Center for Devices and Radiological Health, Medical Devices Advisory Committee, Circulatory Systems Devices Panel. Testimony of Dr. Cara Krulewitch, Branch Chief, Division of Epidemiology, Food and Drug Administration. January 25, 2011, *at* 29-31. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247593.pdf . Accessed April 3, 2013.

[15] 21 C.F.R. § 870.3610.

[16] 21 C.F.R. § 870.3925.

[17] 21 C.F.R. § 884.2620.

[18] 21 C.F.R. § 878.3540.

[19] 21 U.S.C. § 360c (a)(3)(A) (requiring evidence from well-controlled investigations, including 1 or more clinical investigations where appropriate, by qualified experts).

However, under limited circumstances the FDA may accept other valid scientific evidence as proof of effectiveness, if it "can fairly and responsibly be concluded by qualified experts" that the device is effective upon the basis of such evidence.[20] Also, the FDA has authority to grant a special exemption, known as "humanitarian device exemption" for devices that are designed to treat rare diseases or conditions (affecting fewer than 4,000 individuals in the United States), provided certain conditions are met.[21]

The 1976 Amendments did not require that manufacturers of device types in commercial distribution before the 1976 Amendments (the "Pre-amendment Device Types") submit PMAs immediately. Instead, makers of these Pre-amendment Device Types classified into Class III could continue to use the 510(k) premarket notification process until such time as the FDA published final regulations requiring PMAs for that device type.[22]

The process for publishing final regulations requiring premarket approval for the Pre-amendment Device Types has been slow, and as a result, many device types that were initially classified into Class III have languished in a regulatory gray area, undergoing 510(k) premarket clearance rather than the stricter requirements envisioned by Congress for Class III devices. In 1990, Congress passed the Safe Medical Devices Act (SMDA), amending Section 515(i) of the FDCA and requiring the FDA to order all manufacturers of Pre-amendment Device Types to submit safety and effectiveness information to facilitate finalizing rules for these devices or reclassifying them into Class I or II. SMDA also directed the FDA to establish a schedule to finalize PMA requirements for the remaining Pre-amendment Class III devices, and established a hard deadline of December 1, 1995, for completing the process.[23]

In April 1994, the FDA proposed a strategy for prioritizing actions on the remaining 117 Pre-amendment Class III Device Types for which final regulations had not yet been issued.[24] Over the next decade, the FDA reclassified or issued final rules requiring PMAs for many of the remaining Pre-amendment Device Types. Nevertheless, by 2009, there remained 27 types of Class III devices that still

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[20] 21 U.S.C. § 360c (a)(3).

[21] Under 21 U.S.C. § 360j(m), the FDA may grant a humanitarian device exemption upon finding that
(A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States,
(B) the device would not be available to a person with a disease or condition referred to in subparagraph (A) unless the Secretary grants such an exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition, and
(C) the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

[22] 21 U.S.C. § 360e (b).

[23] Pub. L. No. 101-629, § 4(b), 104 Stat. 4511, 4515-17 (*codified as* 21 U.S.C. §§ 360e(i)).

[24] US Government Accountability Office. Medical devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process. GAO-09-190. January 2009. http://www.gao.gov/new.items/d09190.pdf. Accessed March 19, 2013.

had no final regulations requiring PMAs.[25] On April 9, 2009, the FDA published the order required under Section 515(i) ("515(i) order") requiring the manufacturers of 25 of the 27 remaining Class III Pre-amendment Device Types to submit the relevant safety and efficacy information needed in order to either reclassify the devices or issue a final regulation requiring PMAs.[26]

Between 2010 and 2012, the FDA published proposed rules under section 515(b) to require PMAs for the sorbent hemoperfusion, cranial electrotherapy stimulator, and transilluminator for breast evaluation, three of the remaining preamendment devices for which a final rule had not yet been issued.[27] Thereafter, in 2012, before these proposed rules had been finalized, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted. Section 608(b) of the FDASIA changed the process for requiring premarket approval for a preamendment Class III device from a rulemaking to an administrative order. On April 4, 2013, the FDA issued a new proposed administrative order to comply with the new procedural requirements of the FDASIA.[28]

C. Proposed Actions

The Food and Drug Administration has proposed maintaining the following devices in Class III and issuing a final rule require the filing of premarket approval[29]:

- Sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbance
- Cranial electrotherapy stimulator for the treatment of depression, anxiety, and insomnia
- Transilluminator for breast evaluation

In addition, the FDA has proposed reclassifying sorbent hemoperfusion devices for the treatment of poisoning and drug overdose into Class II. The FDA has also proposed special controls for this device in conjunction with the proposed reclassification.[30]

II. Legal Standard for Reclassification

The standard governing classification of a device into Class III is described in Section 513(a) of the Food, Drug and Cosmetics Act, *codified as* 21 U.S.C. § 360c(a). A device is to be classified as Class III and subject to premarket approval if:

(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because

[25] 74 FR 16214, April 9, 2009. http://www.gpo.gov/fdsys/pkg/FR-2009-04-09/html/E9-8022.htm. Accessed April 3, 2013.
[26] 74 FR 16214, April 9, 2009. http://www.gpo.gov/fdsys/pkg/FR-2009-04-09/html/E9-8022.htm. Accessed April 3, 2013.
[27] 78 F.R. 20268, Thursday April 4, 2013.
[28] *Ibid.*
[29] *Ibid.*
[30] 78 F.R. 20268, Thursday April 4, 2013.

> insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
> (ii) (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury.[31]

"General controls" are a set of regulatory standards promulgated under the FDA's general authority to regulate adulterated drugs and devices, impose labeling and advertising requirements, register and inspect manufacturing facilities, impose good manufacturing practice requirements, and take other regulatory actions.[32] "Special controls" are more specific requirements that can include performance standards, post-market surveillance, patient registries, or specific FDA guidelines.[33]

Where a device has already been classified into Class III, it may be reclassified under Section 513(e) of the FDCA, *codified as* 21 U.S.C. § 360c(e), which states that the Secretary or CDRH director and FDA commissioner may reclassify the device:

> to class II if the Secretary [or CDRH Director] determines that special controls would provide reasonable assurance of the safety and effectiveness of the device and that general controls would not provide reasonable assurance of the safety and effectiveness of the device, or … to class I if the Secretary determines that general controls would provide reasonable assurance of the safety and effectiveness of the device. [34]

The party seeking to reclassify the device bears the burden of proving that the device meets the requirements for reclassification.[35]

III. Discussion

Public Citizen supports the FDA's proposed order to maintain the following devices in Class III and require PMAs for these devices.

A. Sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances

We agree with the FDA's conclusion that the safety and effectiveness of sorbent hemoperfusion devices has not been established by adequate scientific evidence for the treatment of hepatic coma, because only a few randomized, controlled trials have been conducted using this device, and these were small, poorly designed, and not adequately powered. We also agree with the FDA that

> bench testing is not adequate in establishing the devices' safety and effectiveness, particularly since characterizing a sorbent hemoperfusion system's performance and adsorption capabilities

[31] 21 U.S.C. § 360c(a).
[32] 21 U.S.C. §§ 360c(a)(1), 351, 352, 360, 360f, 360h, 360i, and 360j.
[33] 21 U.S.C. §§ 360c(a)(1)(B).
[34] 21 U.S.C. § 360c(e).
[35] *Gen. Med. Co. v. U.S. Food & Drug Admin.*, 770 F.2d 214, 219 (D.C. Cir. 1985).

> has not correlated to patient outcomes, such as resolution of the patients' hepatic coma, or improvements in mortality.[36]

Moreover,

> there is no consensus [within the scientific literature] 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.[37]

Sorbent hemoperfusion also carries a large number of severe risks to health, including but not limited to:

- Large losses of blood platelets lost due to adsorbtion by the device
- Transient loss of leukocytes (white blood cells)
- Hemolysis (breaking of red blood cells)
- Leak of fine particles into the lungs and other organs
- Infection
- Toxic and/or pyrogenic reactions (sudden fever with collapse and chills)
- Sudden decrease in blood pressure
- Adverse immune or allergic reaction
- Clotting, with or without blood loss due to clogged circuits
- Removal or depletion of vital nutrients
- Metabolic disturbances

Premarket approvals are necessary to establish the safety and efficacy of this device and prove that its possible benefits outweigh these substantial known risks.

B. Cranial electrotherapy stimulators for the treatment of depression, anxiety, and insomnia

Public Citizen has already submitted comments urging the FDA to maintain cranial electrotherapy stimulators (CES) for the treatment of depression, anxiety, and insomnia in class III and require premarket approval for these devices.[38] In our prior comments, we explained that the primary safety concern with these devices is a worsening of the condition being treated, due to the ineffectiveness of the device. Such ineffective treatment presents serious risks, particularly in patients with severe conditions.[39] Moreover, the FDA has consistently stated that the effectiveness of this device has not been established by adequate scientific evidence.[40] We also noted that the CES device carries several

[36] 78 F.R. 20268, Thursday April 4, 2013.
[37] *Ibid.*
[38] Public Citizen. Letter to Jeffry Shuren, Director, Centers for Devices and Radiological Health, Food and Drug Administration. February 28, 2012. http://www.citizen.org/documents/follow-up-comments-to-fda-on-reclassification-of-ces-devices.pdf. Accessed May 3, 2013.
[39] *Ibid.*
[40] *Ibid.*

additional risks, including risk of seizure, headaches, blurred vision, skin irritation, and other potential unknown adverse effects from electrical stimulation of the brain, which have not been studied systematically.[41]

The FDA Neurological Devices Panel met on February 10, 2012 to consider the CES device for the treatment of insomnia, depression, and anxiety. While the panel did not agree that seizures and blurred vision were associated with use of the device, they agreed that the quality of evidence on effectiveness was generally poor and there was not enough evidence to conclude that the probably benefits of the device outweighed its probable risks.[42]

We agree with these conclusions, and believe that the device should remain in Class III for use in treating insomnia, anxiety, and depression, because these uses are of substantial importance in preventing impairment of human health, and insufficient information exists to determine that general or special controls would provide reasonable assurance of its safety and effectiveness.

C. Transilluminators for breast evaluation.

We agree with the FDA's conclusion that the transilluminator for breast evaluation should remain classified into Class III and that PMAs should be required for this device. The most significant risk of this device is that it will result in a missed or delayed diagnosis of breast cancer if it is used in place of more effective screening procedures. Ultimately, missed or delayed diagnoses could result in the need for more aggressive treatment and a potentially higher risk of death. Inappropriate screening may result in a patient incorrectly believing that she has cancer, which could lead to additional unnecessary screening and procedures, as well as substantial anxiety for the patient.[43]

The FDA Radiological Devices Panel considered this device on April 12, 2012, and determined that the device presents a potential unreasonable risk of illness or injury to a patient if a physician or patient relies on the device and misdiagnoses the presence or absence of cancer.[44] The panel also determined that because there are no published studies or clinical data demonstrating the safety and effectiveness of the device, insufficient evidence exists at this time to determine that special controls can be established to provide reasonable assurance of the safety and effectiveness of the device for its intended use. We agree with these conclusions and support requiring PMAs for this device type.

[41] *Ibid.*
[42] 78 F.R. 20268, Thursday April 4, 2013.
[43] *Ibid.*
[44] *Ibid.*

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

In May 2012, Public Citizen submitted comments urging the FDA to maintain sorbent hemoperfusion devices in class III and require PMAs for these devices.[45] Our position remains unchanged following the most recent FDA notice of proposed order.

In its April 4 notice, the FDA acknowledged that the published clinical literature is limited with regard to sorbent hemoperfusion devices. In particular, data from prospective randomized controlled clinical trials are not available to establish that treatment with the device improves clinical outcomes when compared with an appropriate control.

Nevertheless, the FDA concluded that evidence from animal and bench testing, as well as human case reports, was sufficient to "demonstrate that these devices are of clinical value in treating poisoning and overdose patients."[46] To explain this decision, the FDA stated that in the case of poisoning and drug overdose, the patient population "is often relatively healthy prior to the poisoning or overdose event," and "quick removal of the poison or drug can greatly impact clinical outcomes." The FDA also explained that appropriate bench testing methodologies have been developed to provide assurance that the device can be used to remove a particular poison or drug from the blood stream.[47]

The fact that quick removal of a poison or drug can generally be expected to impact clinical outcomes does not establish that sorbent hemoperfusion is effective in treating poisoning and drug overdose. Several alternative mechanisms are available to remove poisons and drugs from the body, including 1) allowing the human body to clear a drug from the bloodstream through endogenous means (i.e. in absence of any enhanced assistance), and 2) hemodialysis. Hemodialysis is more effective at removing water-soluble low molecular weight compounds, and is considered preferable to hemoperfusion because it will also correct a concurrent acid-base disturbance. It is also generally better-understood and more widely available than hemoperfusion.[48] Hemoperfusion treatment carries substantial risks, and death or long-term morbidity may result due to complications from treatment. In order to assess whether these substantial risks are outweighed by potential benefits, the device must be compared with alternative approaches in well-controlled clinical investigations.

We also oppose re-classification into Class II on the ground that the proposed special controls will not adequately deter off-label use of these devices for treatment of hepatic coma and metabolic disturbances, conditions that are far more prevalent in the general population than accidental poisonings or drug overdoses. We believe that there will be substantial financial incentives for potentially harmful off-label use of these devices, and the proposed protections will fail to adequately deter such use.

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[45] Coalition Comments SorbentHemoperfusionDevices May 16. http://www.regulations.gov/#!documentDetail;D=FDA-2012-M-0076-0002. Accessed May 6, 2013.
[46] 78 F.R. 20268, Thursday April 4, 2013.
[47] *Ibid.*
[48] Winchester JF, Hemoperfusion. UpToDate. www.uptodate.com Accessed May 6, 2013.

The FDA has noted that randomized, controlled, clinical trials are "not practical to conduct" given the "emergent nature" of poisoning and drug overdose events.[49] This assertion, even if true, is not relevant to the standard for reclassification. If poisonings are so rare and unpredictable that it would be impractical to submit a premarket approval application, manufacturers of the device may seek a humanitarian device exemption, which the FDA will grant after making the appropriate findings.[50]

There may be rare conditions for which controlled clinical testing is unnecessary because efficacy of the device has been established through other means. Controlled trials may also be unethical under such circumstances, because hemoperfusion represents the unquestionable standard of care.[51] Yet the fact that hemoperfusion of established clinical value under limited circumstances does not justify reclassifying *all* poisoning and overdose indications into Class II. Instead, the FDA may waive the requirement for well-controlled clinical testing and grant premarket approval for such limited use on an individualized basis, after making a determination that efficacy for that device has been established by other valid scientific evidence.[52] This approach is preferable, because it requires that the FDA conduct an individualized assessment of the clinical evidence available for each device to determine whether safety and effectiveness have been established under the conditions of use described in the labeling, rather than broadly exempting these devices from pre-market approval as an entire class.

Public Citizen therefore disagrees with the FDA's proposed order reclassifying sorbent hemoperfusion devices into Class II, and urges the FDA to maintain the device in class III and require pre-market approval for these devices.

Thank you in advance for your thoughtful consideration of our comments.

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[49] 78 F.R. 20268, Thursday April 4, 2013.

[50] Under 21 U.S.C. § 360j(m), the FDA may grant a humanitarian device exemption upon finding that
(A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States,
(B) the device would not be available to a person with a disease or condition referred to in subparagraph (A) unless the Secretary grants such an exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition, and
(C) the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

[51] For example, hemoperfusion is recommended as a standard treatment where the poisoning or overdose involves a compound that is more effectively removed by hemoperfusion than by hemodialysis (i.e. for compounds that are lipid soluble or highly protein bound), the half-life of the compound is relatively long, and intoxication is severe or the patient experiences progressive deterioration or the development of complications such as coma, pneumonia or septicemia. Winchester JF, Hemoperfusion. UpToDate. www.uptodate.com Accessed May 6, 2013.

[52] 21 U.S.C. § 360c (a)(3).

Sincerely,

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