Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Citizen Petition - Activities Related to the Issuance of the Final Order Regarding Cranial Electrotherapy Stimulator Devices on December 20, 2019 (84 FR 70003)

**CITIZEN PETITION**

Fisher Wallace Laboratories, Inc. ("Fisher Wallace" or "Petitioner"), is a leading manufacturer of cranial electrotherapy stimulator ("CES") devices cleared by the Food and Drug Administration ("FDA") and legally marketed in the United States, for the treatment of depression, anxiety, and/or insomnia.

CES devices are preamendment devices that were legally marketed in the United States prior to May 28, 1976, the enactment date of the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FDCA), and have been successfully regulated under the general controls of the FDCA for 44 years and commercially available in the US for an even longer period of time. On December 20, 2019, FDA issued a Final Order that subjects CES devices to premarket approval (PMA) requirements when these devices are intended to treat depression and subjects them to potentially burdensome special controls when they are intended to treat anxiety and/or insomnia (84 FR 70003).The burdens outlined in the Final Order constitute a significant and unnecessary departure from FDA's longstanding approach to the regulation of these devices, and threatens the commercial availability of CES devices in the United States. As a small medical device manufacturer, Fisher Wallace is among the companies that will be negatively impacted by unnecessarily burdensome FDA regulation.

There is no public health issue that warrants these new burdens. Rather, it appears FDA's action is driven by at least two considerations. First, it appears that FDA has taken action in the absence of any particularized concern about the safety or effectiveness of these devices to further the administrative objective of concluding the classification process for preamendment devices. Second, and perhaps more importantly, the Final Order appears grounded on feedback from an advisory committee that failed to consider valid scientific evidence gained from direct current CES devices, also known as transcranial direct current stimulation ("tDCS") devices intended to treat depression, anxiety, and/or insomnia, despite the Final Order including such devices within the scope of CES. The advisory committee was only permitted by FDA to consider evidence gained from alternating current CES devices.

The Final Order requires manufacturers to submit clinical testing data for CES devices intended to treat anxiety and/or insomnia, as part of class II special controls. FDA did not formally consider direct current CES device evidence in formulating these special controls. As a relevant point of comparison, FDA <u>does not</u> require clinical testing for electroconvulsive therapy ("ECT") devices intended for use in treating catatonia or a severe major depressive episode ("MDE") associated with major depressive disorder ("MDD") or bipolar disorder ("BPD") in patients who are treatment-resistant or who require a rapid

response due to the severity of their psychiatric or medical condition (83 FR 66102). Despite ECT devices producing a seizure, requiring anesthesia to administer, often causing memory loss and sanctioned for use on patients as young as 13 years-of-age, FDA only requires “non-clinical testing” of ECT devices with the aforementioned intended use.

The Petitioner believes that clinical testing is appropriate for ECT devices and CES devices; the Petitioner also believes that CES clinical testing should be deferred to CES manufacturers and not be unreasonably burdensome given the extremely low risk that CES devices pose.

Direct current CES devices employ electrodes that are either anode or cathode, whereas alternating current CES devices employ electrodes that switch (alternate) between anode and cathode. At the time of the 2012 panel meeting, FDA informed the Panel that CES devices do not employ direct current. As a result, **the robust clinical data demonstrating the safety and effectiveness of direct current CES devices, particularly for the treatment of depression - and, by extension, the safety and effectiveness of all CES devices – was not considered by the Panel.** The Final Order’s explicit inclusion of direct current (“DC”) devices within the scope of CES devices indicates FDA’s clinical judgement that DC devices fall within the generic type of device known as CES and its classification and that scientific evidence demonstrating the safety and effectiveness of such devices is applicable to the generic type of device generally. **FDA’s Final Order is thus based on a flawed advisory proceeding that expressly excluded relevant information of safety and effectiveness from the deliberation.**

For these reasons, the Petitioner respectfully asserts that the Final Order is not grounded in the best available science and imposes unnecessarily burdensome requirements on CES manufactures. It is on this basis that the Petitioner submits this Citizen Petition in accordance with 21 CFR § 10.30 to request that the Commissioner of Food and Drugs ("Commissioner") take the following action.

## I. ACTION REQUESTED

The Petitioner requests that the Commissioner:

(1) withdraw the Final Order regarding CES Devices (the “Final Order”), and

(2) convene a new Neurological Devices Panel of the Medical Devices Advisory Committee to review all available valid scientific evidence of safety and effectiveness pertaining to CES devices, including evidence from direct current CES devices, also known as transcranial direct current stimulation (“tDCS”) devices intended to treat depression, anxiety and/or insomnia, so that the Panel may render a recommendation to FDA regarding the device’s appropriate regulatory classification.

**Alternatively,** the Petitioner requests that the Commissioner withdraw the Final Order, consider the valid scientific evidence of CES safety and effectiveness, including evidence pertaining to direct current CES devices, and reissue the order so that CES devices intended to treat depression, anxiety and/or insomnia are reclassified into class II, subject to reasonable special controls.

## DEVICE DESCRIPTION

FDA's Final Order provided the following regulatory identification of CES devices, which, notably, does not distinguish between direct current and alternating current devices:

> ***A cranial electrotherapy stimulator is a prescription device that applies electrical current that is not intended to induce a seizure to a patient's head to treat psychiatric conditions. (84 FR 70003)***

The Final Order also **explicitly includes direct current devices within the scope of CES**:

> *(Comment 11) One comment suggests that FDA should correctly categorize CES as either Direct Current (DC) or Alternating Current (AC) stimulation and not whether it is the same waveform as the predicate CES devices used. Comment also suggests that clinical trials are necessary to determine regions of influence by current.*
>
> ***(Response 11) Based on our interpretation of this comment, FDA believes that CES devices could use AC or DC stimulation and that clinical trials conducted to comply with the special controls could be used to characterize the degree of activation in different brain regions.***

The regulatory Identification of CES prior to the Final Order also did not exclude direct current devices:

> *A cranial electrotherapy stimulator is a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety. (21 CFR 882.5800)*

## BRIEF MARKETING HISTORY

Only sixteen 510(k)s have been cleared for CES devices since they became FDA-regulated on May 28, 1976[1]. The clearances began in 1977 to treat the symptoms of depression, anxiety and insomnia. FDA recognizes CES devices as low risk (84 FR 70003). Multiple well-controlled clinical trials have been published regarding direct current (DC) and alternating current (AC) CES devices (see Appendix A).

Fisher Wallace manufactures an AC CES device called the Fisher Wallace Stimulator®. The company has sold over 55,000 devices, prescribed by approximately 10,000 providers in the United States. Patients typically purchase the Fisher Wallace device out-of-pocket, at an average cost of a few hundred dollars. Fisher Wallace provides patients with a 30-day return and refund policy. Approximately 15% of patients return their Fisher Wallace device for a refund. The majority of patients in clinical trials and practice report durable symptom reduction or remission within 1-3 weeks of use. The device causes only minor side effects, such as temporary headache or dizziness, in approximately 1% of patients - a fraction of the

[1] CES devices on the market prior to May 28, 1976 do not require FDA clearance to be marketed in the U.S. unless the devices undergo a significant change of modification requiring premarket notification.

38% side effect rate of SSRI medication (Cascade, E., Kalali, A. H., & Kennedy, S. H. (2009). Real-World Data on SSRI Antidepressant Side Effects. *Psychiatry, 6*(2), 16–18).

Since 2014, Fisher Wallace's CES device has been approved (CE-ISO) for sale over-the-counter in Europe for the treatment of depression, anxiety and insomnia. In the Final Order, FDA requires a prescription for a CES device.

Fisher Wallace devices are used by many healthcare organizations, including Phoenix House, the nation's largest non-profit drug and alcohol rehabilitation network, to treat patients suffering from depression, anxiety and/or insomnia. In 2018, the device was approved by Medicaid in Maine (MaineCare).

A double-blind, placebo-controlled clinical trial, using the Fisher Wallace CES device for the treatment of depression was conducted at Mount Sinai Beth Israel Hospital and published in the Journal of Nervous and Mental Disease in 2015 (McClure D, Greenman SC, Koppolu SS, Varvara M, Yaseen ZS, Galynker II. A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression. *J Nerv Ment Dis*. 2015;203(11):827–835. doi:10.1097/NMD.0000000000000378). This study represents one of hundreds that document the safety and effectiveness of alternating current and direct current CES devices (Appendix A).

## REGULATORY BACKGROUND

CES devices are "preamendment class III devices" (i.e., they are devices that were in commercial distribution in the United States prior to May 28, 1976, the date of enactment of the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FDCA)), that were subsequently classified by FDA into class III. A preamendment device that has been classified into class III is subject to the premarket notification (510(k)) process without submission of a PMA, until FDA issues a final regulation under section 515(b) of the FDCA requiring premarket approval.

Under section 513(d) of the FDCA, FDA established a process to evaluate and classify preamendment devices. On April 3, 2011, the Government Accountability Office ("GAO") issued a report on FDA's progress under the program and admonished the Agency for failing to reclassify the remaining class III preamendment device types that were on the market through the 510(k) process, or require PMAs for these devices. The GAO was concerned with preamendment class III devices that actually posed high risk, as described in the first sentence of the report: "FDA has begun to take steps to address GAO's 2009 recommendation about high-risk devices that are allowed to enter the U.S. market through the less stringent 510(k) process, but progress has been limited. High-risk devices include those which are implantable or life sustaining." While CES devices were technically preamendment class III devices at the time of the GAO report, CES devices do not pose high risk.

On August 8, 2011, FDA published a proposed rule to require PMA applications for CES devices for all indications (Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator, Docket No. FDA-2011-N-0504).

As set forth in section 515(b)(2)(A) of the FDCA and 21 CFR § 860.132, FDA is required as part of this process 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 must proceed under section 513(e) of the FDCA, and a request for a change in the classification should 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. Accordingly, the Petitioner filed a reclassification petition with FDA on August 22, 2011, requesting that CES devices be reclassified to class I or class II.

On January 13, 2012, the US Army sent a letter to FDA requesting expedited review of reclassification for CES devices, citing the limited efficacy of drug therapy for the treatment of depression in soldiers with PTSD (Appendix B).

A meeting of the Neurological Device Panel (the "Panel") was convened on February 10, 2012 to consider reclassification of CES devices.

In the executive summary ("panel pack") that FDA provided the Panel, the Agency included the regulatory identification of CES devices and described CES stimulation characteristics, neither of which excluded direct current devices from their scope. However, FDA excluded direct current devices from the scope of CES in section 1.2.4 of the panel pack, entitled "Devices That Are Not Considered CES," alongside TMS, ECT and TENS devices (see panel pack excerpt in Appendix C),. As a result, the panel pack excluded from the Panel deliberation valid scientific evidence of the safety and effectiveness of direct current CES devices, preventing the Panel from making an informed evaluation or recommendation about CES technology as a whole.

Many high-quality direct current CES device clinical trials have been published regarding the treatment of depression (Appendix A). Because these trials demonstrate the safety and effectiveness of CES devices generally, the Petitioner respectfully asserts that it was a mistake for FDA to exclude such valid scientific evidence from the Panel's consideration. That error is reinforced by the fact that, without fanfare or explanation, FDA explicitly included direct current devices in the definition of CES in the Final Order.

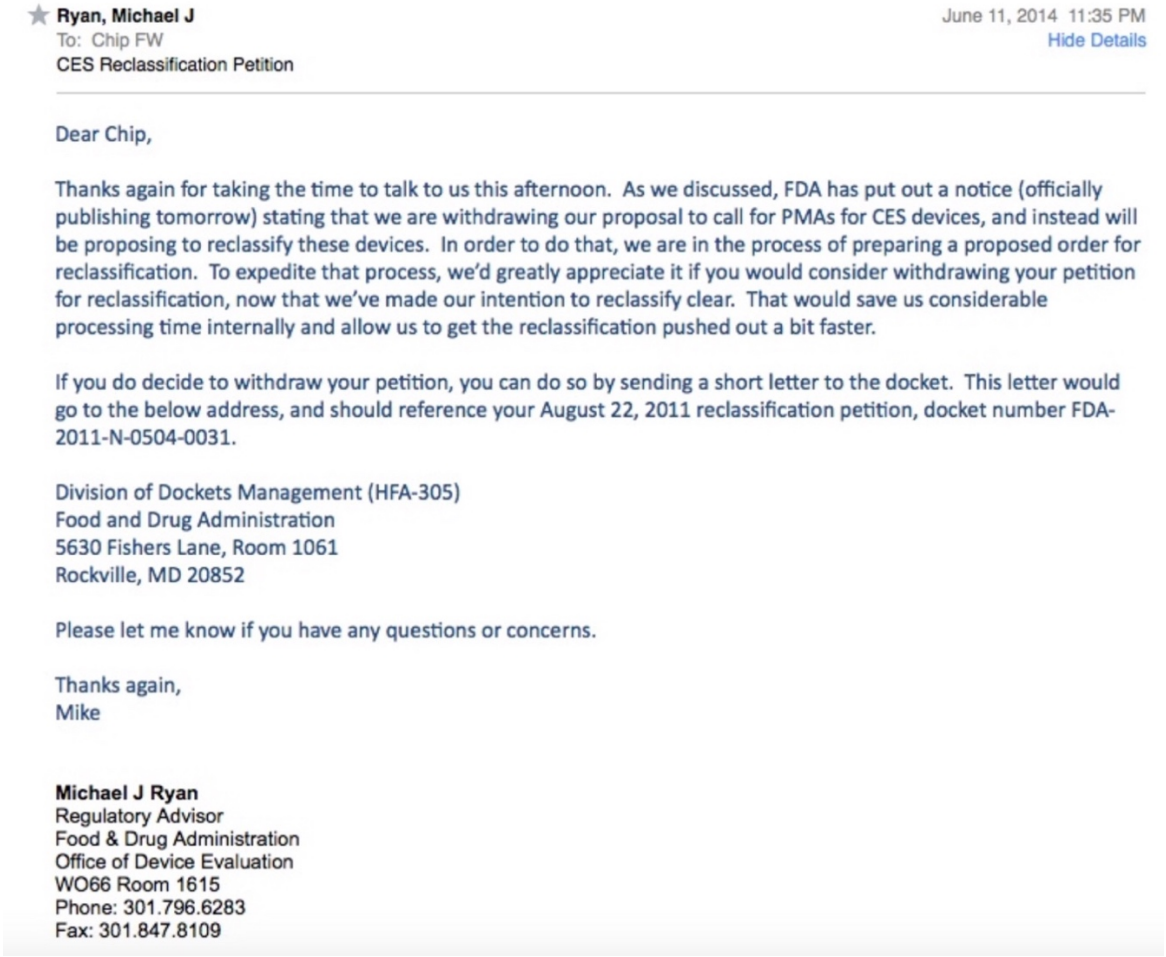
FDA also prevented the only panel member with expertise in non-invasive brain stimulation, Alvaro Pascual-Leone, PhD, from attending the panel meeting, despite the Agency granting him a COI waiver to attend; the Agency then misrepresented the reason for his absence at the opening of the panel proceedings, as documented below and in the Petitioner's original Citizen Petition. FDA also informed the Panel, inaccurately and without evidence, that CES devices posed a risk of seizure, a claim the Agency later withdrew. FDA also provided inaccurate and misleading information to the Panel regarding device classification, particularly with regard to the eligibility of CES devices to be reclassified to class I (section 513(a)(1)(A)(ii) of the statute). On March 9, 2012, this Petitioner filed a Citizen Petition with FDA (FDA-2012-P-0260-0001) that catalogued these and other actions which potentially biased the Panel against reclassification of CES devices to class I or class II for all indications and requested that the Commissioner investigate possible noncompliance with applicable Federal requirements, or misconduct, by FDA, and that the Agency not use any advice or recommendation provided by the Panel, refrain from issuing a final rule to require

the filing of a premarket approval ("PMA"), and place CES in class I or class II for all indications.

On June 3rd, 2013, US Congresswoman Caroline B. Maloney (12th District, NY, and Acting Chair of the House Oversight Committee) sent a letter to FDA Commissioner Margaret Hamburg expressing concern regarding CES regulatory proceedings (Appendix D).

On March 25, 2014, representatives from Fisher Wallace and its law firm, Sidley Austin LLP, met with Ms. Lisa Barkley, the Commissioner's Chief of Staff (2014), and Ms. Nancy Stade, Deputy Director of Policy, FDA (2014), in the Office of the Commissioner. Representatives of FDA's Office of Chief Counsel joined the meeting by conference call. During the meeting, the FDA representative acknowledged problems with the reclassification process, apologized to Fisher Wallace for how the company had been treated, and assured the company that corrective action would be taken.

On June 11, 2014, Mr. Michael J. Ryan, Regulatory Advisor, FDA (2014), emailed Fisher Wallace requesting that the company withdraw its reclassification petition in the interest of accelerating the reclassification process, citing the Agency's clear intention to reclassify CES into class II for all indications:



**Ryan, Michael J** June 11, 2014 11:35 PM
To: Chip FW Hide Details
CES Reclassification Petition

Dear Chip,

Thanks again for taking the time to talk to us this afternoon. As we discussed, FDA has put out a notice (officially publishing tomorrow) stating that we are withdrawing our proposal to call for PMAs for CES devices, and instead will be proposing to reclassify these devices. In order to do that, we are in the process of preparing a proposed order for reclassification. To expedite that process, we'd greatly appreciate it if you would consider withdrawing your petition for reclassification, now that we've made our intention to reclassify clear. That would save us considerable processing time internally and allow us to get the reclassification pushed out a bit faster.

If you do decide to withdraw your petition, you can do so by sending a short letter to the docket. This letter would go to the below address, and should reference your August 22, 2011 reclassification petition, docket number FDA-2011-N-0504-0031.

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Please let me know if you have any questions or concerns.

Thanks again,
Mike

**Michael J Ryan**
Regulatory Advisor
Food & Drug Administration
Office of Device Evaluation
WO66 Room 1615
Phone: 301.796.6283
Fax: 301.847.8109

On June 12, 2014, the Agency withdrew its proposal to require burdensome premarket approval ("PMA") for CES devices and stated its intention to reclassify CES for all indications; in the Federal Register notice, FDA stated that it "... has considered the information before the Agency, including the deliberations of the February 10, 2012, Neurological Devices Panel and the reclassification petitions submitted for these devices, and has determined that there is sufficient information to establish special controls, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness for CES devices." (79 FR 33712)

In a letter dated June 17, 2014, Fisher Wallace complied with the Agency's request to withdraw its reclassification petition, stating that since "... the Agency has committed to grant the relief we sought in our petition, and in light of the agency's representation that the petition could be withdrawn without prejudice, we are withdrawing our petition to enable the Agency to devote limited resources to the reclassification proceeding."

FDA did not honor its commitment, however. Rather, on January 22, 2016, the Agency published a proposed order that once again proposed PMA requirements for CES devices intended to treat depression (81 FR 3751). The Federal Register notice cited no new information that supported a reversal of the Agency's 2014 position, nor did it cite new information that supported burdensome special controls for established manufacturers. However, in citing its reliance on the Panel meeting, the proposed order relied on a process bereft of valid scientific evidence of direct current CES devices.

On February 23, 2016, Fisher Wallace filed an amendment to its Citizen Petition (FDA-2012-P-0260-0021) that provided new evidence that suggested the proposed regulation of CES devices had been unduly and inappropriately influenced by a highly political non-profit organization, Public Citizen, and a Senior Advisor to FDA, Peter Lurie, who later became Associate Commissioner for Public Health Strategy and Analysis. In the amendment, Fisher Wallace submitted the following federal email to FDA, obtained through the Freedom of Information Act (continued on next page):

**From:** Lurie, Peter
**Sent:** Wednesday, March 14, 2012 11:57 AM
**To:** Sigelman, Daniel
**Subject:** From FDA Webview today

CDRH does have one friend in its treatment of CES devices. Public Citizen Health Research Group director **Sidney Wolfe**, who can usually be relied upon to oppose any corporate position, has strongly urged CDRH director **Jeffrey Shuren** to hold fast to the Center's Class III decision. When attorney Pilot pointed out the flaws and legal failings in that decision, Wolfe declined to alter HRG's position, saying it was based on "publicly available material."

Peter Lurie, MD, MPH
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Email: peter.lurie@fda.hhs.gov

In 2017, Peter Lurie resigned from FDA following an investigation of his actions pertaining to CES reclassification, conducted by the Office of Scientific Integrity (Appendix E). In a second amendment to its Citizen Petition (FDA-2012-P-0260-0024), Fisher Wallace criticized the investigation as patently inadequate in that it did not conduct interviews with the most relevant witnesses, nor did it perform its own review of relevant federal emails or investigate the irregularities associated with the 2012 panel meeting (Appendix F).

The procedural flaws associated with CES regulation predate the arrival of Peter Lurie at the Agency, and continued after his departure. As a result, the Petitioner does not assert that Peter Lurie is singularly responsible for the mishandling of CES regulatory proceedings.

By 2019, CES devices were the only device class of the original 140 preamendment class III devices which had not been reclassified or made subject to PMA requirements.

On December 20, 2019, FDA filed a Petition Response Letter (FDA-2012-P-0260-0026, see Appendix G), officially responding to Fisher Wallace's original Citizen Petition (filed more than seven years prior) and its subsequent amendments. In the letter, the Director of the Center for Devices and Radiological Health denies that there were any flaws in how the panel meeting or any other aspect of CES regulatory proceedings were handled, and asserted that Fisher Wallace's Citizen Petition did not provide "any factual support" for its allegations "other than conclusory statements." Apparently, the Director did not consider documentary evidence of panel proceedings, interviews with witnesses, and federal email evidence obtained through the Freedom of Information Act as "factual support." Furthermore, the letter states that "FDA did issue a conflict of interest waiver for an expert to participate on the panel; however, FDA reversed the decision because the Agency received additional information on the specific potential SGE immediately prior to the meeting that resulted in the person having a conflict of interest. That SGE did not participate

in the panel meeting." The potential, special government employee ("SGE") referred to in this letter was Alvaro Pascual-Leone, PhD, who did not appear at the 2012 panel meeting. The explanation provided in the letter appears to contradict the explanation given by James Swink, Acting Advisory Committee Coordinator (2012), FDA, two days prior to the panel meeting:

> From: Kelly Roman [mailto:kelly@fisherwallace.com]
> Sent: Wednesday, February 08, 2012 11:29 AM
> To: Swink, James P
> Subject: Re: FDA Website URL
>
> Thanks James,
>
> Is Alvaro Pascual-Leone going to be present on the Panel on Friday? I see he has a waiver but the link states "Alvaro Pascual-Leone, M.D., Ph.D. was unable to attend this meeting"
>
> Thanks for clarifying.
>
> Kelly
>
> On Feb 8, 2012, at 11:35 AM, Swink, James P wrote:
>
> It looks like he is not going to make this meeting, Avena will be here shortly, I will have her post the roster today as well.
> Thank you,
>
> James Paul Swink Acting Advisory Committee Coordinator Medical Devices Advisory Committee Center for Devices and Radiological Health James.Swink@fda.hhs.gov Phone: 301-796-6313

The Petition Response Letter's explanation for Dr. Pascual-Leone's absence also appears to contradict the announcement that Avena Russell, FDA, made at the outset of the panel meeting (excerpted from the panel transcript):

> RUSSELL: Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 US Code Section 208 B3 to Alvaro Pascual-Leone, MD. However, he was unable to attend this meeting.

Additionally, while the Petition Response Letter insists that FDA did not withhold any valid scientific evidence from the Panel deliberations, the Agency, in fact, excluded all evidence of safety and effectiveness of direct current CES devices from panel consideration.

On December 20, 2019, the same day that FDA published its Petition Response Letter, the Agency *also* published the Final Order requiring PMA for CES devices intended to treat

depression, and reclassified CES devices intended to treat anxiety and/or insomnia into class II, subject to potentially burdensome special controls that include “clinical testing.”

## II. STATEMENT OF GROUNDS

It is of paramount importance that the Commissioner understand the circumstances and the significance of the Agency’s issuance of the Final Order Regarding Cranial Electrotherapy Stimulator Devices on December 20, 2019 (84 FR 70003) and its impact on the manufacturers and distributors of these devices, as well as the sizeable population that currently prescribes and uses CES devices for the treatment of depression, anxiety and/or insomnia, and the immensity of the patient population that could potentially benefit from these low-cost, low-risk devices in the future.

**1) In the executive summary provided by FDA to the Neurological Device Panel convened on February 10, 2012, FDA inappropriately advised the Panel that tDCS devices intended to treat depression, anxiety and/or insomnia are not CES devices.**

Specifically, the following excerpt appeared within the executive summary that FDA provided members of the Panel in 2012 (relevant portion in **BOLD**):

> ***1.2.4. Devices That Are Not Considered CES***
>
> ***The following types of devices should not be confused with CES and are not the subject of these proceedings****:*
>
> *Transcranial magnetic stimulation (TMS): these devices are defined in 21 CFR 882.5805, and are used to treat depression. TMS devices function by inducing a current through the use of an electromagnetic coil placed on the patient’s head, which is a different technology. They are regulated separately from CES.*
>
> *Transcutaneous electrical nerve stimulation (TENS): these devices are defined in 21 CFR 882.5890, and are used for pain relief. Many TENS devices have a higher output than CES devices. They also allow for greater control of the stimulation parameters, and generally include warnings against CES-style electrode placement that allows current to flow trans-cerebrally (through the head).*
>
> *Electroconvulsive therapy (ECT): these devices are used for treating “severe psychiatric disturbances (e.g., severe depression),” and are defined in 21 CFR 882.5940. They require much higher levels of current because they are intended to induce a “major motor seizure.”*
>
> ***Transcranial direct current stimulation (tDCS): This type of therapeutic stimulation is characterized primarily by the intentional use of a direct current (DC) bias that may or may not have an associated alternating signal. Electrode placement may also be different from that of cleared CES devices. There is no regulation for therapeutic tDCS.***

**2) By excluding direct current CES devices (tDCS devices intended to treat depression, anxiety and/or insomnia) from the scope of the Neurological Device Panel's deliberations on February 10, 2012, FDA excluded relevant valid scientific evidence from Panel consideration, thereby undermining the scientific validity of the Panel's recommendations**.

The executive summary that FDA provided the Panel did not include any available valid scientific evidence of safety and effectiveness for direct current CES devices for the treatment of depression, anxiety and/or insomnia.

As the PubMed links listed in Appendix A of this Petition demonstrate, substantial evidence of the safety and effectiveness of direct current CES devices, also known as tDCS devices intended to treat depression, anxiety and/or insomnia, was published before and after the 2012 panel meeting. The following meta-analysis is one notable example:

> *Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis.* Prog Neuropsychopharmacol Biol Psychiatry. 2019 Dec 16;99:109836. doi: 10.1016/j.pnpbp.2019.109836.

While the above meta-analysis exclusively examined direct current devices intended to treat major depressive disorder, other well-controlled studies have been performed using direct current devices for the treatment of bipolar depression, such as the following:

> *Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial.* JAMA Psychiatry. 2018 Feb 1;75(2):158-166. doi: 10.1001/jamapsychiatry.2017.4040.

The number of published studies of direct current CES devices intended to treat depression is signficantly larger than the number of published studies of alternating current CES devices intended to treat depression. FDA and the Panel failed to consider the majority of the valid scientific evidence of CES device safety and effectiveness when determining how CES devices should be regulated. Moreover, the evidence of effectiveness of direct current CES devices, when combined with alternating current device evidence, appears to categorically provide a positive benefit-risk profile for CES devices intended to treat depression, as well as anxiety and/or insomnia.

**3) Direct current CES devices clearly fall within 21 CFR § 882.5800 and should not have been excluded from consideration by FDA and the Neurological Device Panel.**

The regulatory Identification of CES devices that appeared in the classification regulation prior to FDA issuance of the Final Order did not exclude DC devices:

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

The regulatory Identification of CES devices specified within the Final Order also does not exclude direct current devices:

(a) Identification. A cranial electrotherapy stimulator is a prescription device that applies electrical current that is not intended to induce a seizure to a patient's head to treat psychiatric conditions.

In furtherance of the position that AC and DC CES devices should be regulated within the generic type of device known as CES, the Petitioner points out that the alternating or fixed polarity of electrode montages (AC or DC) has never been the sole determinant of the device's regulatory classification. While a manufacturer changing its legally marketed CES device from AC to DC output (and vice versa) may require the submission of a new 510(k), to our knowledge FDA has never determined that a device modified from AC to DC (or vice versa) is not substantially equivalent (NSE) to a legally marketed predicate device based on this type of change.

**4) In issuing the Final Order, FDA explicitly includes direct current devices within the scope of CES:**

In the Final Order, FDA states that the definition of CES devices explicitly includes DC devices (relevant portion in **BOLD**):

> *(Comment 11) One comment suggests that FDA should correctly categorize CES as either Direct Current (DC) or Alternating Current (AC) stimulation and not whether it is the same waveform as the predicate CES devices used. Comment also suggests that clinical trials are necessary to determine regions of influence by current.*
>
> ***(Response 11) Based on our interpretation of this comment, FDA believes that CES devices could use AC or DC stimulation and that clinical trials conducted to comply with the special controls could be used to characterize the degree of activation in different brain regions*.**

**5) The benefit-risk profile that FDA presents in the Final Order for CES devices intended to treat depression does not take into account the valid scientific evidence of the safety and effectiveness of direct current CES devices.**

Within the same Final Order that states direct current devices are within the scope of CES, FDA describes an analysis of CES benefit-risk that is bereft of direct current CES evidence:

> *As established in section 513(a)(1)(C) of the FD&C Act and § 860.3(c)(3), a device is in class III if insufficient information exists to determine that general controls and/or special controls are sufficient to provide reasonable assurance of its safety and effectiveness and the device is purported or represented to be for a use that is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. FDA believes that the risks to health, identified earlier in this section, for the use of CES devices for treating depression, in the absence of an established positive benefit-risk profile, presents a potential unreasonable risk of illness or injury. FDA therefore concluded that there was insufficient information regarding the risks and benefits of the device for FDA to establish special controls that, in combination with general controls, would provide*

*reasonable assurance of the safety and effectiveness of CES for treating depression.*

The Petitioner strongly disagrees with the Agency's assertion that multiple well-controlled published studies of alternating current CES devices for the treatment of depression, combined with an extremely low side effect rate, amount to an "absence of an established positive benefit-risk profile." Regardless of this disagreement, by not taking into account the valid scientific evidence of direct current CES devices, the Agency has not accurately assessed the benefit risk-profile of CES devices and should not have issued the Final Order.

**6) The Final Order requires established CES manufacturers to submit clinical testing data from currently marketed CES devices as part of special controls for devices intended to treat insomnia and/or anxiety. FDA did not consider direct current CES device evidence in formulating these special controls, and depending on the level of evidence FDA requires for clinical testing, these special controls may be overly burdensome and/or intended to prevent current manufacturers from accessing or competing in the psychiatric treatment market.**

Given the history of CDRH regulatory proceedings regarding CES, the American public and CES manufacturers have no reason to trust that CDRH will act in good faith when evaluating clinical testing data submitted by CES manufacturers. Therefore, the American public and CES manufacturers must rely on the Commissioner to ensure that such evaluations are fair and take into consideration the low risk that CES devices pose when determining the benefit risk profile of a device that clinical testing informs.

As noted previously in this petition, FDA does not require clinical testing for electroconvulsive therapy ("ECT") devices intended for use in treating catatonia or a severe MDE associated with MDD or BPD in patients who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition (83 FR 66102). Despite ECT devices producing a seizure, requiring anesthesia to administer, often causing memory loss and sanctioned for use on patients as young as 13 years-of-age, FDA only requires "non-clinical testing" of ECT devices with the aforementioned intended use.

## ENVIRONMENTAL IMPACT

An environmental impact statement was deemed unnecessary for this petition.

## ECONOMIC IMPACT

According to 21CFR10.30, an economic impact statement is to be submitted only when requested by the Commissioner following review of the petition.

## CONCLUSION

US spending on mental health treatment currently exceeds $200 billion per year – more than the US spends treating cancer, heart disease or diabetes (SAMHSA). The standards of care – medication and behavioral therapy – provide low to moderate efficacy at a high cost and, for medication, a high rate of side effects. As a result, the integrity of FDA regulation of new and alternative treatments for depression, anxiety and insomnia is paramount if it is to service the national interest.

FDA's mishandling of CES regulatory proceedings appears to reflect a bias against the technology and an intent to limit its market access, particularly its access to the depression treatment market which profoundly needs effective, low-cost, low-risk alternatives to medication, behavioral therapy and ECT. This should concern the American public, their representatives in Congress, the Secretary of the Department of Health and Human Services and the Commissioner of Food and Drugs.

The abundant evidence of procedural flaws relating to CES regulation, documented in this and the Petitioner's previous Citizen Petition, speaks to issues larger than those faced by CES manufacturers; the evidence reflects the values, culture and operating principles of the FDA and CDRH. An Agency that values and acts upon valid scientific evidence must also value and act upon evidence of its own procedural failings – neither form of evidence should be dismissed by the Agency.

The Petitioner has demonstrated in this Petition and in its previous Petition that the Agency treated the evidence of alternating current CES devices in a biased fashion. By also excluding all direct current CES device evidence of safety and effectiveness from Panel consideration, FDA rendered the Panel incapable of making an informed recommendation regarding CES classification. Likewise, by not taking into account the valid scientific evidence of direct current CES devices, FDA could not accurately assess the benefit risk-profile of CES as a class.

The Petitioner therefore requests that the Commissioner withdraw the Final Order regarding CES Devices (the "Final Order"), and convene a new Neurological Devices Panel of the Medical Devices Advisory Committee to review all available valid scientific evidence of safety and effectiveness pertaining to CES devices, including evidence pertaining to direct current CES devices, and render a recommendation to FDA regarding the appropriate regulatory classification of CES. **Alternatively,** the Petitioner requests that the Commissioner withdraw the Final Order, consider the valid scientific evidence of CES safety and effectiveness, including evidence pertaining to direct current CES devices, and reissue the order so that CES devices intended to treat depression, as well as anxiety and/or insomnia, are reclassified into class II, subject to reasonable special controls.

## CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

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