4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA-2014-N-1209]

Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Devices Intended to Treat Anxiety and/or Insomnia; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Devices Intended to Treat Depression

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to reclassify the cranial electrotherapy stimulator (CES) device intended to treat anxiety and/or insomnia, a preamendments class III device, into class II (special controls) and subject to premarket notification. FDA is also issuing this final order to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for CES devices intended to treat depression (product code JXK) and clarify the device identification of the CES device to include it as a prescription device.

DATES: This order is effective on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. See further discussion in section V, "Implementation Strategy."

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SUPPLEMENTARY INFORMATION:

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I. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation or Acronym	What It Means
2012 Panel	2012 Neurological Devices Panel
510(k)	Premarket Notification
AC	Alternating Current
CES	Cranial Electrotherapy Stimulator Device
CFR	Code of Federal Regulations
CNS	Central Nervous System
DC	Direct Current
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT	Electroconvulsive Therapy Device
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food, Drug, and Cosmetic Act

Abbreviation or Acronym	What It Means
FR	Federal Register
IDE	Investigational Device Exemption
MAUDE	Manufacturer and User Facility Device Experience
MDR	Medical Device Reporting
OMB	Office of Management and Budget
PDP	Product Development Protocol
PMA	Premarket Approval Application
PRA	Paperwork Reduction Act of 1995
RCT	Randomized Controlled Trial
Ref.	Reference
RWD	Real-World Data
RWE	Real-World Evidence
U.S.C.	United States Code
VSE	Valid Scientific Evidence

II. Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976, (generally referred to as preamendments devices) are classified after FDA has: (1) received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed classification regulation classifying the device; and (3) published a final classification regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, (generally referred to as postamendments devices) are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process.[1] Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

A. Reclassification

Under section 515(i)(2) of the FD&C Act, following publication of a proposed order, a meeting of a device classification panel, and consideration of the comments of a proposed order, FDA has the authority to issue an administrative order revising the classification of a device that FDA has classified as a class III device and for which no administrative order has been issued calling for PMAs under section 515(b) of the FD&C Act, so that the device is classified into

[1] CES devices with intended uses outside the scope of those listed in 21 CFR 882.5800 are considered postamendments devices that are subject to classification under section 513(f)(1) of the FD&C Act or, if the relevant requirements are met, under section 513(f)(2) of the FD&C Act.

class I or II. In determining whether to revise the classification of a device or to require a device to remain in class III, FDA applies the criteria set forth in section 513(a) of the FD&C Act. Section 513(a)(1)(B) of the FD&C Act defines class II devices as those devices for which the general controls in section 513(a)(1)(A) by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls that, together with general controls, provide a reasonable assurance of safety and effectiveness of a device.

FDA published a proposed order in the *Federal Register* of January 22, 2016 (81 FR 3751) and held a meeting of the Neurological Devices Panel for a discussion of the CES device classification on February 10, 2012 (the 2012 Panel), as described in section 513(b) of the FD&C Act with respect to CES devices (Ref. 1). FDA also published an order in the *Federal Register* of September 10, 2009 (74 FR 16214), that was issued under section 515(i) of the FD&C Act that required submission of safety and effectiveness information on CES devices. FDA has considered the information available to the Agency, including the deliberations of the 2012 Panel meeting, the reclassification petitions submitted for these devices, and comments from the public docket to determine that there is sufficient information to establish special controls to effectively mitigate the risks to health identified in section III, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness when applied to CES devices intended to treat anxiety and/or insomnia.

Therefore, in accordance with sections 513(e)(1) and 515(i) of the FD&C Act, based on information with respect to the CES device and taking into account the public health benefit of the use of the CES device and the nature and known incidence of the risk of the device, FDA, on

its own initiative, is issuing this final order to reclassify CES devices intended for treatment of anxiety and/or insomnia from class III to class II (special controls).[2]

B. Requirement for Premarket Approval

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order requiring PMAs. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) publication of a proposed order in the *Federal Register*; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payers, and providers. As noted above, FDA published a proposed order that would require PMAs for CES devices intended to treat depression in the *Federal Register* of January 22, 2016. FDA held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to CES devices (Ref. 2). Finally, FDA received and considered over 300 comments on the proposed order, as discussed in section III. Therefore, FDA has met the requirements under section 515(b)(1) of the FD&C Act.

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) was enacted. Section 608(a) and (b) of FDASIA amended sections 513(e) and 515(b) of the FD&C Act, amended sections 513(e) and 515(b) of the FD&C Act, changing the mechanism for, respectively, reclassifying a device and requiring premarket approval for a preamendments device from rulemaking to an administrative order. In the *Federal Register* of December 17, 2018 (83 FR 64443), FDA published a final rule entitled "Medical Device Classification Procedures: Incorporating Food and Drug Administration Safety

[2] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

and Innovation Act Procedures," which codified those sections of FDASIA (Medical Device Classification Procedures Final Rule).

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

Under section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B)), a preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (or a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. Because CES devices that are the subject of this final order were classified in 1979 (44 FR 51770, September 4, 1979), the 30-month period has expired and, thus, the later of these two time periods is the 90-day period. However, for currently legally marketed CES devices intended to treat depression, FDA does not intend to enforce compliance with this 90-day requirement for an additional 90 days (i.e., 180 days after the effective date of this final order), as long as a notice of intent to file a PMA is submitted within 90 days of the effective date of this final order. The notification of the intent to file a PMA should include a list of all model numbers for which a manufacturer plans to seek marketing approval through a PMA. FDA does not intend to enforce compliance with the PMA requirements with respect to an applicant of a currently legally marketed CES device intended to treat depression during FDA's review of the PMA. FDA intends to review any PMA for the

device within 180 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that "the continued availability of the device is necessary for the public health."

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see 21 CFR part 812) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed and it has been determined that the device is a "significant risk" under § 812.3(m). If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed within 90 days after the issuance of a final order, and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. As stated above, FDA does not intend to enforce the requirement that a PMA be filed or that it has an approved IDE, if applicable, within 90 days, if a notice of intent to file a PMA is filed within 90 days of the effective date of this order. Other enforcement actions include, but are not limited to, the following: shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). FDA requests that manufacturers take action to prevent the further use of devices for which no PMA has been filed.

C. Valid Scientific Evidence

The evidentiary standard FDA relies on to determine the safety and effectiveness of a device is valid scientific evidence. Section 860.7(c)(2) (21 CFR 860.7(c)(2)) defines valid scientific evidence. As described in section III, in finalizing this order, FDA has assessed the totality of the valid scientific evidence available to FDA. This evidence includes the literature discussed in the proposed order and the information provided in response to the proposed order, including several comments that referenced additional clinical studies. FDA also considered randomized controlled clinical studies, single arm studies, and systematic literature reviews that were submitted in the comments. Single case reports or opinion-based commentary were also submitted to the dockets for consideration; however, without well controlled empirical experimentation, these types of information are generally not considered valid scientific evidence and were not relied upon to support this reclassification.

Section 860.7(c)(2) also explains that although random experience and reports lacking sufficient details to permit scientific evaluation are not regarded as valid scientific evidence to show safety or effectiveness, such information may be considered in identifying a device, the safety and effectiveness of which is questionable (§ 860.7(c)(2)). Such random experience and reports lacking sufficient details to permit scientific evaluation may be early and, sometimes, informal indications that the device is unsafe and/or ineffective (43 FR 32988 at 32990, July 28, 1978). Where FDA is considering the classification of a device, such random experience and reports are not considered valid scientific evidence (§ 860.7(c)(2)).

FDA received many comments from healthcare professionals describing their practices, the length of time they have been practicing, and the utilization of CES devices in treating patients with certain conditions. While FDA acknowledges receiving comments in providing

information for recommending the reclassification of CES devices for treatment of certain conditions including anxiety, insomnia, and depression, statements by individual healthcare professionals that they have used CES devices to treat individual patients do not constitute valid scientific evidence to demonstrate reasonable assurance of safety and effectiveness (see Valid Scientific Evidence (VSE) discussion in 48 FR 56778 at 56787-56788, comments 16-21, December 23, 1983 (Ref. 3)). Such comments do not contain sufficient detail to capture the use of the device, exposures, and outcomes in the appropriate population and are not interpretable using informed clinical and scientific judgment.

FDA also received many comments from patients, or friends and family of patients, in support of and against reclassification of CES devices for specific indications for use. These comments described the experience of the patient that received treatment from a CES device. FDA acknowledges receiving comments from patients and other individuals about their positive experiences with CES devices being considered for reclassification; however, FDA does not consider such comments to be valid scientific evidence. Because these comments did not contain sufficient data sources to capture the use of the device, exposures, and outcomes in the appropriate population and are not interpretable using informed clinical and scientific judgment, such comments are not considered valid scientific evidence.

For medical devices, available evidence traditionally consists of clinical and non-clinical studies conducted and provided to FDA by the device manufacturer or sponsor. However, FDA recognizes that a wealth of data covering medical device experience is routinely collected in the course of treatment and management of patients. Under certain circumstances, these real-world data (RWD) may constitute real-world evidence (RWE), or clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD, that may be

of sufficient quality to help inform or augment FDA's understanding of the benefit-risk profile of devices at various points in their life cycle, and could potentially be valid scientific evidence used to aid FDA in regulatory decision making. See FDA's guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (82 FR 41418, August 31, 2017) (Ref. 4), which clarifies how FDA evaluates RWD to determine whether it may be sufficiently relevant and reliable to generate the types of RWE that can be used in FDA regulatory decision making for medical devices, including potentially generating valid scientific evidence.

In order to determine the suitability of RWD for regulatory decision making, FDA will assess the relevance and reliability of the source and its specific elements. This assessment will be used to determine whether the RWD source(s) and the proposed analysis can generate evidence that is sufficiently robust to be used for a given regulatory purpose. Whether evidence is sufficiently relevant and reliable for use will, in part, depend on the level of quality necessary to make a particular regulatory decision (Ref. 4). Although FDA received numerous comments to the proposed order of patient and healthcare professionals' experiences with CES devices, many of the comments did not include sufficient data sources as evidence for consideration of reclassification of CES devices intended for treatment of depression in finalizing this order.

III. Public Comments in Response to the Proposed Order

On January 22, 2016, FDA published in the *Federal Register* a proposed order to reclassify from class III to class II, subject to premarket notification, the CES devices intended to treat anxiety and/or insomnia and to require filing of a PMA for CES devices intended to treat depression. The comment period on the proposed order closed on April 21, 2016.

In response to the January 22, 2016, proposed order, FDA received over 300 comments from industry, professional societies, trade organizations, and individual consumers by the close of the comment period, each containing one or more comments on one or more issues.

We describe and respond to the comments in this section of the document. The comments are grouped based on common themes; we grouped similar comments together under the same number and listed them numerically. The number assigned to each group is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received. Please note that in some cases we separated different issues discussed by the same commenter and designated them as distinct comments for purposes of our responses.

(Comment 1) FDA received numerous comments in favor of the proposed reclassification of CES for treatment of anxiety and/or insomnia into class II with special controls.

(Response 1) Based on the consideration of the deliberation at the 2012 Panel meeting, valid scientific evidence, and review of relevant scientific articles and comments received in response to the 2016 proposed order, FDA continues to believe that CES devices intended to treat anxiety and/or insomnia should be reclassified from class III to class II (Refs. 1, 5, and 6), as initially specified in the proposed order. FDA has made this determination based upon an assessment (or, in some cases, reassessment) of the following sources of information: (1) published literature referenced in the Executive Summary to the 2012 Panel; (2) comments and literature received in public dockets including the call for safety and effectiveness information for all preamendments class III devices (74 FR 16214), the 2012 Panel (76 FR 6625, February 7, 2011), and the proposed order (81 FR 3751); and (3) review of medical device reports (MDRs) in the FDA Manufacturer and User Facility Device Experience (MAUDE) database. The

reevaluation of the scientific evidence presented to and discussed at the 2012 Panel meeting, and the review of additional post-2012 scientific information, further supports this finding. Based on the totality of this available evidence, FDA has determined that the designated special controls, together with general controls, mitigate the risks to health associated with use of CES for the specific indications of treating anxiety and/or insomnia and provide a reasonable assurance of safety and effectiveness, as initially specified in the proposed order. Table 1 identifies the risks associated with CES for treatment of anxiety and/or insomnia and the necessary mitigation measures by the required special controls. In this final order, FDA has included a non-substantive, clarifying edit in table 1 for the mitigation measures for skin irritation by changing "biocompatibility testing" to "biocompatibility evaluation" in table 1. As a result, FDA is adopting the special controls identified in the proposed order for CES devices for the treatment of anxiety and/or insomnia. Therefore, FDA has determined that the proposed special controls identified in this final order, in combination with general controls, provide a reasonable assurance of safety and effectiveness of CES for treatment of anxiety and/or insomnia.

FDA will also create a new product code for CES devices intended for the treatment of anxiety and/or insomnia.

Table 1.--Identified Risks to Health and Mitigation Measures for Treatment of Anxiety and/or Insomnia in CES Devices

Identified Risk	Mitigation Measures
Ineffective treatment	Clinical Performance Testing Non-clinical (bench) performance testing Characterization and Verification of technical Parameters Labeling
Skin irritation	Biocompatibility Evaluation Labeling
Headaches	Clinical Performance Testing Labeling
Dizziness	Clinical Performance Testing Labeling

Electrical shocks and burns	Electrical safety and electromagnetic compatibility testing Software verification, validation and hazard analysis

(Comment 2) Several comments opposed maintaining the classification of CES for the treatment of depression in class III and the call for PMAs for the following reasons: (1) there are little to no safety or effectiveness concerns; (2) maintaining the classification of CES for treatment of depression as class III is inconsistent with the statutory definition of class III because, among other things, it does not "present a potential unreasonable risk of illness or injury" based on valid scientific evidence available at the time of premarket clearance; (3) CES for treatment of depression may be addressed by requiring clinical performance data to support a premarket notification (510(k)); and (4) there is prevalence of comorbidity of anxiety disorders and depression that supports the reclassification of CES for treatment of depression to class II.

(Response 2) Based on the totality of evidence, including consideration of the deliberation at the 2012 Panel meeting, recent review of relevant scientific articles, and comments received in response to the 2016 proposed order (81 FR 3751), FDA continues to disagree with reclassification of CES for treatment of depression into class II. FDA has identified the following reasons for maintaining CES for the treatment of depression in class III and the call for PMAs:

(Response 2A) FDA disagrees that there are no safety or effectiveness concerns with reclassifying CES devices for treatment of depression into class II. As noted previously, the evidentiary standard FDA relies on to determine the safety and effectiveness of a device is valid scientific evidence as defined in § 860.7(c)(2). In finalizing this order, FDA has assessed the totality of the valid scientific evidence for treatment of depression that was discussed at the 2012 Panel meeting and provided in comments to the 2016 proposed order, including several

comments that referenced additional clinical studies. In addition, this assessment also included an updated analysis of the publicly available safety data in FDA's MAUDE database and an updated review of the literature.

For the treatment of depression, FDA concluded in the 2016 proposed order that there was insufficient information to establish special controls that, in addition to general controls, would provide reasonable assurance of safety and effectiveness of CES devices for treating depression (81 FR 3751 at 3760).

The Agency's previous literature assessment identified 12 papers that examined the effect of CES on measures of depression (6 Randomized Controlled Trials (RCT) and 6 observational studies). In most RCTs, depression levels did not differ significantly between patients who were treated with active CES compared to those treated with placebo (Refs. 7-11), although one randomized trial by Hearst et al. reported fewer depression symptoms in the active CES treatment versus placebo groups (Ref. 12). Of the six observational studies that were reviewed, four studies reported improvement in depression symptoms after treatment with CES (Refs. 13-16). Moore et al. also reported improvement in depression post- (versus pre-) CES treatment, but the findings were not statistically significant (Ref. 17). The observational study by Marshall et al. reported no difference in depressive symptoms between the CES and placebo arms (Ref. 18). Moreover, the observational study Marshall et al. reported no difference in depressive symptoms between the CES and placebo arms (Ref. 18).

Among the intended uses of insomnia, anxiety, and depression, the evidence supporting the effectiveness of CES for treating depression was the weakest. 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.

As of the date of this final order, there is still insufficient information to establish special controls that, in addition to general controls, will provide reasonable assurance of safety and effectiveness of CES devices for treating depression. FDA has reviewed all the scientific literature that was cited in comments submitted to the docket of the 2016 proposed order. While these articles had not been discussed specifically in the proposed order, FDA is clarifying that they are not-supportive to the reclassification of CES for treatment of depression. Specifically, these articles have significant shortcomings, such as lacking a well-controlled design (Ref. 19), lacking a diagnosis for eligibility (Ref. 20), having uncertain correlation with diagnostic criteria used in the United States (Ref. 21), containing an exclusion for unipolar depression (Ref. 22), lacking an appropriately matched control group (Ref. 23), and/or including studies that did not focus specifically on CES (Refs. 24 and 25). In one case, while FDA considered a reference supportive of reclassification for anxiety, there was insufficient information to support reclassification for depression because the two groups were not matched with respect to the

diagnosis (Ref. 26). Thus, these articles do not justify FDA changing the classification of CES devices intended for treatment of depression. Following the closure of the comment period for the 2016 proposed order, as part of the assessment of the current state of scientific evidence for CES devices, FDA also conducted an updated review of scientific literature. The search used a similar methodology as previous searches conducted in support of the preceding *Federal Register* orders, and the 2012 Panel meeting. As part of FDA's systematic identification of literature, FDA did not identify studies regarding the use of CES to treat depression as the primary diagnosis. However, FDA did identify four studies either where symptoms of depression were studied in populations of subjects where the primary diagnosis was not a psychiatric condition (Refs. 27 to 29), or where there was one single session administered to examine acute physiological changes only (Ref. 30). FDA evaluated these studies to determine whether they were designed to assess the use of CES to treat depressive disorders that are recognized by the clinical community as identified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, published 2013) (Ref. 31). FDA concluded that the four studies published after January 1, 2016, through November 1, 2019, did not contribute sufficient information in the form of valid scientific evidence to demonstrate that the subjects met the criteria for any recognized depressive disorder, as defined in DSM-5 (Ref. 31).

In addition, FDA conducted a review of adverse event reporting for CES devices since the publication of the proposed order. The FDA's MAUDE database search resulted in a total of three additional CES-related medical device reporting (MDRs) and one possibly pertinent to CES between January 1, 2016, and September 1, 2019. Two MDRs were injury reports submitted by voluntary reporters for a CES device manufacturer. A third MDR was a malfunction report submitted by a device manufacturer for an implanted intestinal stimulator and

noted concomitant use of an unspecified CES device and a fourth MDR report was used to "improve brain functioning" with a report of a third-degree burn. Although there are a low number of MDRs related to CES devices, the adverse reports for treatment of depression are only one factor (e.g., other factors may include the patient population targeted, alternative therapies) for FDA to consider in concluding that there is insufficient information to establish special controls that, in combination with general controls, will provide a reasonable assurance of safety and effectiveness of CES for the treatment of depression. FDA continues to believe that the risks to health identified 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. Thus, following the review of all the evidence presented, FDA has concluded that there is insufficient evidence to establish special controls that, in addition to general controls, will provide a reasonable assurance of safety and effectiveness for CES in treating depression. Accordingly, it is appropriate to maintain CES for treatment of depression in class III.

(Response 2B) FDA disagrees that maintaining the classification of CES for treatment of depression in class III is inconsistent with the statutory definition of class III. Section 513(a)(1)(C) of the FD&C Act (21 U.S.C. 360c(a)(l)(C)) defines class III, premarket approval as the following:

> (1) a device which because it 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, (2) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide a reasonable assurance of its safety and effectiveness, and 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 (3) presents a potential unreasonable risk of illness or injury.

Both class II and class III devices may present a potential unreasonable risk of illness or injury; however, the distinction is that devices in class II have sufficient evidence from which special controls can be established, in combination with general controls, that will provide a reasonable assurance of safety and effectiveness. As stated above, the CES proposed order indicated that there was insufficient evidence that would allow FDA to develop special controls that, in combination with general controls, would provide a reasonable assurance of safety and effectiveness of CES devices intended for treatment of depression, and FDA has determined that there is not sufficient new information that would satisfy that requirement to mitigate a potential unreasonable risk of illness or injury.

(Response 2C) Some comments stated that CES for treatment of depression can be addressed by requiring clinical performance data to support a premarket notification (510(k)). However, in order to classify CES into class II for the treatment of depression, it is necessary for the evidence to first exist that permits the establishment of special controls to provide a reasonable assurance of safety and effectiveness. As mentioned above, FDA has conducted an extensive review of scientific literature and such evidence was not available at the time of the proposed order, and there continues to be a lack of effectiveness data to mitigate a potential unreasonable risk of illness or injury for CES devices for treatment of depression. Furthermore, there is lack of sufficient evidence to support development of special controls that would provide a reasonable assurance of safety and effectiveness for CES devices in treating depression.

(Response 2D) A comment also stated that there is a prevalence of comorbidity of anxiety disorders and depression that supports the reclassification of CES for treatment of depression to class II. While the articles by Jansson-Frojmark et al. and Coplan et al. (Refs. 24 and 25) discuss this connection, they are not studies of CES (as mentioned above) (Refs. 24 and

25). The available evidence where CES was investigated in an anxiety population where depression was a comorbidity is Barclay et al. (Ref. 6). This study, which investigated the use of CES to treat primary anxiety, also included subjects with "comorbid depression" provided that a subject's anxiety was more severe than the depression (Ref. 6). However, the study does not clearly demonstrate that these subjects met the DSM 5 criteria for a recognized depressive disorder (Ref. 31). Therefore, the evidence is insufficient to enable FDA to establish a reasonable assurance of safety and effectiveness to support reclassifying CES devices intended for treatment of depression from class III to II.

(Comment 3) A few comments supported the proposal for a call for PMAs for treatment of depression because they believed there was a lack of valid scientific evidence to support the effectiveness of CES devices for treatment of depression.

(Response 3) FDA agrees with the comments to maintain the classification of CES for treatment of depression as class III. As stated in the preceding response, FDA has determined that there is a lack of sufficient evidence that would satisfy the requirement to mitigate "a potential unreasonable risk of illness or injury" to warrant the reclassification for depression into class II with special controls. As a result, there is insufficient evidence to establish special controls to provide a reasonable assurance of safety and effectiveness of CES devices for treatment of depression.

(Comment 4) One comment compared the reclassification of CES with that of Electroconvulsive Therapy (ECT) devices. Specifically, the commenter states that FDA's reclassification of ECT devices, which provide the largest amount of electricity, to class II should equate to reclassification of CES devices, which provide less electricity, as class I.

(Response 4) FDA disagrees with this commenter's comparison of ECT and CES devices. 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 published in the *Federal Register* (December 26, 2018, 83 FR 66103) 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. FDA also believes that general controls alone are insufficient to mitigate the risks to health of CES devices; therefore, the special controls are also needed to provide reasonable assurance of safety and effectiveness for CES devices intended for treating anxiety and/or insomnia.

(Comment 5) Several comments oppose the proposal to identify CES devices as prescription devices. Also, one comment opposes a prescription for treatment of depression and suggests that Federal and State laws mandate that physicians advise patients about CES before

prescribing psychiatric, sleeping and/or pain medications so that patients can make a reasonable decision and possibly reduce medication-induced mental health issues.

(Response 5) As stated in the proposed order, the CES device is a prescription only device for all three intended uses, i.e., anxiety, insomnia, and depression, and may not be safe for use except under the authorization of a healthcare professional licensed by law to administer the use of the device. As such, the device identification in § 882.5800(a) (21 CFR 882.5800(a)) has been revised to clarify that CES is a prescription device in accordance with 21 CFR 801.109. Per § 801.109(c), a prescription device must include labeling that describes the indications and other information for use, such as methods, frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions under which the healthcare professionals can use the device safely (see § 882.5800(b)). Accordingly, healthcare professionals will have access to and be aware of the warnings and precautions in the labeling, and as such, healthcare professionals should be adequately informed of the risks associated with these devices. The healthcare professional can inform the patients of the relevant risks. The warning and precaution statements are an appropriate mitigation for CES intended for the treatment of anxiety and insomnia.

(Comment 6) Several comments expressed the desire for insurance coverage to reduce the cost of the device.

(Response 6) FDA understands the concerns with cost and insurance coverage. However, FDA has no authority over commercial health insurance carriers. Under sections 513(e) and 515(i) of the FD&C Act, FDA has no authority to consider as part of a classification decision whether an indication or a device is covered by commercial health insurance companies. FDA

recommends that patients check with their insurance company regarding coverage before receiving CES treatment.

(Comment 7) One comment stated that a manufacturer's website of a currently marketed CES device includes misleading marketing material that may persuade consumers to use this device. The comment also claims that the marketed CES device is not effective.

(Response 7) FDA takes seriously any alleged claims of false or misleading claims by a device manufacturer. Several complaints have been received by the agency claiming that CES devices have not demonstrated effectiveness for treating anxiety and/or insomnia. FDA reviews all complaints and follows the appropriate steps to address complaints received. As a result, FDA continues to believe that the special controls proposed and finalized in this final order should include clinical performance data that demonstrates, among other things, that a CES device, when used as directed, will provide clinically meaningful results in the indicated patient population and provide a reasonable assurance of effectiveness for the intended use of CES devices for treating anxiety and/or insomnia. FDA also believes that a call for PMAs is appropriate for CES devices for treatment of depression to mitigate the potential unreasonable risk of illness or injury.

(Comment 8) One comment suggested FDA should not rely on the recommendations of the 2012 Panel because the meeting was not conducted properly due to the following alleged errors by FDA: (1) failure to include any panel members with the knowledge of or experience with CES devices; (2) failure to allow all interested parties ample time to present at the 2012 Panel; and (3) failure to provide adequate information by not presenting to the 2012 Panel for consideration the comments received from the proposed rule published in the *Federal Register* on August 8, 2011 (76 FR 48062), or articles of valid scientific evidence.

(Response 8) FDA believes the 2012 Panel was properly conducted based on the requirements under the FD&C Act. FDA also disagrees with the alleged errors stated for the following reasons.

First, FDA has specific procedures and protocols for all panel meetings that are followed to provide an objective outcome of the panel meetings. For more information, please refer to the FDA's Guidance, "Procedures for Meetings of the Medical Devices Advisory Committee" (Ref. 32). Also, FDA may exclude a healthcare professional from participating on an advisory committee if the person has a conflict of interest. Although a healthcare professional was excluded from the 2012 Panel, there was adequate representation of professionals with experience in using CES devices on the 2012 Panel. For more information on conflicts of interest as it relates to FDA advisory committees, please refer to the relevant FDA guidance entitled, "Public Availability of Advisory Committee Members' Financial Interest Information and Waivers" (Ref. 33).

Second, under section 513(b)(6)(A)(iii) of the FD&C Act, any person whose device is specifically the subject of review by a panel shall have the same opportunity as the Secretary to participate in meetings of the panel, including, subject to the discretion of the panel chairperson, by designating a representative who will be provided a time during the panel meeting to address the panel for the purpose of correcting misstatements of fact or providing clarifying information, and permitting the person or representative to call on experts within the person's organization to address such specific issues in the time provided. Furthermore, section 513(b)(6)(B) of the FD&C Act, before and after the enactment of the 21st Century Cures Act (Pub. L. 114-255), requires that meetings shall provide adequate time for initial presentations; and encourage free and open participation by all interested persons. FDA provided the appropriate allocated time

for all interested parties to speak or present at the 2012 Panel and for the 2012 Panel to consider their concerns with CES devices (Ref. 32).

Third, during the 2012 Panel, FDA's presentation included a listing of scientific articles (Refs. 1 and 2) and the 2011 proposed rule (76 FR 48062) with a summary of the comments received to the docket for the proposed rule. Therefore, the 2012 Panel members received sufficient information on the 2011 proposed rule and other information to make an informed decision on the classification of CES devices.

(Comment 9) Some comments questioned FDA's effectiveness claims for reclassification and suggested that more research is needed on CES before the device should be reclassified. One comment stated that the proposed order did not provide sufficient valid scientific evidence through tests to prove the effectiveness of CES for reclassification into class II because most of the studies conducted were inconclusive.

(Response 9) FDA disagrees with these comments. The proposed order acknowledged that no individual published study on CES provides definitive evidence of effectiveness of CES for the treatment of anxiety and/or insomnia. FDA noted, however, that in 18 of the 24 small published studies (those that enrolled fewer than 50 patients) that included assessments of anxiety and/or insomnia, each study had a main finding that indicated a greater benefit of CES versus control for at least 1 of the outcome measures evaluated. Furthermore, CES treatment group outcomes improved in all large published studies (although not all studies demonstrated improvement compared with control patients), including two studies identified after the 2012 Panel (Refs. 5 and 6). Based on the available information, the proposed order concluded that there is valid scientific evidence of effectiveness for CES in the treatment of anxiety and/or

insomnia. Since the proposed order was published, FDA has not become aware of new information that changes this position.

Importantly, however, FDA acknowledges that because different CES devices were evaluated and the methodology of CES delivery (e.g., electrode placement, stimulation parameters, duration and frequency of treatment sessions) varied, the data are insufficient to determine the technical performance parameters, adequate directions for use, and warnings for unsafe use for specific devices, and whether the devices, when used in accordance with such directions, will provide clinically meaningful results. As explained in the proposed order, although the evidence available to FDA collectively demonstrates a class effect of CES devices for treating anxiety and/or insomnia, it cannot be concluded, based on available information alone, that specific CES devices will be effective for treating anxiety and/or insomnia. As a result, FDA believes that the special controls must include clinical performance data that demonstrates that a device, when used as directed (including instructions for electrode placement, stimulation parameters, duration and frequency of treatment sessions, and other relevant characteristics), will provide clinically meaningful results in the indicated patient population and provide a reasonable assurance of safety and effectiveness for the intended use of CES devices for treating anxiety and/or insomnia.

(Comment 10) One comment recommended that FDA should obtain valid scientific evidence which supports that Central Nervous System (CNS) disorders are treatable with the use of CES.

(Response 10) The category of "CNS disorders" is very broad, while the classification of CES devices is only based on the treatment of anxiety, insomnia and/or depression, as they are the only indications that have been currently allowed for marketing authorization; therefore,

valid scientific evidence for all CNS disorders are not relevant for this reclassification. This final order does not address the treatment of broader CNS disorders as they are outside the scope of this final order. Manufacturers seeking to indicate a device for a specific CNS disorder would be responsible for the collection of any valid scientific evidence that may be necessary to support a new indication for marketing CES devices.

(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.

IV. The Final Order

Based on the information discussed in the preamble to the proposed order (81 FR 3751), the comments received for the proposed order, a review of medical device reports in the FDA MAUDE database, a review of current scientific literature, and 2012 Panel deliberations (Ref. 1), FDA concludes that special controls, in conjunction with general controls, will provide reasonable assurance of the safety and effectiveness of CES devices intended for treatment of anxiety and/or insomnia. Under sections 513(e), 515(b), and 515(i) of the FD&C Act, FDA is adopting its findings, as published in the preamble to the proposed order. For the reasons described in section III, FDA is issuing this final order to reclassify CES devices intended for treatment of anxiety and/or insomnia from class III to class II (special controls). CES devices intended to treat anxiety and/or insomnia must comply with the special controls following the

effective date of the final order. However, FDA does not intend to enforce compliance with the special controls for currently legally marketed CES devices intended to treat anxiety and/or insomnia until 1 year after the effective date of the final order.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For the CES devices classified as class II (i.e., for treatment of anxiety and/or insomnia), FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the device they intend to market.

FDA is also requiring the filing of a PMA for CES devices intended for the treatment of depression under section 515(b) of the FD&C Act. Under section 515(b)(1)(A) of the FD&C Act, PMAs for CES devices are required to be filed on or before 90 days after the effective date of a final order.

V. Implementation Strategy

A. Date to File a PMA

In accordance with section 515(b) of the FD&C Act, CES devices intended to treat depression must have a PMA or a notice of completion of PDP filed with the Agency by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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 provided that the PMA is timely filed. For currently legally marketed CES devices intended to treat depression, FDA does not intend to enforce compliance with this 90-day requirement for an additional 90 days (i.e., 180 days after the effective date of any final order), as long as notice of intent to file a PMA is submitted within 90 days of the effective date of the final order. The notification of the intent to file a PMA submission should include a list of all model numbers for which a manufacturer plans to seek marketing approval through a PMA. FDA does not intend to enforce compliance with the PMA requirements with respect to an applicant of a currently legally marketed CES device intended to treat depression during FDA's review of the PMA. FDA intends to review any PMA for the device within 180 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that "the continued availability of the device is necessary for the public health." If a PMA for a class III device is not filed with FDA by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], the device will be deemed adulterated under section 501(f) of the FD&C Act. Table 2 shows the regulatory timetable for currently legally marketed CES devices intended to treat depression.

Table 2.--Timetable for CES Devices Intended to Treat Depression

	Timetable for Which FDA Does Not Intend to Enforce Compliance (Time After Effective Date of Final Order)	Distribution Period (Time After Effective Date of Final Order)
Intent to file a PMA	90 days	Devices included in an intent to file: 180 days.
File a PMA	Devices included in an intent to file: 180 days Devices not included in an intent to file: 90 days	Until a not approvable decision or denial decision is issued; can continue distribution if an approval order is issued.

Under § 812.2(d), the exemption from the requirements of the IDE regulations for preamendments class III devices in § 812.2(c)(1) and (2) will cease to apply to CES devices indicated for depression that are: (1) not legally on the market on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN *THE FEDERAL REGISTER*] or (2) legally on the market on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] but for which a PMA or notice of completion of a PDP is not filed by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], or for which PMA approval has been denied or withdrawn.

The device may be distributed for investigational use only if the requirements of the IDE regulations are met. The requirements for significant risk devices include submitting an IDE application to FDA for its review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to avoid interrupting investigations. There will be no extended period for filing an IDE nor exemption from IDE requirements, and studies may not be initiated without appropriate IDE approvals, where necessary.

B. Compliance with Special Controls

Following the effective date of this final order, CES devices intended to treat anxiety and/or insomnia must comply with the special controls. FDA notes that a firm whose CES device was legally in commercial distribution before May 28, 1976, or whose device was found to be substantially equivalent to such a device and who does not intend to market such device for

uses other than to treat insomnia and/or anxiety, may remove such intended uses from the device's labeling.

The special controls identified in this final order are effective as of the date of publication of this order, [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. CES devices intended to treat anxiety and/or insomnia must comply with the special controls following the effective date of this order. However, FDA does not intend to enforce compliance with the special controls for currently legally marketed CES devices intended to treat anxiety and/or insomnia until 1 year after the effective date of the final order. Manufacturers who wish to continue to legally market a CES device for treatment of anxiety and/or insomnia must submit an amendment to their previously cleared 510(k) that demonstrates compliance with the special controls by [INSERT DATE 365 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Such amendment will be added to the 510(k) file but will not serve as a basis for a new substantial equivalence review. A submitted 510(k) amendment in this context will be used solely to demonstrate to FDA that a CES device is in compliance with the special controls. If a 510(k) amendment is not submitted by [INSERT DATE 365 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] or if FDA determines that the amendment does not demonstrate compliance with the special controls, then this compliance policy would not apply, and FDA would intend to enforce compliance with these requirements. In that case, the device is deemed adulterated under section 501(f)(1)(B) of the FD&C Act as of the date of FDA's determination of noncompliance or 1 year after the effective date of the final order, whichever is sooner.

For models of CES devices intended to treat anxiety and/or insomnia that have not been legally marketed prior to [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*],

or models that have been legally marketed but are required to submit a new 510(k) under § 807.81(a)(3) because the device is about to be significantly changed or modified, manufacturers must obtain 510(k) clearance, among other relevant requirements, and demonstrate compliance with the special controls included in the final order, before marketing the new or changed device.

VI. Codification of Orders

Sections 513(e) and 515(b), as amended by FDASIA, and 515(i) of the FD&C Act require FDA to issue final orders rather than regulations to reclassify devices. Therefore, FDA will continue to codify reclassifications and requirements for approval of an application for premarket approval, resulting from changes issued in final orders, in the Code of Federal Regulations. Accordingly, under sections 513(e)(1)(A)(i) and 515(b) of the FD&C Act, as amended by FDASIA and FDA's Medical Device Classification Procedures final rule (83 FR 64443), in this final order, we are codifying the amendment of § 882.5800 by: (1) revoking the requirements in § 882.5800(b) and (c) related to the classification of CES devices intended to treat anxiety and/or insomnia as class III devices and codifying the reclassification of CES devices intended to treat anxiety and/or insomnia to class II (special controls); (2) retaining the requirements in § 882.5800(b) and (c) related to the classification of CES devices intended to treat depression as class III devices subject to the requirement of approval of an application for premarket approval, as described in section IV; and (3) clarifying the device identification of CES devices to include it as a prescription device.

VII. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act of 1995

This final order refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in part 807, subpart E, have been approved under OMB control number 0910-0120. The collections of information in part 812 have been approved under OMB control number 0910-0078. The collections of information in 21 CFR part 814, subparts A through E have been approved under OMB control number 0910-0231. The collections of information in part 801 have been approved under OMB control number 0910-0485. The collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073.

IX. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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List of Subjects in 21 CFR Part 882

Medical devices, Neurological devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 882 is amended as follows:

PART 882--NEUROLOGICAL DEVICES

1. The authority citation for part 882 continues to read as follows:

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

2. Revise § 882.5800 to read as follows:

§ 882.5800 Cranial electrotherapy stimulator.

(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.

(b) *Classification*. (1) Class II (special controls) when intended to treat insomnia and/or anxiety. The special controls for this device are:

(i) A detailed summary of the clinical testing pertinent to use of the device to demonstrate the effectiveness of the device to treat insomnia and/or anxiety.

(ii) Components of the device that come into human contact must be demonstrated to be biocompatible.

(iii) The device must be designed and tested for electrical safety and electromagnetic compatibility (EMC) in its intended use environment.

(iv) Appropriate software verification, validation, and hazard analysis must be performed.

(v) The technical parameters of the device, including waveform, output mode, pulse duration, frequency, train delivery, maximum charge, and energy, must be fully characterized and verified.

(vi) The labeling for the device must include the following:

(A) The intended use population and the intended use environment;

(B) A warning that patients should be monitored by their physician for signs of worsening;

(C) A warning that instructs patients on how to mitigate the risk of headaches, and what to do should a headache occur;

(D) A warning that instructs patients on how to mitigate the risk of dizziness, and what to do should dizziness occur;

(E) A detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device;

(F) Instructions for use that address where to place the electrodes, what stimulation parameters to use, and duration and frequency of treatment sessions. This information must be based on the results of clinical studies for the device;

(G) A detailed summary of the device technical parameters, including waveform, output mode, pulse duration, frequency, train delivery, and maximum charge and energy; and

(H) Information on validated methods for reprocessing any reusable components between uses.

(vii) Cranial electrotherapy stimulator devices marketed prior to the effective date of this reclassification must have an amendment submitted to the previously cleared premarket notification (510(k)) demonstrating compliance with these special controls.

(2) Class III (premarket approval) when intended to treat depression.

(c) Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], for any cranial electrotherapy stimulator device with an intended use described in paragraph (b)(2) of this section, that was in commercial distribution before May 28, 1976, or that has, on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], been found to be

substantially equivalent to any cranial electrotherapy stimulator device with an intended use described in paragraph (b)(2) of this section, that was in commercial distribution before May 28, 1976. Any other cranial electrotherapy stimulator device with an intended use described in paragraph (b)(2) of this section shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: December 13, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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