FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

August 30, 2021

Kelly Roman
Co-Founder & CEO
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515 Madison Avenue, 22nd Floor
New York, NY 10022

Re: Citizen Petition, FDA-2020-P-0893

Dear Mr. Roman:

This letter is in response to the above referenced citizen petition (CP) that was received and filed with the Food and Drug Administration (FDA or Agency) on February 18, 2020. The petition specifically requests that the FDA[1]:

1. Withdraw the Final Order regarding Cranial Electrotherapy Stimulator (CES) Devices (December 20, 2019; 84 FR 70003[2]); 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 (DC) CES devices, also known as transcranial direct current stimulation (tDCS) devices intended to treat anxiety, depression and/or insomnia, so that the Panel may render a recommendation to FDA regarding the device's appropriate regulatory classification.

FDA has reviewed the petition and for the reasons discussed below, your requests are denied.

I. Discussion

A. Background on Reclassification of CES Devices

CES devices were initially classified into class III through rulemaking (21 CFR 882.5800(b)) for all uses under section 513(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Because CES devices were marketed before May 28, 1976 (the date of enactment of the Medical Device Amendments), and subsequently classified into class III, this device type is a "preamendments class III device." 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 may be marketed without submission of a premarket approval application (PMA) until FDA issues a final order

[1] CP, 2
[2] Available at: https://www.federalregister.gov/documents/2019/12/20/2019-27295/neurological-devices-reclassification-of-cranial-electrotherapy-stimulator-devices-intended-to-treat

under section 515(b) of the FD&C Act requiring premarket approval. Both the preamendments and substantially equivalent devices are referred to as "preamendments class III devices."

On February 10, 2012, FDA consulted with the Neurological Devices Classification Advisory Panel (2012 Panel), which held a meeting to discuss the classification of CES devices for treatment of anxiety, depression, and insomnia. The FDA Executive Summary (Executive Summary) prepared for the 2012 Panel discussion noted in section 1.2.4, entitled "Devices That Are Not Considered CES," that tDCS devices were explicitly not included in the scope of the 2012 Panel's discussion. These devices are described in that document as follows:

> 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.[3]

Based on its review of the data, indications for use of the devices that have been cleared for marketing, and information presented during an open meeting, the majority of the 2012 Panel did not think there was valid scientific evidence supporting effectiveness of CES for treatment of insomnia, depression, or anxiety. The 2012 Panel also pointed out that there was a lack of device risk, meaning that a benefit-risk analysis might be favorable with any demonstrated effectiveness. The majority of the 2012 Panel recommended that CES should be kept in class III at that time. The 2012 Panel did not consider, however, the possibility of splitting different indications into different classifications (though one 2012 Panel member did state that there seemed to be effectiveness of CES for treatment of anxiety), or whether there was sufficient evidence to establish clinical performance testing as a special control. The 2012 Panel transcript and other meeting materials are available on FDA's Web site.[4]

On January 22, 2016, following the procedural change from rulemaking to administrative order process for reclassification of devices under the FDA Safety and Innovation Act (FDASIA), FDA issued a proposed order entitled "Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Intended To Treat Insomnia and/or Anxiety; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Intended To Treat Depression" (81 FR 3751[5]) (2016 Proposed Order). The 2016 Proposed Order proposed, among other things, to (a) reclassify the uses of the CES devices for treating insomnia and/or anxiety

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[3] 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, available at, https://wayback.archive-it.org/7993/20170404140724/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM290787.pdf, 8.

[4] Transcript, February 10, 2012, meeting of the Neurological Devices Panel of the Medical Device Advisory committee, available at, https://wayback.archive-it.org/7993/20170404140746/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296891.pdf.

[5] Available at: https://www.federalregister.gov/documents/2016/01/22/2016-01173/neurological-devices-reclassification-of-cranial-electrotherapy-stimulator-intended-to-treat

into Class II; and (b) maintain the use of CES devices for treating depression in Class III and require the filing of PMAs for that intended use.

After receiving and considering more than 300 public comments, including literature accompanying specific comments, submitted to the 2016 Proposed Order, FDA issued a final order (Final Order) on December 20, 2019 (84 FR 70003): (1) reclassifying CES devices from class III to II for use in treating anxiety and/or insomnia; and (2) maintaining class III classification and requiring PMAs for CES devices for use in treating depression. The Final Order identifies CES devices as follows: 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.

B. Your Petition and Its Assertions

Your petition includes six assertions in Section II, entitled "Statement of Grounds," which purportedly support your requests. Assertions one through five relate, generally, to the conduct and scope of the 2012 Panel and the Final Order issued after the Panel. Those assertions will be addressed together in Section B.1. of this letter. Assertion six relates to a specific special control identified in the Final Order and will be addressed separately, in Section B.2. of this letter.

1. Exclusion of tDCS from the 2012 Panel Was Appropriate and Thus Does Not Warrant Withdrawal of the Final Order and Convening of a New Panel

Your petition alleges that FDA wrongfully "excluded 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" - resulting in a "flawed advisory proceeding."[6] Section II.1 of your petition claims that "FDA inappropriately advised the Panel that tDCS devices intended to treat depression, anxiety and/or insomnia are not CES devices."[7] Section II.4 of your petition also claims that because FDA "explicitly includes direct current devices within the scope of CES"[8] in the Final Order, devices using tDCS should have been included for deliberation by the 2012 Panel. In Section II.3 of your petition, you claim that 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."[9] FDA disagrees with these claims.

Although FDA referenced that CES devices could use alternating current (AC) or DC stimulation in response to a comment in the Final Order, the Agency's intent was to state that nothing precludes inclusion in the CES regulation of devices that use DC stimulation that may be authorized for marketing by FDA in the future. To further clarify, FDA explicitly described the CES stimulation modalities that were within the scope of the 2012 Panel in the FDA Presentation as "Variable stimulation characteristics," including "[c]urrent up to 4mA," "[b]iphasic or

[6] CP, 2
[7] CP,10
[8] CP, 12
[9] CP, 11

monophasic, square or sine wave," and "[s]everal specific frequencies (e.g., 0.5 Hz, 100 Hz)." [10] These stimulation characteristics had been previously cleared in devices within the CES regulation at the time of the 2012 Panel proceedings and were included in the systematic literature review evaluating reported effectiveness and adverse events for CES devices. FDA excluded tDCS devices from the 2012 Panel because FDA was only able to pursue reclassification for CES devices that had been previously cleared. Since FDA had not (and still has not) cleared any devices within the CES regulation that would meet the description of tDCS in section 1.2.4 of the Executive Summary discussed above in Section I.A. of this letter, FDA was unable to include such devices in the 2012 Panel discussion.

FDA also disagrees with your claim in Section II.2 that "FDA excluded relevant valid scientific evidence from Panel consideration, thereby undermining the scientific validity of the Panel's recommendations."[11] Similarly, FDA disagrees with your claim in Section II.5 of your petition that 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."[12] As stated in the Final Order, the evidentiary standard FDA relies on to determine the safety and effectiveness of a device is valid scientific evidence (VSE, 21 CFR 860.7(c)(2)). FDA assessed the totality of VSE available to FDA prior to the 2012 Panel and prior to the publication of the Final Order. This evidence included the literature analyzed prior to and presented during the 2012 Panel meeting, information included in the 2016 Proposed Order, and the information provided in response to the 2016 Proposed Order, including several comments that referenced additional clinical studies. As stated above, because tDCS devices had not been previously cleared, FDA did not include tDCS in the panel discussion or as part of the revised literature search for finalizing the proposed order for CES. Your petition specifically references two scientific articles, which you claim provide evidence in support of the safety and effectiveness of tDCS devices.[13] The two referenced scientific articles are not relevant because, as stated above, tDCS was appropriately excluded from the scope of the 2012 Panel and, therefore, these articles were similarly appropriately not considered as part of the extensive literature review for the Final Order for CES devices.

FDA has determined that the record for the Final Order supports the actions taken and your petition has provided no justifications for withdrawing the Final Order or for convening a new Panel for consideration of VSE from tDCS devices since such devices were appropriately excluded from the scope of the 2012 Panel discussions and Final Order.

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[10] FDA Presentation, available at: https://wayback.archive-it.org/7993/20170404140737/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM291630.pdf, slide 4.

[11] CP, 11

[12] CP, 12

[13] Sampaio-Junior, et al., *Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression*, JAMA Psychiatry. 2018 Feb; 75(2): 158–166. Moffa, et al., Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Apr 20; 99:109836.

2. Requirement of Clinical Testing to Demonstrate Effectiveness of CES Devices Intended for Treatment of Anxiety and/or Insomnia Is Appropriate.

Section II.6 of your petition claims that the special control relating to Clinical Performance Testing "may be overly burdensome and/or intended to prevent current manufacturers from accessing or competing in the psychiatric treatment market." Further, your petition asserts that clinical testing is appropriate for both Electroconvulsive Therapy (ECT) and CES devices even though FDA does not require clinical testing for ECT devices intended for use in treating catatonia or severe Major Depressive Episode (MDE) associated with Major Depressive Disorder (MDD) or Bipolar Disorder (BPD) patients. In addition, your petition claims that CES clinical testing should be deferred to the CES manufacturers.[14] FDA disagrees with these claims. As stated in the CES Final Order**:**

> …the safety and effectiveness evidence in support of reclassifying ECT for specific uses was substantial and demonstrated benefits more consistently, in comparison to the evidence evaluated for reclassifying CES intended for treatment of depression from class III to II, although sufficient information exists to establish special controls that, in addition to general controls, will provide reasonable assurance of safety and effectiveness of the CES devices intended for treatment of anxiety and/or insomnia, as discussed above. FDA assessed the totality of the valid scientific evidence that was provided in response to the proposed ECT order, including several comments that referenced new clinical studies. Several of these studies included safety and effectiveness data for adult as well as adolescent patients as well as randomized controlled clinical studies, open-label observational trials, case series reports, systematic literature reviews, and practice guidelines that were submitted in the comments. Additionally, the final order for the reclassification of ECT devices (December 26, 2018, 83 FR 66102) identifies ECT devices as applying a brief electrical stimulation of the brain to produce a seizure, while CES devices provide lower stimulation current that is not intended to result in seizure in patients.[15]

FDA maintains its determination that there is a distinction between the use of ECT and CES devices. Additionally, the special control requiring a "detailed summary of clinical testing pertinent to use of the device to demonstrate the effectiveness" for CES devices intended for treatment of anxiety and/or insomnia is consistent with the Agency's least burdensome provisions and has had the benefit of public comments through the appropriate administrative order process.[16] As part of the process for issuing the Final Order, FDA considered other options for the minimum required information, including such as receiving full reports of all clinical tests, and determined that summaries would be less burdensome while still meeting the standard for making a determination of substantial equivalence.

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[14] CP, 2

[15] Final Order, 70008

[16] See FDA's Guidance entitled, The Least Burdensome Provisions: Concept and Principles," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

II. Conclusion

In accordance with 21 CFR 10.30(e), for the reasons discussed above, FDA denies the requests in your Petition to withdraw the CES Final Order and to convene a new Neurological Devices Classification Panel for consideration of reclassification of CES devices.

If you have any questions, please contact Joshua Chetta in our Office of Policy by e-mail at joshua.chetta@fda.hhs.gov or by phone at (240) 402-4910.

Sincerely yours,

Ellen J. Flannery -S Digitally signed by Ellen J. Flannery -S
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