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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

Dear Dr. Shuren:

These comments from Public Citizen's Health Research Group are being submitted in follow-up to the deliberations of the Food and Drug Administration's (FDA's) Neurological Devices Panel (NDP) of the Medical Devices Advisory Committee on February 10, 2012, regarding the possible reclassification of cranial electrotherapy stimulator (CES) devices, which are indicated for the treatment of depression, anxiety, and insomnia, from class III to class II.

> (1) We strongly urge the FDA to accept the recommendations of the agency's review staff and the majority of the NDP members and maintain the classification of CES devices as class III, given the risks of harm that these devices present and the lack of sufficient evidence from well-designed clinical trials demonstrating their efficacy for depression, anxiety, or insomnia.
>
> (2) The FDA should promptly finalize its proposed rule requiring premarket approval (PMA) applications for all CES devices. CES device manufacturers should be required to conduct rigorous, well-designed, controlled, double-blind clinical trials to evaluate the safety and effectiveness of these devices for their current indications for use, and submit data from such trials to the FDA for review and evaluation under PMA applications.

I. Background

CES devices are devices that apply electrical current to a patient's head to treat insomnia, depression, or anxiety. They are categorized by the FDA as class III devices.[1] Some of these devices were marketed prior to the passage of the Medical Devices Amendments of 1976. The FDA published a final rule requiring submission of PMAs for CES devices in 1995, but subsequently revoked this rule in June 1997, although the class III designation for these devices was retained.[2]

Because the FDA has failed to complete the regulatory process for requiring CES devices to be approved under the PMA process or for reclassifying them into a lower class, new CES devices may currently be cleared for marketing under the 510(k) premarket notification process if they are determined to be "substantially equivalent" to a legally marketed predicate device, thereby exempting them from the need for a PMA application.

On August 8, 2011, the FDA published a notice of proposed rulemaking (NPRM) that would require PMA applications for CES devices.[3] The agency specifically proposed the following:

> …to require that a PMA or a notice of completion of a [product development protocol (PDP)] be filed with the Agency for the cranial electrotherapy stimulator within 90 days after issuance of any final rule based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, will be permitted to continue marketing such class III devices during FDA's review of the PMA or notice of completion of the PDP. FDA intends to review any PMA for the device within 180 days, and any notice of completion of a PDP for the device within 90 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the [Food, Drug, and Cosmetic] 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."

In response to the FDA's August 2011 NRPM, three manufacturers of CES devices petitioned the FDA to reclassify these devices into class II, arguing that special controls would be sufficient to provide a reasonable assurance that the devices are safe and effective.[4]

II. The risks of CES devices

The most serious risk presented by treatment with CES devices is a worsening of the condition being treated due to the ineffectiveness of the device. The FDA in particular noted the following:[5]

> The primary safety concern is a worsening of the condition being treated, due to the ineffectiveness of the device. As noted in Section 10.3 below, the indications make few distinctions about the condition, and if a patient with a more serious condition were to be treated with an ineffective device, **FDA believes that there may be an unreasonable risk of illness or injury**. [Emphasis added]

The FDA also identified the following as additional risks of these devices:[6]

- Potential risk of seizure; electrical stimulation of the brain may result in seizures, particularly in patients with a history of seizure.

- 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.
- Headaches; reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation.
- Blurred vision; placement of electrodes over the eyes may cause blurred vision.
- Skin irritation; the electrodes or the conductive cream used with the electrodes may cause skin irritation.

III. The potential benefits of CES devices

The FDA conducted an extensive review of the scientific literature for CES devices prior to the February 10, 2012 NDP meeting. The agency's review found little evidence that treatment with CES devices is effective for treating depression, anxiety disorders, or insomnia. In particular, the agency's summary and conclusions of its literature review stated the following:[7]

> Of the 39 papers included in this literature review, some reported a beneficial effect of CES treatment on depression, anxiety and insomnia while others demonstrated no effect. **Among studies that reported a clinical benefit of CES, few can be considered rigorous, high quality clinical studies**. [Emphasis added]
>
> FDA believes that there are basic elements that should be present in any study seeking to evaluate the effectiveness of CES, including, but not limited to: randomized with a sham control group, eligibility criteria based on a specific diagnosis, a clinically relevant measure of effectiveness, adequately powered sample size, predefined success criteria, and consideration for durability of effect. None of the studies identified in the literature review met all of these criteria.
>
> Regardless of the main findings, many of these studies had key limitations in study design that likely obscure the true effectiveness of CES. For example, only 12.8% (5 of 39) of the studies reported using the DSM criteria to diagnose depression, anxiety or insomnia. Without the use of established and clinically accepted diagnostic criteria, it is unclear what psychiatric condition, if any, CES was attempting to treat in the remaining 87.2% of studies.
>
> Furthermore, the body of research lacks cohesion in the device model, dosage and duration studied. While the literature review was not limited to cleared devices, FDA sought to ensure that the output characteristics were generally consistent with the ranges of values we have evaluated in premarket submissions. In the papers that we reviewed, there were 25 different models of CES devices used, excluding 7 that were custom built and some studies did not report the CES device model. Since the electrical output characteristics also vary

> across the different device types …, making assumptions about the applicability of positive findings by one CES device to other CES devices is not possible. Other important study limitations that have been previously mentioned include: small sample size, placebo effect (due to either no masking or unsuccessful masking) and inadequate statistical methods.
>
> In the absence of a reasonable assurance of effectiveness, a key concern stemming from our review of the literature is that use of CES in lieu of more effective, proven therapies may present undue risk to patients whose psychiatric conditions may worsen if untreated.

IV. Overall risk-benefit assessment

Given the evidence from the currently available literature, the only reasonable conclusion regarding the risk-benefit relationship of CES devices is that the risks of treatment with these devices outweigh their benefits.

A. The FDA's Assessment

In an unusually strongly worded summary prepared for the February 10, 2012 NDP meeting, the FDA stated the following regarding CES devices:[8]

> **10.1 Special Controls**
> The petitioners have proposed special controls (see Section 3.2) to be enacted in conjunction with reclassification. FDA is concerned that none of the controls address the underlying issue that has persisted since the original classification meetings [in 1977 and 1978]; namely, that there has been no systematic attempt to determine the set of stimulation characteristics that are necessary for effectiveness. As the literature reviews have shown, there is little consensus about any of the characteristics. Electrode placement is also variable. **Without greater knowledge of the critical stimulation parameters and ranges that may be effective, FDA believes special controls cannot be written for CES.** [Emphasis added]
>
> **10.2 Reasonable Assurance of Safety**
> According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."
>
> As the literature reviews demonstrate, CES is not without risk. Adverse events have been experienced with the devices, and several were reported in the

comments to the docket. While the events reported in the literature have generally not been serious, the lack of consistent reporting makes it difficult to draw conclusions about the safety of CES … **FDA believes that there may be an unreasonable risk of illness or injury**. [Emphasis added]

10.2 Reasonable Assurance of Effectiveness
According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

As stated, the regulation refers to a "significant portion of the target population." FDA is concerned about the ability of the current indications to adequately identify a target population. If down-classified, all existing CES devices that are legally on the market would be affected, and could continue to market the device using "treatment of anxiety, depression, and insomnia" as the indications for use statement. Similarly, under the paradigm a new manufacturer would be allowed to claim substantial equivalence to one of the existing devices, and would also be allowed to use this indications for use statement. In either case, there is no distinction between the following:

- Treatment of symptoms vs. treatment of the underlying disorder
- Pediatric populations vs. adult populations
- Use as monotherapy vs. use as adjunctive therapy
- Use as first-line treatment vs. use in refractory populations

Two of the petitions have proposed a more specific indications for use statement that includes an adult substance abuse population …. FDA believes that this represents a different population. FDA is also concerned about the use of the general terms "anxiety, depression, and insomnia," despite the more specific population.

Regarding the available literature, with the exception of the 1997 revocation of the premarket approval requirement, **FDA has consistently stated that the effectiveness of CES has not been established by adequate scientific evidence.** The reviews that FDA has performed on the data have demonstrated that while there is an abundance of published literature on the use of CES for the treatment of anxiety, depression, and insomnia, **the studies have limitations that preclude favorable interpretations of the effectiveness results, even if those results are mostly positive**. [Emphasis added]

The FDA concluded its summary analysis by stating the following:[9]

> **FDA believes that the available scientific evidence supports a class III determination because the data do not support a reasonable assurance of safety and effectiveness, the proposed special controls would be insufficient to provide such assurance, and there is an unreasonable risk of illness or injury.** [Emphasis added]

B. The Neurological Devices Panel's assessment

The brief summary of the NPD meeting indicates the following:[10]

- [T]he majority of panel members agreed [with the FDA] that the scientific evidence does not support a reasonable assurance of effectiveness for the indications for use.
- [T]he majority of panel members concluded that current evidence does not clearly establish probable benefits to health from use of CES for these indications (treatment of insomnia, depression, and anxiety) and conditions of use that would outweigh the probable risks.
- [T]he panel generally concluded that since the benefits did not outweigh the risks, the device should be class III.
- In light of the available scientific evidence, a majority of the panel recommended class III for insomnia, depression and anxiety.

V. Summary and conclusions

In summary, the only reasonable course of action for the FDA to take regarding CES devices is to accept the recommendations of the agency's review staff and the majority of the NDP members and maintain the classification of CES devices as class III, given the risks of harm that these devices present and the lack of sufficient evidence from well-designed clinical trials demonstrating their efficacy for depression, anxiety, or insomnia.

The FDA should promptly finalize its proposed rule requiring PMA applications for all CES devices. CES device manufacturers should be required to conduct rigorous, well-designed, controlled, double-blind clinical trials to evaluate the safety and effectiveness of these devices for their current indications for use, and submit data from such trials to the FDA for review and evaluation under PMA applications.

Thank you for considering our comments in this very important matter.

Sincerely,

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Sidney M. Wolfe, M.D.
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[1] 21 CFR 882.5800. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=882.5800. Accessed February 20, 2012.
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[3] Food and Drug Administration. Effective date of requirement for premarket approval for cranial electrotherapy stimulator (proposed rule). 76 FR 48062-48070. Available at http://www.gpo.gov/fdsys/pkg/FR-2011-08-08/pdf/2011-19957.pdf. Accessed February 20, 2012.
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[7] Food and Drug Administration. Executive summary prepared for the February 10, 2012 meeting of the Neurological Devices Panel. Web pages 36-37. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM290787.pdf. Accessed February 20, 2012.
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[9] Food and Drug Administration. Executive summary prepared for the February 10, 2012 meeting of the Neurological Devices Panel. Web pages 39. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM290787.pdf. Accessed February 20, 2012.

[10] Food and Drug Administration. Brief Summary of the Neurological Devices Panel Meeting—February 10, 2012. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM291805.pdf. Accessed February 20, 2012.