4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA-2014-N-1210]

Neurological Devices; Reclassification of Electroconvulsive Therapy Devices; Effective Date of Requirement for Premarket Approval for Electroconvulsive Therapy Devices for Certain Specified Intended Uses

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to reclassify the electroconvulsive therapy (ECT) device for use in treating catatonia or a severe major depressive episode (MDE) associated with major depressive disorder (MDD) or bipolar disorder (BPD) in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition, which is a preamendments class III device, into class II (special controls). 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 the preamendments class III ECT devices for all other uses that are not being reclassified to class II (product code GXC).

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

Table of Abbreviations and Acronyms

Abbreviation or Acronym	What It Means
510(k)	Premarket Notification
2011 Panel	2011 Neurological Devices Panel Meeting
AACAP	American Academy of Child and Adolescent Psychiatry
APA	American Psychiatric Association
BPD	Bipolar Disorder
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement scale
ECT	Electroconvulsive Therapy Device
FDA	Food and Drug Administration
FDARA	FDA Reauthorization Act of 2017
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FR	Federal Register
IDE	Investigational Device Exemption
MAUDE	Manufacturer and User Facility Device Experience
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDR	Medical Device Reporting
M-ECT	Maintenance ECT
MMSE	Mini Mental State Exam
OMB	Office of Management and Budget
PDP	Product Development Protocol
PMA	Premarket Approval Application
PRA	Paperwork Reduction Act of 1995
Ref.	Reference
RWD	Real-World Data
RWE	Real-World Evidence
SE	Safety and Effectiveness
U.S.C.	United States Code
WFSBP	World Federation of Societies of Biological Psychiatry

II. Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 (SE). 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 regulation classifying the device; and (3) published a final 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)[1] are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. 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).

[1] ECT devices with intended uses outside the scope of those listed in paragraphs 21 CFR 882.5940(b)(1) and (2) are considered postamendments device, 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.

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.

On August 18, 2017, section 513(f) of the FD&C Act was amended by the FDA Reauthorization Act of 2017 (FDARA; Pub. L. 115-52). Under section 513(f)(6) of the FD&C Act, FDA has authority to issue an administrative order classifying an accessory based on the risks of the accessory when used as intended and the level of regulatory controls necessary to provide a reasonable assurance of SE of the accessory, notwithstanding the classification of any other device with which such accessory is intended to be used. FDA's "Medical Device Accessories--Describing Accessories and Classification Pathways" guidance describes the statutory mechanisms to request: (1) classification for accessories that have been granted marketing authorization as part of a PMA, premarket notification (510(k)), or De Novo request for another device with which the accessory involved is intended to be used and (2) classification for accessories included in a PMA or 510(k) that FDA has not classified distinctly from another device under the FD&C Act (Ref. 1).

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 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 SE, but for which there is sufficient information to establish special controls to provide a reasonable assurance of SE of a device.

FDA published a proposed order in the *Federal Register* of December 29, 2015 (80 FR 81223), held a meeting of a device classification panel on January 27-28, 2011, as described in section 513(b) of the FD&C Act with respect to ECT devices, and considered comments from public dockets, and, therefore, has met the requirements under sections 515(i)(2) of the FD&C Act.

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. As noted above, FDA has published a proposed order that would require PMAs for an electroconvulsive therapy device for certain uses other than a severe MDE associated with MDD or BPD, in the *Federal Register* of December 29, 2015. FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to ECT devices. Finally, FDA has received and has considered over 3,400 comments on the proposed order, as

discussed in section II. 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 section 515(b) of the FD&C Act, changing the mechanism for requiring premarket approval for a preamendments device from rulemaking to an administrative order.

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) of the FD&C Act (21 U.S.C. 351(f)), 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 ECT devices were classified in 1979, the 30-month period has expired (44 FR 51776, September 4, 1979), and the later of these two time periods is the 90-day period. Therefore, if a PMA is not filed for ECT devices for certain specified intended uses within 90 days after the issuance of a final order, the device will be deemed adulterated under section 501(f) of the FD&C Act.

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 part

812 (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. 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. 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 SE 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 that was provided in response to the proposed order, including several comments that referenced additional clinical studies. Several of these studies included SE data for adult as well as adolescent patients. FDA also considered randomized controlled clinical studies, open-label observational trials, case series reports, systematic literature reviews, and practice guidelines 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.

FDA received many comments from healthcare professionals describing their practices, the length of time they have been practicing, and the utilization of ECT devices in treating patients with certain conditions. While FDA acknowledges receiving comments in support of the proposed reclassification, statements by individual healthcare professionals that they have used ECT devices to treat individual patients do not constitute valid scientific evidence to demonstrate reasonable assurance of SE (see valid scientific evidence discussion in 48 FR 56778 at 56786-56788, comments 16-21, December 23, 1983, Ref. 2). 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 judgement.

FDA also received many comments from patients, or friends and family of patients, in support and against reclassification of ECT devices. These comments described the experience of the patient that received treatment from an ECT device. FDA acknowledges receiving comments from patients and other individuals about their experience with the device being considered for reclassification; however, FDA does not consider such comments to be valid scientific evidence. Because these comments did 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 judgement, such comments are not considered valid scientific evidence.

For medical devices, available evidence is traditionally comprised 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. 3), 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 identifying a device, the SE of which is questionable, § 860.7(c)(2) also explains random experience and reports lacking sufficient details to permit scientific evaluation may be considered valid scientific evidence. Such random experience and reports lacking sufficient details to permit scientific evaluation may be early and sometimes informal indications of the danger or ineffectiveness of a device (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.

III. Public Comments in Response to the Proposed Order

On December 29, 2015, FDA published a proposed order to reclassify from class III to class II the ECT device for use in treating a severe MDE associated with MDD or BPD in patients 18 years of age and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition and to require the filing of a PMA for

ECT devices for the intended uses of schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia. The comment period on the proposed order closed on March 28, 2016.

In response to the December 29, 2015, proposed order, FDA received over 3,400 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 over 3,400 comments are grouped based on the common themes listed below. We have grouped similar comments together under the same number and numbered them sequentially.

A. Comments in Support of Reclassifying ECT into Class II (Comments 1-2)

B. Comments on Reclassifying ECT Based on Safety and Effectiveness (Comments 3-9)

C. Comments on Patient Concerns (Comments 10-16)

D. Comments on Regulatory Process of the Proposed Order (Comments 17-23)

E. Comments on Labeling Concerns (Comments 24-29)

F. Comments Outside the Scope of this Final Order (Comments 30-34)

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. 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.

In the proposed order we asked interested persons to submit comments on two specific questions. FDA sought comments on whether: (1) the term "treatment resistant" and the phrase "require rapid response" provide sufficient clarity to the population for which ECT benefits outweigh risks and (2) if 60 days is an appropriate time to allow existing manufacturers who do

not intend to market their ECT device(s) for uses other than use in treating severe MDE associated with MDD and BPD in patients 18 years of age and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition to prepare and submit 510(k) amendments for ECT devices. FDA continues to believe the term "treatment resistant" and the phrase "require rapid response" provide sufficient clarity to the population for which ECT benefits outweigh risks. Because there were no comments submitted on the second question, FDA's discussion of when 510(k) holders should submit an amendment to a 510(k) is in section V.B., Compliance with Special Controls, of this final order.

A. Comments in Support of Reclassifying ECT into Class II

(Comment 1) FDA received many comments generally supporting the proposed reclassification to class II. Comments included many literature references including references published since the 2011 Neurological Devices Classification Panel meeting (the 2011 Panel). Several comments noted that ECT had been used safely and effectively in their practice or on themselves as a patient or on a family member or a friend.

(Response 1) After examination of the totality of the scientific evidence, FDA continues to believe that there is sufficient evidence to establish special controls that, together with general controls, provide a reasonable assurance of SE to reclassify ECT to class II for use in treating a severe MDE associated with MDD or BPD, as initially specified in the proposed order. In addition, FDA has determined that there is adequate support for the reclassification of ECT into class II for the treatment of catatonia and expanding the adolescent age subpopulation from 18 to 13 years of age. FDA has made this determination based upon a reassessment of the following sources of information: (1) published literature referenced in the Executive Summary to the 2011 Panel; (2) comments and literature received in public dockets including the call for SE

information for all preamendments class III devices (74 FR 16214, April 9, 2009), the call for ECT SE information in a separate docket (74 FR 46607, September 10, 2009), the 2011 Panel (75 FR 72832, November 26, 2010), the ECT Draft Guidance (80 FR 81330, December 29, 2015) and the proposed order (December 29, 2015) (these five dockets are to be referred to as "ECT public dockets" in this document, discussed below in response 2); (3) clinical practice guidelines; and (4) 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 2011 Panel meeting, and the review of additional post-2011 scientific information that was provided to FDA in comments to the proposed order, further supports this finding.

(Comment 2) Several comments supported the reclassification of ECT to class II for a severe MDE associated with MDD or BPD, but said the reclassification was too restrictive in its scope. Several additional indications, many of which are outside the scope of this classification effort, were mentioned. Comments suggested that classification should be expanded to some or all of the following indications and populations (ordered alphabetically):

- Adolescents
- Adolescents and children
- Autism
- Catatonia
- Delirium
- Delusional disorders
- Developmental disability
- Maintenance or continuation ECT

- Mania in BPD
- Mania--refractory, intractable, acute
- Neuroleptic malignant syndrome
- Other psychiatric disorders and conditions for which ECT has been used
- Parkinson's disease
- Patients with contraindications to drug treatment including women who are pregnant/nursing, the elderly, or those who have comorbid conditions
- Psychosis--treatment resistant, puerperal
- Schizophrenia--clozapine resistant, refractory
- Schizoaffective disorder
- Severe self-injurious behavior
- Shy-Drager syndrome
- Status epilepticus
- Suicidal patients

(Response 2) As part of the review of the public comments received in response to the proposed order, FDA considered over 400 scientific articles cited in comments or attached to comments filed in the ECT public dockets. Many of the scientific articles included information not within the scope of this order; however, some of the articles included studies that investigated the SE of ECT for catatonia, mania, schizophrenia, and schizoaffective disorder, and use of ECT in children, adolescents, and adults, which are indications within the scope of this final order. Many of these articles also provided information on research published since 2010, after the literature review was conducted for the 2011 Panel on classification of ECT devices.

Of the information submitted in response to the proposed order, FDA reviewed many articles containing valid scientific evidence regarding the SE of ECT for certain intended uses, which are within the scope of this reclassification effect, including catatonia and severe MDE associated with MDD or BDP for the indicated populations. In addition, 29 articles referenced in the ECT public dockets contain valid scientific evidence on the SE of ECT in the adolescent subpopulation (patients age 13 years to less than 18 years). The sections below further discuss FDA's review of this evidence and conclusions.

Based on evaluation of this evidence, FDA is including in the final order to reclassify ECT the indication of catatonia for patients who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition in addition to treating a severe MDE (associated with MDD or BPD). FDA believes that the totality of evidence supports the determination that the special controls identified in this final order, along with general controls, are sufficient to provide a reasonable assurance of SE for these indications. For the other indications cited in the ECT public dockets that are within the scope of this classification effort, FDA has concluded that there was insufficient scientific evidence to support reclassification.

Several comments posted to the ECT public docket in response to the proposed order, including comments from professional societies and organizations, physicians, and other ECT practitioners, were supportive of a class II recommendation for catatonia or a severe MDE associated with MDD or BPD in adolescents, and in some cases, younger children. While ECT devices are historically cleared with no specific age indicated, the proposed order for ECT recommended that the indications for use be limited to use of the device in patients 18 and above. Consistent with the cleared indications, FDA's Executive Summary for the 2011 Panel to

discuss reclassification did not include a review on the use of ECT in different age groups; however, substantive comments were provided during the open public hearing section both for and against the use of ECT in children and adolescents (Ref. 4). In response to the comments recommending expansion of the age range of adolescent patients, under section 515(i)(2) of the FD&C Act, FDA assessed the articles submitted in the ECT public dockets (sources of information listed in response to Comment 1 above) to evaluate the SE evidence supporting the use of ECT in younger populations (i.e., children and adolescents).

FDA evaluated ECT use in treating a number of psychiatric or medical conditions (e.g., a severe MDE associated with MDD or BPD, catatonia, schizophrenia, schizoaffective disorder, and mania) in these younger populations. Limited experience and only a few reports were available for patients less than and including 12 years of age (i.e., children). The majority of studies focused on catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older. For those studies that did report clinical outcomes in adolescent patients, results were generally favorable in treating catatonia or a severe MDE associated with MDD or BPD. Treatment approaches (i.e., electrode placement, administration, and safeguards) were similar between adult and adolescent subpopulations. As such, the literature provided in the ECT public dockets supports a reclassification to class II for the use of ECT in treating catatonia or a severe MDE associated with MDD or BPD, for patients age 13 years and older who are treatment-resistant and who require a rapid response due to the severity of their psychiatric or medical condition, with the establishment of special controls (discussed in more detail below in section III.A.3). FDA's evaluation is based on a reassessment of the published literature referenced in the Executive Summary to the 2011 Panel, comments and literature received in the ECT public dockets, and review of the 2011 Panel meeting transcript.

Based upon FDA's review of the scientific literature submitted in the comments received in the ECT public dockets, and an assessment of the totality of the evidence, FDA is reclassifying ECT devices for a broader population than identified in the proposed order. The reassessment of evidence including scientific articles are organized into four subsections consisting of: (1) safety of ECT in treating catatonia or a severe MDE associated with MDD or BPD; (2) effectiveness of ECT for catatonia; (3) effectiveness of ECT for patients 13 years and older; and (4) effectiveness of ECT for schizophrenia, schizoaffective disorder, and mania. The specific indications within the scope of this final order include only those for which FDA has cleared 510(k) submissions. In this summary, we do not include isolated case reports.

1. Safety of ECT in Treating Catatonia or a Severe MDE Associated with MDD or BPD

Overall, the published literature provided since 2010 in the comments received in the ECT public dockets and reviewed by FDA provided information on over 1,000 patients, and included information regarding ECT treatment outcomes in adults, adolescents, and children. The reviewed published literature included prospective and retrospective studies, randomized patient treatment schedules (e.g., number of treatments per week), and either administered unilateral or bilateral stimulation. The majority of studies reported the safe use of ECT with minimal and reversible adverse events, and in some cases, patient memory and mood improved while treating catatonia or a severe MDE associated with MDD or BPD; positive results included outcomes in both adults and adolescent subpopulations. Six studies (Refs. 5-10) provided detailed safety data on patients (N=609) for review and further discussion below.

Fernie et al. (Ref. 5) conducted a retrospective study to evaluate the persistence of cognitive side effects of ECT in a retrospective case study of 126 patients treated with ECT between June 2010 and October 2012 at the Royal Cornhill Hospital, Aberdeen, Scotland.

Results from validated longitudinal neuropsychological tests (the Cambridge Neuropsychological Test Automated Battery spatial recognition memory test (CANTAB)) and subjective reports of memory function showed that while the performance was poorer compared with baseline for tests administered up to 3 months following completion of ECT therapy, these effects were transient and improved at 6 months. In some cases, mood and subjective memory scores improved following ECT. The Mini Mental State Exam (MMSE) demonstrated improvement over baseline starting from 1 month following therapy. Overall, the application of ECT had reversible cognitive deficiencies compared to pre-ECT treatment scores, a measure of safety, and in some assessments (CANTAB, subjective reports of memory function, and MMSE) showed patient improvement.

Kirov et al. (Ref. 6) conducted a retrospective review of 10 years of cognitive performance data that included 199 patients and 500 assessments. Cognitive testing consisted of a battery of nine tests including backward digit span, word, shape, and face recognition, verbal fluency, complex figure immediate recall, and trail making. Not all subjects were capable of performing all tests and parts of the battery changed over time. Results (linear mixed regression analyses) demonstrated that age, severity of depression at the time of testing, and number of days since the last ECT session were the major factors affecting cognitive performance, but the total number of previous ECT sessions did not have a measurable impact on cognitive performance, which further supports the safety of ECT in not leading to cumulative cognitive deficits.

Maric et al. (Ref. 7) prospectively studied 30 patients with MDD at baseline, shortly after ECT treatment, and at 1 month post treatment using the learning and visual, spatial, and figural memory tests of CANTAB. Severity of depressive symptoms as measured by healthcare professional-rated and self-rated instruments was significantly reduced over time with treatment,

as a measure of the effectiveness of ECT. At the same time, the neuropsychological tests did not detect any significant memory impairment and showed improvement on visual memory and learning at 1 month and in the immediate post-treatment period, indicating no prolonged or significant ECT-related memory deficits. These improvements correlated with improvement in depression while serious adverse events were not reported.

Spaans et al. (Ref. 8) compared unilateral brief pulse ECT with unilateral ultra-brief pulse ECT for the treatment of major depression. In this double-blind randomized study conducted in 3 tertiary psychiatric hospitals in the Netherlands, 116 patients entered the study and of those, 87 completed the study (until remission or 12 treatments). Seventy-six (n=76) patients were available with pre- and post-ECT assessments. Blinded cognitive assessment was done before ECT treatment was started and again within 2 days to a week after all treatments were completed. Patients on average received about eight treatments (average 7.1 in the brief pulse group vs. 9.2 in the ultra-brief pulse group). To assess cognitive function, several neuropsychological tests were administered including the Autobiographical Memory Interview and the Amsterdam Media Questionnaire, which is a public event questionnaire with questions grouped by decade about events from the decades of the 1970s through the 2000s. Other cognitive domain tests were also conducted. No significant difference was seen in retrograde amnesia between the two treatment groups. Change in recall performance and fluency tests were also similar between the two groups. There was not a significant difference in performance in the cognitive tests following ECT for any of the cognitive tests during the course of study. The authors also reported mitigating adverse effects on cognition by lengthening the time between treatments to provide patients with more time to recuperate, thereby further characterizing how ECT treatment can be applied safely.

Semkovska et al. (Ref. 9) prospectively studied 138 patients with major depressive episodes who were treated in a national ECT study in which patients were randomly assigned to receive bitemporal (69 patients) or right-side unilateral ECT (69 patients). This study included 3-month and 6-month followup assessments. Adverse events were similar for the unilateral and bitemporal groups. Following treatment, headache was the most commonly reported adverse physical effect (approximately 27 percent of subjects). Nausea (approximately 14 percent), and muscle pain (approximately 10 percent) were also reported. Significant acute adverse events associated with treatment included six patients (4 unilateral, 2 bitemporal) who experienced ECT related hypertension. Also, one patient developed laryngospasm with temporary drop in oxygen saturation, one patient required treatment for sinus tachycardia, one patient developed bradyarrhythmia, and one patient developed a pulmonary embolus after the fifth treatment. No adverse events required patients to discontinue the study, thereby enabling patients to continue treatment. Positive responses to the treatments were seen in both treatment groups.

Ghaziuddin et al. (Ref. 10) conducted a retrospective study of 16 adolescents treated for depression with ECT. Cognitive tests before ECT treatment were compared to tests administered an average of 7 days following completion of the ECT treatment (immediate testing) and again at an average of 8.5 months following completion of ECT treatment. The comparison of pre-ECT and the immediate post-ECT testing demonstrated significant impairments of concentration and attention, verbal and visual-delayed recall, and verbal fluency. A complete recovery of these functions was noted in the cognitive testing conducted at 8.5 months. There was no deficit in the ability to problem solve during the initial or the subsequent testing. Cognitive parameters found to be impaired during the first few days of ECT were recovered over several months following the treatment. Therefore, there was no evidence of long-term damage to concentration, attention,

verbal and visual memory, or verbal fluency. There were also no impairments of motor strength and executive processing, even during the early (within 7 to 10 days) post-ECT period.

Considering the studies summarized above as well as the additional literature referenced in the ECT public dockets and the deliberation of the 2011 Panel, there is sufficient scientific evidence demonstrating, with the establishment of special controls in combination with general controls, a reasonable assurance of the SE for the use of ECT in treating a severe MDE associated with MDD or BPD and safety for treating catatonia in patients who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition (see effectiveness of ECT for catatonia discussion in following subsection). ECT in the indicated populations provides a treatment option for serious diseases where other treatments are less or minimally effective. Based on the totality of available evidence, FDA has determined that the designated special controls mitigate the risks associated with use of ECT in this patient population and provide a reasonable assurance of SE.

2. Effectiveness of ECT for Catatonia

The 2011 Panel was evenly split regarding their recommendation for the reclassification of the use of ECT for catatonia. Several members of the 2011 Panel who recommended class II for catatonia pointed out that this psychiatric disorder is among the most severe and potentially life-threatening and requires a rapid response.

In the public comments in response to the proposed order, 24 published articles were submitted as attachments related to the use of ECT for catatonia. Of these, 14 were published after FDA's systematic literature review performed for the 2011 Panel meeting (Refs. 11-25). As was the case at the 2011 Panel, there remain no randomized controlled trials of ECT in catatonia. The articles published after the 2011 Panel are primarily case series reports,

retrospective chart reviews, and systematic literature reviews. All the studies reported on patient outcomes, with the majority of studies reporting favorable SE data.

The systematic review from 2015 by Luchini et al. (Ref. 18) identified 8 retrospective or observational studies that included at least 10 or more subjects. Collectively, these 8 studies represented 346 catatonic patients who received ECT. Response rates ranged from 80 percent to 100 percent. Rates for adverse events were not provided, but with regard to safety, the authors cite the transient cardiovascular events that need to be monitored and managed, including parasympathetic mediated bradycardia or temporary asystole and post-seizure sympathetic stimulation that can lead to sinus tachycardia, bigeminy or trigeminy, or ventricular arrhythmia in as many as 80 percent of patients with known cardiovascular risk. Other risks are those associated with administration of anesthesia in a catatonic patient. These side effects are generally transient and resolve without adverse sequelae.

A noteworthy series of the case series reports (Refs. 19 and 20) all consistently found ECT to be very effective for the treatment of catatonia with relatively few adverse events reported in the treated patients. Given the clinical presentation of patients with catatonia, including the lack of verbal and motor response due to the etiology of the disease, the positive clinical outcome is unlikely to be susceptible to placebo effects; therefore, FDA believes the well-documented case series and open-label trials for the use of ECT in catatonia support the recommendation to include catatonia in class II.

The valid scientific evidence evaluated has enabled FDA to determine that ECT for catatonia can be classified as class II because general controls, in combination with special controls, are sufficient to provide a reasonable assurance of SE. Based on a review of the published literature to date, the recommendations from the 2011 Panel meeting, and comments

received in the ECT public dockets, FDA has determined that sufficient evidence exists to establish special controls and support a revision of the proposed classification of ECT for the treatment of catatonia to class II. ECT for catatonia presents the same types of risks to health and would be subject to the same types of special controls identified for 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. Further, clinical guidelines for schizophrenia published in 2012 from the World Federation of Societies of Biological Psychiatry (WFSBP) (Ref. 26) recommend consideration of ECT for catatonia as an alternative when rapid resolution is necessary or when an initial trial of benzodiazepines has failed. Therefore, instead of calling for PMAs for ECT devices for the treatment of catatonia, FDA has satisfied the requirements under section 515(i)(2) of the FD&C Act for revising the proposed classification from class III to class II (special controls) following reassessment of the published literature referenced in the Executive Summary to the 2011 Panel, and comments and literature received in the ECT public dockets.

3. Age Limitations on Adolescent Subpopulation for use of ECT

In the 2015 proposed order, FDA proposed that ECT devices should be classified as class II (special controls) when used for treating adults and adolescents 18 years and older with a severe MDE associated with MDD or BPD, who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. In response to the proposed order, public comments included submission of 29 articles regarding the use of ECT in children and adolescents. Some of these comments recommended the age for using ECT should be lower than 18 years of age. Half of these articles (Refs. 13-17, 21, 25 and 27-31) were published after the 2011 meeting. Articles published after the 2011 Panel meeting included

children and adolescents with a variety of psychiatric conditions, including catatonia, a severe MDE associated with MDD or BPD and childhood schizophrenia.

Because the current labeling of legally marketed ECT devices does not include specific age limitations for any indication within the scope of this classification and FDA received public comments advocating expansion to include the adolescent age range, FDA believed it was important to reassess the evidence and conduct a systematic re-review of valid scientific evidence for the use of ECT in catatonia or a severe MDE associated with MDD or BPD in different age groups. Accordingly, similar to the treatment of catatonia, FDA conducted a reevaluation of the SE of ECT for use in the adolescent subpopulation by reassessing the published literature referenced in the Executive Summary to the 2011 Panel, and in comments and literature received in the ECT public dockets relating to the adolescent age range for using ECT under section 515(i)(2) of the FD&C Act. Unlike the evidence reported for the adolescent population, limited experience and only a few isolated reports were available for patients less than or including 12 years of age. Therefore, this age range was not re-evaluated.

With regard to safety of ECT in treating catatonia or a severe MDE associated with MDD or BPD, specifically in individuals under the age of 18, Jacob et al. (Ref. 17) conducted a 10-year retrospective chart review of all adolescents and children who had received at least one session of ECT therapy in the Child and Adolescent Psychiatry Centre, National Institute of Mental Health and Neurosciences. Twenty-two patients, most who were severely ill, received therapy in the 10-year window. In this group, the majority of patients had no adverse effects; four patients (18.4 percent) experienced headache immediately after the ECT procedure, and three of eight monitored patients had prolonged seizures (greater than 2 minutes). At discharge,

approximately 80 percent were rated as "much improved" or "very much improved" based on the Clinical Global Impressions-Improvement (CGI-I) scale.

Cohen et al. (Ref. 32) investigated cognitive impairment at long-term followup in adolescents treated with ECT for severe mood disorders and compared the neuropsychological test results of the ECT-treated subjects with psychiatric comparison subjects matched for sex, age, and diagnosis. This study found that cognitive test scores of the subjects treated with ECT were similar to those subjects who did not receive ECT. In the ECT treated group 6 of the 10 subjects reported having had memory losses immediately after ECT treatment and 1 reported long-term subjective memory impairment. In the long-term followup study (3.5 years average), the cognitive tests of anterograde memory in the ECT treated group showed no measurable difference compared to the matched group.

A systematic review by Lima et al. (Ref. 28) published in 2013 found 212 published studies on the use of ECT in children and adolescents. Of these, 39 studies met the authors' criteria for inclusion in their systematic review. The reviewed studies specified indications of ECT use in adolescents, evaluated the effectiveness of this therapy in producing remission, and explored the potential risks and complications of the procedure. Overall, the results of this systematic review found that the use of ECT in adolescents is considered a highly effective option for treating several psychiatric disorders including MDE and catatonia, achieving high remission rates, and presenting few and relatively benign adverse effects. These authors conclude that the risks to adolescents can be mitigated by the correct use of the technique and are considered minimal when compared to the treatment benefit.

Consoli et al. (Ref. 33) investigated the use of ECT in adolescents with a primary diagnosis of catatonia. These authors reviewed the published literature (1985-2009) on the use

of ECT in child and adolescent patients with catatonia. In their meta-analysis of studies that included 10 patients or more, only 1 study of 12 patients included subjects below the age of 13 (it included patients in the age range of 12 to 18). This review found that ECT is used as a second-line management after high-dose benzodiazepine trials and that ECT is an effective, safe, and useful procedure in the treatment of catatonic adolescents (n=59).

The largest systematic review of the use of ECT in young people was reported by Rey and Walter (Ref. 34). This 1997 review assessed 60 studies comprising nearly 400 patients, with the majority of patients between the ages of 13 and 18 years and found rates of improvement across studies, including 63 percent for depression and 80 percent for catatonia. Serious complications were very rare, whereas minor, transient side effects appeared common. These authors concluded that ECT in young people appears to be similar in SE to that found in adults, but note that these results are limited by the lack of controlled clinical trials.

FDA's review of other retrospective studies submitted as comments to the proposed order have found similar results. Walter and Rey (Ref. 35) studied 42 patients aged 14 to 18 with a variety of psychiatric diagnoses who received ECT therapy and observed marked improvement or resolution of symptoms in about half of the patients who completed the therapy. Ghaziuddin et al. (Ref. 36) observed clinically significant improvement in 11 of 11 adolescent patients in the 13- to 18-year range with major depressive episode. Of these 11 adolescents 7 achieved euthymia, which is defined as a Children Depression Rating Scale-Revised (CDRS-R) of 40 or less. Strober et al. (Ref. 37) reviewed the treatment of 10 adolescents (13-17 years) with major depression or BPDs and observed complete remission in 6 patients and partial remission in the other 4. Cohen et al. (Ref. 38) studied 21 adolescents (age 14-19) and observed 100 percent response in major depression and 75 percent response in bipolar-mania. In one of a few studies

with a control arm, Kutcher and Robertson (Ref. 39) studied 32 bipolar patients and compared 16 subjects who received ECT to 16 (serving as controls) who were offered ECT but refused it. The ECT group improved significantly more than the group who did not receive ECT and the duration of their hospitalization was cut in half (74 vs. 176 days on average). Taken as a whole, these reports are consistent in reporting effectiveness of ECT in treating depressive episodes and catatonia in young adolescents.

In addition, the American Academy of Child and Adolescent Psychiatry (AACAP) has published guidelines for the use of ECT in adolescents and children. In the AACAP publication on practice parameters (Ref. 40), they reviewed selected publications since 1990. While the use of ECT in adolescents is uncommon within the age of 13 to 17 (representing about 1.5 percent (Ref. 40) of the total population of individuals who receive ECT), the benefits of therapy are acknowledged. This publication also indicates that while the use of ECT in patients 12 years of age or younger is rare and necessitates further study, the guidelines identify risk mitigations of the technique. Overall the AACAP recommends that patients 13 years of age and older are appropriate for considering use of ECT in treating catatonia or a severe MDE associated with MDD or BPD.

While the discussion at the 2011 Panel meeting of ECT use in treating adolescents with catatonia or a severe MDE associated with MDD or BPD was limited, the 2011Panel did hear and discuss comments during the open public hearing both on adolescent age groups as well as considerations as it relates to ECT (Ref. 41). Although a primary emphasis was upon adult populations towards the conclusion of the 2011 Panel proceedings, sufficient and compelling discussion was heard regarding adolescent response to ECT, especially during the opening public hearing comments. In summary, there was the 2011 Panel discussion focused on adolescent

patient use of ECT, as well as many comments including literature references addressing inclusion and exclusion on the basis of age for specific indications for use of ECT (e.g. schizophrenia, bipolar manic states, schizoaffective disorder, and schizophreniform disorder).

Additionally, FDA conducted a review of the MAUDE database from August 2016 to December 2017. The additional MDRs from the MAUDE database do not appear to be significantly different from those compiled for the 2011 Panel meeting and the small number of MDRs is consistent with the safety record reported in the literature for ECT.

As stated previously, FDA has reevaluated the valid scientific evidence for use of ECT in treating adolescents and, in the case of catatonia or a severe MDE associated with MDD or BPD, we believe the requirements under section 515(i)(2) of the FD&C Act for revising the classification of the age limitation for the adolescent subpopulation are satisfied. Based upon the assessment of the totality of evidence, FDA believes that special controls, along with general controls, can provide a reasonable assurance of SE of the use of ECT for all adolescent age groups (13-21 years) and, therefore, is modifying the designation for class II for the indications of catatonia or a severe MDE associated with MDD or BPD in the adolescent subpopulation to include individuals 13 years and older who are treatment resistant or require a rapid response.

4. Effectiveness of ECT for Schizophrenia, Schizoaffective Disorder, and Mania

During the 2011 Panel meeting, members expressed diverse opinions on the effectiveness of ECT for treatment of schizophrenia, schizoaffective disorders, and mania, but the majority of the 2011 Panel members supported class III designation for these indications. A number of published articles on the use of ECT to treat schizophrenia and schizoaffective disorder were submitted and reviewed as attachments to the ECT public dockets. Of these, approximately 15 were published after the 2011 Panel meeting. The majority of these articles published after the

2011 Panel meeting review were either isolated case reports or retrospective chart reviews. SE data, including clinical outcomes, for both adults and adolescents with a primary diagnosis of schizophrenia or schizoaffective disorder (Refs. 14, 23, 30, 42, and 43-47) resulted in variable patient outcomes, while mania had more positive outcomes. However, the available evidence across patients for these conditions was limited when compared to the available evidence for other conditions presented in this final order for which class II is designated.

There was one published practice guideline (Ref. 48) that provided updated treatment recommendations for the acute treatment of schizophrenia and the management of treatment resistance. This guideline concludes that there is limited evidence for general efficacy of ECT in treatment-resistant schizophrenia, but that in certain cases ECT as an adjunct to antipsychotic therapy may be appropriate. This is in contrast to the guideline recommendation for catatonia where ECT is considered an important therapeutic alternative (see above discussion in section III.A.2, Effectiveness of ECT for Catatonia).

Iancu et al. (Ref. 44) conducted a retrospective chart review of 20 consecutive patients with schizophrenia or schizoaffective disorder who were individually treated with at least 30 ECT sessions at the Tel Aviv University. All of these patients had been hospitalized for most or all of the previous 3 years. In this group of chronically hospitalized patients, the authors conclude that ECT treatment improves general function and reduces verbal aggression and self-harm. This patient group had a mean age of 65 and the average age at disease onset was 22 years. Patients were selected for treatment based on inadequate response to medications, history of a good response to ECT in the past, aggression, self-injury, and refusal to eat or drink. Improvement was seen on all assessed scales including the Global Assessment of Functioning,

Clinical Global Impression-Severity and Overt Aggression Scale but most changes before and after ECT were not clinically meaningful or statistically significant.

Kristensen et al. (Ref. 45) reviewed the treatment of 72 consecutive hospitalized patients between 2003 and 2008 from two hospitals in the Copenhagen area. Fifty-five had a diagnosis of schizophrenia and 17 a diagnosis of schizoaffective disorder. All patients had been hospitalized for at least a week and the indication for ECT was an increase in acute episodes or symptom severity leading to hospitalization. The patient ages ranged from 18 to 79 and the disease duration ranged from 1 to 40 years. The duration of the patients' psychotic behavior ranged from a few weeks to over 5 years. ECT was effective in this severely ill population as reflected by a measure of relief from psychosis and disruptive behavior as described in the patient charts. Using information about the size of the catchment area for the involved hospitals, the authors were able to estimate that only about 1.5 percent of patients with schizophrenia received ECT over the 6-year study period in this area of Copenhagen. Because this represents a select and small fraction of the population with schizophrenia, it is not possible to generalize these results to the general population of schizophrenic individuals.

Petrides et al. (Ref. 47) studied patients with clozapine-resistant schizophrenia in a single-blind study where 20 clozapine-resistant patients received ECT as an adjunct to the clozapine treatment and 19 received usual (clozapine) care. Response was defined as a 40 percent or greater reduction in symptoms based on the psychotic symptom subscale of the Brief Psychotic Rating Scale, a Clinical Global Ratings-Severity (CGI-S) rating of less than 3, and a CGI improvement rating less than or equal to 2 following an 8-week course of treatment. Fifty percent of patients in the treatment group that received the ECT met the response criteria compared to none of the patients in the control group. FDA believes that these results, while

promising, have significant limitations. The Denmark Study represents a population of hospitalized patients who may not be representative of the general population of schizophrenic individuals. The Petrides study was small and focused on the subpopulation of clozapine resistant patients and again cannot be extrapolated to the general schizophrenic patient population. The available valid scientific data on the schizophrenic patient population are limited and insufficient to demonstrate that the use of ECT in schizophrenia patients can be safe and effective with the use of special controls.

Other studies have focused on the use of maintenance ECT in the treatment of patients with schizophrenia and schizoaffective disorders (Refs. 23, 27, and 46). In each of these studies, the patient populations are highly selected and represent a small minority of the schizophrenic or schizoaffective populations. Also, a number of additional therapies were given to patients, with limited use of ECT in some cases. While the results are promising in these selected patient populations, the evidence available is limited. Moreover, practice guidelines have not called out schizophrenia and schizoaffective disorders for treatment with ECT. With limited data on different select subpopulations, FDA believes that there is insufficient evidence, at this time, to establish special controls for the subpopulations that might benefit from the treatment. Therefore, FDA believes that the use of ECT to treat schizophrenia or schizoaffective disorder is appropriately currently regulated in class III.

Ten published articles were submitted to the ECT public dockets regarding the SE of ECT for mania. All the articles were published prior to the 2011 Panel meeting and no "new information" on the SE of mania was submitted to the ECT public dockets that were not available to the 2011 Panel. In reviewing the ECT public dockets, FDA did not identify additional scientific information since the 2011 Panel meeting supportive of reclassifying mania

to class II. The published reports on using ECT for the treatment of mania are relatively few, have small numbers of patients, and acknowledge that there are viable alternative treatments in this population.

In one study, Black et al. (Ref. 49) systematically reviewed records of patients treated with ECT for mania or depression over a 12-year period at the University of Iowa Hospital Center. Patient outcome was divided into five categories based on patient discharge notes with the category "marked improvement" applied to patients where the discharge notes suggested there was complete resolution of depressive or manic symptoms. In this review, there was marked improvement in a substantial majority of the patients with depression and with mania. However, the total numbers of patients treated included 422 patients treated for depression but only 37 patients treated for mania. As a result of the differences in numbers of patients treated, there is greater uncertainty in the significance of this retrospective study in mania compared with depression.

Mukherjee et al. (Ref. 50) reviewed the treatment of 30 manic patients at a psychiatric institute in India treated for mania with ECT. They observed remission of mania in 26 of 30 patients. Results are confounded though by the concurrent prescription of neuroleptics at the time of admission for treatment.

Small et al. (Ref. 51) compared ECT with lithium maintenance therapy to lithium treatment in 34 patients hospitalized for mania. Although the patients who underwent ECT improved more than the lithium treatment patients during the first 8 weeks, the study found no differences in clinical ratings after 8 weeks and no differences in rates of relapse, recurrence, or re-hospitalization in the followup period, when compared to pharmacotherapy.

FDA concluded that based on the published literature referenced in the Executive Summary to the 2011 Panel, comments and literature received in the ECT public dockets, the small number of patients treated and limited outcomes reported, the existence of confounding factors in studies, and the availability of alternative therapies with similar reported effectiveness, that special controls cannot be established to provide a reasonable assurance of SE, and, therefore, it is appropriate to maintain ECT to treat mania in class III.

B. Comments on Reclassifying ECT Based on Safety and Effectiveness

In this section, comments regarding the SE of ECT are categorically grouped together so that FDA's responses could be addressed by topic instead of each comment considered independently.

(Comment 3) Several comments indicated that ECT was not safe and/or not effective, particularly in the long term. Several comments noted that ECT had not been used safely and/or effectively in their practice, or on themselves as a patient, or on a family member or a friend. Several comments stated ECT injures patients and is not therapy. Several comments also noted long-term memory, cognitive, or functional impairment following ECT administration. Instead of using ECT, several comments recommended alternative treatments, including acupuncture, transcranial magnetic stimulation, or nutritional or solar therapy.

(Response 3) Comment 3 reflects significant concern on the part of some patients and caregivers about the risks of ECT. Table 1 shows how FDA believes that the risks to health associated with ECT for treatment of catatonia or a severe MDE associated with MDD or BPD can be mitigated by the designated special controls.

Table 1.--Identified Risks to Health and Mitigation Measures for ECT

Identified Risks to Health	Mitigation Measure(s)
Adverse reaction to anesthetic agents/neuromuscular blocking agents	Labeling

Adverse skin reactions	Biocompatibility Labeling
Cardiovascular complications	Labeling
Cognitive and memory impairment	Technical parameters Non-clinical test data Labeling
Death	Labeling
Dental/oral trauma	Labeling
Device malfunction	Performance data Electromagnetic compatibility Software verification, validation, and hazard analysis
Manic symptoms	Labeling
Pain/discomfort	Labeling
Physical trauma	Labeling
Prolonged or tardive seizures	Labeling
Pulmonary complications	Labeling
Skin burns	Performance data Labeling
Worsening of psychiatric symptoms	Labeling

FDA acknowledges that the individuals for whom ECT therapy may be prescribed are at significant risk for complications including death from their underlying conditions. Milstein et al. (Ref. 52) completed a retrospective study of 1,494 psychiatric subjects followed for 5 to 7 years following hospitalization for a psychiatric condition. They found 76 deaths in this group of patients with 16 of the deaths being by suicide. In this group, ECT was not protective but also did not increase the risk for death. Labeling will be required to explain the potential risks and benefits to ensure that patients, caregivers, and family members understand the magnitudes of the risks and the benefits of ECT. FDA acknowledges the important role of patient preference and patient choice in selecting treatments. Patient preference is important in balancing the individuals' assessment of risk and benefit, especially in the presence of serious and potentially life-threatening disorders. This classification is concerned with the use of ECT for certain specified uses and does not address the potential use of other treatments that patients may consider. FDA believes that for certain indications, special controls as established in this final

order, along with general controls, provide a reasonable assurance of SE of ECT by mitigating the identified risks to health. As such, FDA disagrees with the comments that ECT should not be reclassified for any indications to class II.

FDA reclassifies devices under section 515(i)(2) of the FD&C Act in accordance with the criteria in section 513(a) of the FD&C Act. The primary purpose of reclassification is to apply the appropriate level of regulatory controls for a device based on the most current information regarding its SE. FDA notes that reclassification does not imply that ECT is a preferred form of treatment. FDA recommends that patients consult with their healthcare providers to determine if ECT is the best treatment option for them or if there are suitable alternative treatments. FDA notes that the patient labeling is required to list alternative treatments (see § 882.5940(b)(1)(ix)(E) (21 CFR 882.5940(b)(1)(ix)(E))).

(Comment 4) Some comments stated that FDA did not consider animal studies and death data in proposing to reclassify these devices.

(Response 4) FDA does not agree with these comments. Information about adverse events, including death, was carefully considered regarding the reclassification action. Section 4.8 of the safety review in the FDA Executive Summary prepared for the 2011 Panel meeting specifically addresses the risk of death. Data for deaths from MDR analyses was also considered and made part of the risks identified in the proposed order. FDA acknowledges that there is uncertainty in the estimate of risk of death from these sources of information and that the risks are likely changing as a result of evolution in the practice of medicine. In light of this risk, the labeling is required to include death (§ 882.5940(b)(1)(ix)(H)(3)(viii)) as a risk of the use of ECT. In some cases where human experience is limited, animal studies can be of significant

value in predicting outcomes in humans.[2] However, in this case where there is a significant and substantive experience with the use of these devices to treat humans, FDA believes that the human study data are the primary sources for review and consideration.

(Comment 5) Several comments opposed the reclassification saying that ECT should remain in class III for all indications. Several comments indicated that current safety or effectiveness information was insufficient to ensure patient protection. Several comments indicated that proof of SE should be required before the device enters the market. Several comments indicated that the 510(k) clearance pathway was not sufficient for ECT devices.

(Response 5) FDA disagrees with these comments that ECT should not be reclassified to class II as specified in this final order for certain indications. As established in section 513(a)(1)(C) of the FD&C Act and 21 CFR 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 SE. Based on FDA's independent review of the scientific evidence, FDA has determined that the special controls established in this final order, including performance data, technical parameters of the device, and extensive labeling requirements, along with general controls, can provide reasonable assurance of SE of ECT for the specified class II indications. ECT devices for indications in class II will require a 510(k) (or an amendment to a previously cleared 510(k) if already legally marketed) that demonstrates compliance with these special controls. ECT devices for indications other than those being classified into class II will require premarket approval as insufficient evidence currently exists to establish adequate special controls for these uses.

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[2] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

(Comment 6) Several comments indicated that ECT did not treat the biological basis of depression or other mental disorders. Several comments indicated that electricity did not treat the underlying cause(s) and could exacerbate mental disorders. Several comments indicated that there is no evidence that mental disorders are neurobiological. Several comments indicated that ECT may be used in patients who are misdiagnosed.

(Response 6) For a device to be determined to have a reasonable assurance of SE, FDA evaluates the device's performance outcomes relative to the indications for use and not necessarily the mechanism(s) of action of the device, which may not be well understood in some cases. For ECT, the clinical data reflecting the device's performance in relation to the indications for use have been discussed above in response to Comment 2. Additionally, knowledge of the underlying causes of mental disorders is not required to evaluate a reasonable assurance of the SE of a device type for a specified intended use. Therefore, the biological basis or cause of the underlying mental disorder is outside of the scope of this reclassification.

(Comment 7) Several comments suggested that reclassification would increase acceptance of ECT. Several comments indicated that ECT is not as safe or effective when compared to other available treatments. Several comments opposed the reclassification saying that reclassification indicated that ECT is a preferred method of treatment.

(Response 7) The primary purpose of reclassification is to apply the appropriate level of regulatory controls for a device type based on the ability to reasonably assure SE. FDA notes that reclassification does not imply that ECT is a preferred form of treatment. This order is neither a recommendation of ECT treatment nor a determinant of whether ECT is safer or more effective than alternative treatments. The purpose of the proposed and final order process is to identify the regulatory controls necessary to reasonably assure SE for ECT and to provide the

evidence supporting this determination. Based upon FDA's assessment, special controls, in combination with general controls, are necessary and sufficient to provide a reasonable assurance of SE for the use of ECT in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. ECT devices for indications other than those identified in the previous sentence, including schizophrenia, schizoaffective disorders, schizophreniform disorder, bipolar manic states, and catatonia or a severe MDE associated with MDD or BPD in patients under 13 years or patients 13 years or older who are not treatment-resistant or who do not require a rapid response due to the severity of their psychiatric or medical condition, will require premarket approval. FDA believes that insufficient evidence currently exists to establish special controls to mitigate the risks to health and provide a reasonable assurance of SE for those uses.

(Comment 8) Several comments indicated that ECT should be banned. Several comments characterized ECT as inhumane. Commenters indicated that the United Nations Special Rapporteur on Torture and Other Cruel Inhuman or Degrading Treatment or Punishment February 16, 2013, defined ECT without consent as torture.

(Response 8) FDA disagrees that ECT should be banned. Section 516 of the FD&C Act (21 U.S.C. 360f) authorizes FDA to ban a device when, based on all available data and information, FDA finds that the device "presents substantial deception or an unreasonable and substantial risk of illness or injury." During review of the scientific evidence, FDA did not identify sufficient evidence to ban ECT. FDA determined that special controls, in combination with general controls, can mitigate the identified risks of ECT for certain intended uses and mitigate risks associated with ECT use. FDA determined that there is a reasonable assurance of

SE for ECT treatment for the identified indications for use and patient populations. Therefore, FDA has determined that ECT does not present substantial deception or an unreasonable and substantial risk of illness or injury.

As noted, we acknowledge the February 1, 2013, United Nations Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment by Juan E. Méndez does recommend banning the administration of non-consensual electrical stimulation against persons with disabilities (Ref. 53). Persons with disabilities include persons with long-term intellectual or sensory impairments. The report does not address the use of electrical stimulation to treat conditions such as a severe MDE associated with MDD or BPD, schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, or catatonia. As noted in the proposed order and adopted in this final order, appropriate directions for use and specific labeling special controls (§ 882.5940(b)(1)(viii) and (ix)) are required for the safe use of ECT.

(Comment 9) Several comments were concerned that reclassification would make it easier for either healthcare professionals or non-healthcare professionals to overly or inappropriately use ECT. Comments indicated that ECT may be used to shorten hospital stays without regard for patient outcomes. Comments indicated that ECT may be used to control patients or reduce unwanted behavior such as screaming rather than as treatment for a medical condition. Several comments questioned the regulation of ECT use in other indications not included in class II in the split classification.

(Response 9) FDA does not regulate the practice of medicine (see section 1006 of the FD&C Act (21 U.S.C. 396)). Diagnosis and treatment of patients are clinical decisions that fall within the practice of medicine. Rather, FDA regulates the use of a device as indicated by the

person or entity offering the device for interstate commerce. The classification of indications for use for ECT devices are specified in the identification language in the codified classification regulation (see § 882.5940). Through the classification process, FDA has determined the level of regulatory control necessary to provide a reasonable assurance of SE of ECT devices for these indications. ECT is a prescription only device that is not safe for use except under the supervision of a practitioner licensed by law to direct the use of the device and for which prescription labeling requirements must be met (see 21 CFR 801.109). The labeled uses of the device must conform to the indications that have been cleared or approved by FDA through the premarket review process. FDA does not regulate off-label use of ECT by physicians.

C. Comments on Patient Concerns

In this subsection, comments on patient concerns with using ECT are categorically grouped together so that FDA's responses could be addressed by topic instead of each comment considered independently.

(Comment 10) Several comments state that FDA's call for PMA applications is disingenuous because PMA applications have not been required for ECT devices since they were originally classified. Comments indicate that because the proposed order states ECT devices for some indications will be in class II, device manufacturers will not have an incentive to apply for additional indications through the PMA process, because, under the practice of medicine, healthcare professionals can use class II ECT devices for indications beyond those cleared via 510(k) for indications that are in class III.

(Response 10) FDA disagrees with these comments. Finalizing the classification of ECT includes a requirement that PMA applications be submitted prior to marketing of ECT devices for indications other than those identified as class II within this final order, and it is the

responsibility of the manufacturer to ensure that a PMA application is submitted in such circumstances. However, FDA is not permitted to limit or interfere with the authority of a healthcare professional to administer any legally marketed device to a patient for any condition or disease within a legitimate clinician-patient relationship.

(Comment 11) Several comments raised concerns about a split classification and the conditions under which devices could be used under either classification. Several comments indicated that a split classification could restrict the use of ECT for indications not included in class II and thereby limit treatment options for patients. Comments asked if there is evidence of patients not receiving treatment when ECT devices are in class III. Comments asked for guidance on whether class II ECT devices can be used on patients with a severe MDE associated with MDD accompanied by another condition. Comments also stated concern that class II ECT devices will be used as predicate devices for other devices with different current or voltage strength, or different pulse length, pattern or waveform, saying such differences could impact safety including cognitive side effects and/or effectiveness of ECT treatment.

(Response 11) FDA's reclassification of ECT to class II for the indications specified in the final order is an effort to make ECT available for the benefit of patients with conditions for which general and special controls can provide a reasonable assurance of SE. For these indications, sufficient scientific evidence exists for FDA to establish special controls that, in combination with general controls, provide reasonable assurance of SE of ECT. For other indications, sufficient scientific evidence does not currently exist to be able to establish special controls to mitigate the risks to health at this time. The indications for which there is currently insufficient evidence to develop special controls will remain class III and require a PMA pursuant to section 513(a)(1)(C) of the FD&C Act. Because of the differing levels of scientific

evidence currently available to establish special controls for the various uses of ECT, a split classification was warranted in this case. If warranted by new scientific evidence, FDA could reclassify ECT for other indications to class II in the future.

Under section 1006 of the FD&C Act, FDA is prohibited from interfering with the authority of a healthcare professional to prescribe or administer any legally marketed device to a patient within a legitimate clinician-patient relationship. As such, FDA does not regulate the practice of medicine. Rather, FDA regulates the use of a device as indicated by the person or entity offering the device for interstate commerce. The indications for which FDA has determined ECT devices have a reasonable assurance of SE based on the general controls and the identified special controls are in the codified classification regulation (see § 882.5940). Once a product is approved or cleared, a healthcare professional is able to prescribe the device based on a patient's condition. ECT is a prescription device and FDA relies on licensed practitioners to direct its use. Treatment of patients remains under the clinical discretion of their healthcare practitioner. While treatment of patients falls under the practice of medicine, healthcare professionals should carefully consider all ECT device labeling, including potential adverse events, warnings, and medical conditions that can increase patient risk when deciding if ECT is appropriate for their patients, including those with comorbid conditions. The healthcare professional is responsible for providing appropriate ongoing medical management to mitigate any patient specific risks associated with comorbid conditions.

If ECT devices are used as predicate devices for subsequent ECT devices, any differences in the technical parameters (e.g., waveform, output mode, pulse duration, maximum charge, and energy as identified in § 882.5940(b)(1)(i)) between the predicate device and the new device

must be characterized and will be considered as part of FDA's substantial equivalence determination to ensure that such differences do not raise different questions of SE.

(Comment 12) Several comments were concerned that adequate, well-informed consent may not take place prior to ECT treatment. Several comments indicated concern over the use of ECT without consent or without full disclosure of risks. Several comments were concerned with involuntary treatment and its outcomes. Comments indicated that conversations about potential benefits, potential risks, alternative treatments, and the typical experience and course of ECT treatment should occur over several sessions prior to ECT treatment. Comments asked that FDA provide additional guidance and recommendations to healthcare professionals on the procedures for informing patients and on obtaining written informed consent from patients or their legally authorized representatives prior to ECT treatment. Comments indicated that family members or other caregivers should be included in the informed consent process and should provide input on how the patient is responding to ECT treatment including any adverse events. Several comments indicated that ECT should only be used in settings of formal informed consent, such as with a documented checklist or when it is specified in a psychiatric advance directive. A comment suggests that FDA develop a patient decision aid related to ECT that considers key clinical variables and alternative therapeutic options as well as incorporating patient values, concerns, and preferences. Several comments indicated that the order should specify that consent is an ongoing process, that information should be provided throughout treatment, and that at any time during the course of ECT treatment, patients can request that treatment be stopped and can withdraw consent for further treatment. Several comments indicated that some patients may not be able to give consent due to their medical condition.

(Response 12) These comments are focused on how patients are informed about the risks, benefits, and alternatives to ECT. FDA agrees that ECT informational material, including information about benefits and risks, should be discussed with the patient and, if applicable, with a designated family member or other individual. In § 882.5940(b)(1)(ix), FDA requires that certain information be provided in the patient labeling for a class II ECT device. The appropriate treatments for a patient with catatonia or a severe MDE associated with MDD or BPD is a complex matter that requires the supervision of a practitioner licensed by law to direct the use of the device. In selecting the appropriate treatment, the practitioner should consider many factors, such as the patient's medical history and the severity of their psychiatric or medical condition. FDA believes that the device labeling required per the special controls will provide patients and healthcare professionals with information that will improve their understanding of the ECT device and assist in selecting the appropriate treatment for patients. ECT is a prescription device, and FDA and licensed practitioners are relied upon to direct its use.

Informed consent procedures may differ across each State agency, institution, hospital, clinic, and practice. For ECT treatment, FDA expects review boards and State agencies to have the appropriate requirements for medical professionals to provide the appropriate informed consent to patients and family members, and to take action when necessary. The patient labeling is required to include information on ECT use, potential benefits, warnings regarding risks of ECT, and alternative treatments. The information required in the patient labeling will help patients make an informed decision about ECT treatment. Patients may also discuss ECT and other treatment options with their healthcare professionals, family members, or other individuals. Patients, or their legally authorized representative, may withdraw consent and request that ECT treatment be stopped at any time.

According to the Surgeon General, involuntary ECT treatment is uncommon in the United States. In every State in the United States, the administration of ECT on an involuntary basis requires a judicial proceeding (Ref. 54). At this time, FDA declines to recommend the development of patient decision aids related to ECT that considers key clinical variables and alternative therapeutic options as well as incorporating patient values, concerns, and preferences. FDA is concerned that including such information may be more confusing than helpful given the complexity of treating a number of different psychiatric disorders. FDA also requires patients consult a practitioner licensed by law to administer or use the ECT device.

(Comment 13) Several comments indicated training or education should be required for healthcare professionals to be eligible to administer ECT. Several comments indicated that the order should specify what type of healthcare professional should be able to administer ECT. Several comments indicated that healthcare professionals other than physicians should be able to administer ECT.

(Response 13) FDA is in agreement that there is a need for ongoing training for healthcare professionals who administer ECT. ECT is a complex procedure that requires specialty training for reasonably safe and effective administration. As stated in the proposed order and adopted in this final order, FDA is requiring device labeling to specify the clinical training that is needed by those using the ECT device to ensure appropriate use and appropriate ongoing medical management of the patient.

(Comment 14) Several comments indicated that those who administer and/or study ECT have conflicts of interest. Several commenters noted that the doctors recommending ECT treatment profit financially from administering ECT. Commenters asked if FDA considers

possible conflict of interests for researchers when assessing the validity of ECT research used to support the reclassification.

(Response 14) The potential for conflict of interest of healthcare professionals administering ECT is outside the scope of this final order and does not bear upon FDA's careful evaluation of the valid scientific evidence on the SE of ECT. FDA's Federal conflict of interest provisions are directed toward the potential for conflict of interest on the part of FDA employees and outside experts used on FDA's advisory committees (see 5 CFR 2640 and 18 U.S.C. 208).

FDA defines valid scientific evidence in § 860.7(c)(2). Isolated case reports, random experience, and unsubstantiated opinions are not regarded as valid scientific evidence. In standard clinical practice as in ECT treatment, healthcare professionals are compensated for providing treatment to patients. Institutional review boards assess potential conflicts of interest for healthcare professionals conducting clinical research on ECT. Under 21 CFR part 54, FDA assesses potential financial conflicts of interest for healthcare professionals conducting clinical research on ECT. Scientific journals typically require disclosure of funding and potential conflicts of interest when publishing research findings.

(Comment 15) Several comments were concerned about the benefit-risk ratio for ECT treatment. Comments raised concerns that the risks of ECT may be higher in vulnerable populations, including the elderly, who could have hemorrhaging from increased intracranial pressure, pregnant women, and patients with multiple disorders, cancer, or multiple medications. Comments indicated that the risks of ECT are higher than acknowledged because adverse reactions are mischaracterized so that they are not associated with ECT. Comments also expressed concern that patient-reported outcomes differ from reported adverse events and study outcomes. Comments said some adverse effects of ECT, such as emotional trauma, have had

limited scientific study but are evidenced by many subjective patient accounts and should be considered further. Comments noted that the benefit-risk ratio could change over the course of an ECT treatment. Comments said the benefit could decrease and the risks could increase because higher stimulation is needed for effectiveness over the course of treatment, leading to a higher risk of adverse events. In addition, comments said the repeated use of general anesthesia for ECT over a relatively short period of time could increase the risk of side effects.

(Response 15) FDA believes there is reasonable assurance that with the special controls codified in the final order, in combination with general controls, the benefit of ECT outweighs the risk for the indicated populations whose condition is treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. The practitioner administering ECT is responsible for ongoing medical management and disclosure of changes in the risks for individual patients during a course of ECT treatment. In considering the benefits and risks, FDA took into consideration all available information, including the existing published scientific literature, practice guidelines published by major psychiatric and lay mental health organizations, input from the external classification panel, and reports of adverse events contained in the MAUDE database. Based upon all of this information, FDA has determined that the probable benefits to health from use of the device outweigh the probable risks for the class II indications and, furthermore, the risks associated with the use of ECT for the class II indications can be mitigated with the proposed special controls.

(Comment 16) Several comments indicated that the special controls were inadequate to properly mitigate severe risks such as the risk of cognitive impairment and death. Comments indicated that special controls cannot be developed for unknown risks. For example, it is not known whether ECT patients return to baseline memory functioning after 6 months. A comment

asserts that FDA must use scientific evidence to evaluate risk to memory and it is not enough for FDA "to believe" the potential benefits of ECT outweigh the risk of memory impairment. The comment also indicates that FDA presents no evidence verifying that the special controls are effective at mitigating risk or that the special controls will ensure patients understand the benefits-risks of ECT.

(Response 16) FDA identified sufficient scientific information to establish special controls, including adequate instructions for use and appropriate precautionary language. The special controls along with general controls provide a reasonable assurance that ECT can be used safely and effectively for the indications being reclassified to class II. Regarding the use of the word, believe, by FDA in the proposed order, FDA's use is of the word believe is a term of art to indicate its current understanding of an issue in administrative orders. The term, believe, is also used in both the FD&C Act and FDA's regulations.

The risk of memory impairment following ECT treatment is addressed in the special controls. The risk of cognitive and memory impairment can be mitigated by establishing the technical parameters for the device along with non-clinical testing data to confirm the electrical characteristics of the output waveform. The existing clinical performance data for ECT in treating catatonia or a severe MDE associated with MDD or BPD provides evidence that the cognitive impairment and related effects are transient (Refs. 5 and 34) and supports a reasonable assurance of SE. This risk is further mitigated by providing information to both the user and patient, in the form of labeling, on the potential adverse effects of the device, alternative treatments, and a prominent warning that ECT device use may be associated with: disorientation, confusion, and memory problems and is limited in its long-term effectiveness (greater than 3 months). These risks can also be mitigated by providing instructions to the user

that include recommendations on cognitive status monitoring prior to beginning ECT and during the course of treatment. Providing this information helps patients and healthcare professionals to make informed choices about how and when to use ECT to maximize benefits and minimize potential adverse effects.

D. Comments on Regulatory Process of the Proposed Order

In this section, comments on process concerns of the order are categorically grouped together so that the responses could be addressed by topic instead of each comment considered independently.

(Comment 17) Several comments provided recommendations on additional sources of information that FDA should consider in regards to reclassification of ECT. Comments suggested that FDA should review State ECT registries for information on use and outcomes. Comments suggested FDA should require new clinical trials, additional postmarket surveillance, and/or establish patient registries for the purposes of: (1) establishing long-term risks, such as the potential for shortened life; (2) monitoring and assessing memory and cognitive functioning over a period of a year or more to determine if memory loss is permanent; and (3) determining if patients experienced any long-term benefit. A comment indicates that MDR data should be used in the classification determination for ECT. The comment attaches an analysis of the FDA MDR database search showing that most patients report lasting memory and cognition impairment, and other side effects that affect work, education, and social relationships. The comment indicates that FDA's MDR database shows systematic discrepant reporting of ECT adverse events (e.g., description of burns coded with event type, malfunction). Comments requested that FDA hold another public meeting about the classification of ECT that includes testimony from ECT patients because of the "new information" provided in the public comments.

(Response 17) FDA agrees that State or national registries may play a role in medical device surveillance to provide additional detailed information about patients, procedures, and devices not routinely collected by electronic health records and administrative or claims data. The State of Texas has for several years maintained a registry of all ECT treatments in the State in a given year. Data on these treatments are provided in an annual report to the governor (see https://www.dshs.texas.gov/mhsa/bhmd/ect/, Ref. 55). The most recent report provides data for fiscal year 2016. This report summarizes 17,006 treatments given to 2,675 patients. Severe complications included 0 fractures, 0 episodes of apnea, 0 cases of cardiac arrest without death, and 1 death within 14 days of treatment that was reported to be the result of a drug overdose. This report concludes that, overall, patients experienced less severe symptomology after ECT treatment, which demonstrates the overall effectiveness of treatment. These data are consistent with the published literature and do not provide "new information" that would change the recommendation in the final order.

FDA requires manufacturers to submit MDRs of adverse events when their device may have caused or contributed to a death, serious injury, or in certain situations when their device has malfunctioned. FDA acknowledges that there are limitations to the use of MDR reports for determining the cause and frequency of adverse events. Confirming whether a device caused a specific event can be difficult based solely on information provided in a given MDR report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated. FDA does not typically have complete information on the number of times devices of a certain type are used from which to calculate adverse event rates. MDR data does not represent all known safety information for a medical device and should be interpreted in the context of other

available information when making device-related or treatment decisions. Healthcare professionals, patients, caregivers, and consumers are encouraged to submit voluntary reports detailing treatment parameters and outcomes to MedWatch: the FDA Safety Information and Adverse Event Reporting Program, for serious adverse events that may be associated with a medical device, as well as use errors, product quality issues, and therapeutic failures (Ref. 56). Reports of adverse events are monitored by FDA for safety signals that may warrant changes to device regulation.

Despite the limitations of MDR data described above, as part of its review of the comments submitted to the ECT public dockets, FDA conducted an updated review of the MDR database covering the period from February 2011 through December 2017. This review identified an additional 27 reports, all of which are voluntary reports. No reports for individuals less than 18 years of age were reported to the MDR database. Similar to the reports included in the Executive Summary for the classification panel, the most commonly cited adverse event type was cognitive changes, notably memory loss (52 percent). Other commonly reported adverse events included general emotional/psychiatric (e.g., anxiety, emotional changes), general motor (e.g., shaking/tremors), and four reports of either tissue damage (not specified) or burns. Thus, FDA concluded that no new types of adverse events have been identified that would warrant changes to the proposed reclassification order.

(Comment 18) Several comments raised concern with how the ECT 2011 classification panel was conducted. Several comments indicated that the proposed reclassification was not supported by the panel, because the classification panel did not reach consensus regarding whether any of the indications should be class II. Comments said that FDA misrepresented the

classification panel results regarding consensus on classification of ECT. Another comment alleges that FDA improperly influenced the makeup and deliberations of the classification panel.

(Response 18) FDA considers the deliberations as well as the recommendations by the classification panel meeting in determining the appropriate classification of a device under section 513(a) of the FD&C Act. The classification panel discussions and recommendations are considered as part of FDA's decision whether to revise classification of a device (see section 515(i)(2) of the FD&C Act). Although the panel provides recommendations with respect to the classification of devices, FDA is also not required to follow the classification panel recommendations. Regarding ECT, the panel did not reach a consensus on its classification for any of the proposed conditions for reclassification. There were a variety of opinions and judgments provided both in support of and in opposition to reclassification. The opinions expressed by the classification panel were carefully reviewed and considered along with other information including professional organization practice guidelines, MDR reports, and published scientific studies.

Based on this evidence from multiple sources, FDA has determined that special controls, in combination with general controls, establish a reasonable assurance of SE by mitigating the risks associated with ECT for the uses being reclassified (as discussed in section X, 80 FR 81223 at 81230, December 29, 2015). In accordance with section 515(i)(2) of the FD&C Act , based on valid scientific evidence with respect to the device and taking into account the public health benefit(s) of the use of the device and the nature and known incidence of the risk(s) of the device, FDA is also now revising the classification of ECT for treatment of catatonia or a severe MDE associated with MDD or BPD who are treatment-resistant or who require a rapid response

due to the severity of their psychiatric or medical condition in patients ages 13 years and older, from class III to class II (special controls) (see subsections A and B of this section).

FDA disagrees with the comment that FDA improperly influenced the 2011 classification panel. On January 27-28, 2011, FDA held a meeting of the Neurological Devices Classification Panel to discuss the classification of ECT devices for treatment of several disorders. FDA has standard procedures in place for establishing a classification panel meeting consistent with the requirements of the Federal Advisory Committee Act, other relevant statutes (e.g., the FD&C Act), regulations (e.g., 21 CFR 14.25 and 14.29), and Agency guidance. As required for all classification panel meetings, FDA conducted the proper screening and vetting of classification panel members for the 2011 Panel meeting. FDA ensured the classification panel included representatives with expertise in several relevant mental health disciplines. The ECT classification panel meeting meets the requirement under section 513(b)(1) of the FD&C Act for a device classification panel meeting.

The conduct of the 2011 Panel meeting is described in the transcript of the meeting and the 24 Hour Summary (Ref. 57). FDA presented the general regulatory background, brief clinical history of ECT use, and ECT-specific regulatory history. This was followed by an open public hearing. Then, FDA presented the FDA's safety analysis, which included a review of responses to a public docket on ECT reclassification, manufacturer docket responses, and an adverse event database review. In addition, FDA presented a focused review of specific adverse events, including cognitive and memory adverse events, neuropathological changes, and death. Following the safety review, FDA presented a review of the effectiveness of ECT. The classification panel then proceeded to their deliberations regarding the questions posed by FDA. The classification panel agreed that the list of risks provided by FDA were appropriate for

inclusion with some minor modifications and deletions. The classification panel recommended physician labeling for pre-ECT assessment, including pertinent history, physical examination, other clinically relevant studies, appropriate procedure monitoring and administration, and appropriate clinical management. When presented with potential regulatory controls that FDA could apply to ECT to mitigate risks of adverse cognitive and memory effects, especially with respect to anterograde and retrograde memory functioning, the classification panel agreed that cognitive function should be monitored prior to ECT and throughout the course of treatment. The classification panel agreed that the existing clinical data do not provide evidence that ECT treatment is associated with neuropathological changes. Finally, the classification panel provided overall recommendations for the class II or III classification of ECT devices for specific indications for use, including depression (unipolar and bipolar), schizophrenia, bipolar manic (and mixed) states, schizoaffective disorder and schizophreniform disorder, and catatonia. There was classification panel consensus recommending class III for schizophrenia, bipolar manic states, and schizoaffective and schizophreniform disorder. The classification panel did not reach consensus on the classification of ECT for depression (unipolar and bipolar) and catatonia.

(Comment 19) Several comments related to the information used to support reclassification. Several comments indicated that the scientific evidence, medical studies, meta-analyses and literature reviews cited in the proposed order do not constitute new evidence or reinterpret previously published evidence and are insufficient to justify the reclassification. Comments say FDA ignored the 2010 meta-analysis from Read and Bentall that found, after reviewing hundreds of studies, no evidence that ECT treatment had any benefit for any population lasting beyond a few days and did not prevent suicide.

(Response 19) In accordance with section 515(i)(2) of the FD&C Act, FDA is reclassifying the ECT device from class III to II (special controls) for use in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. FDA has made this reclassification decision based on FDA's evaluation of the following sources of information: (1) published literature referenced in the Executive Summary to the 2011 Panel; (2) comments and literature received in the ECT public dockets, as discussed above; (3) clinical practice guidelines; (4) review of MDRs in the FDA MAUDE database); and (5) the additional post-2011 scientific information that was provided to FDA in comments to the 2015 proposed order. Based on FDA's evaluation of the totality of the evidence under the criteria set forth in section 513(a) of the FD&C Act, FDA believes that there is valid scientific evidence to support FDA's decision to reclassify the ECT device from class III to II (special controls) for the intended uses described previously.

FDA disagrees with the conclusions of the 2010 Read and Bentall analysis. Specifically, FDA conducted an independent review and several publications, as well as reviews of the published literature, support the use of ECT in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition (Ref. 33, 34 and 58-60). Observations from these individual studies, retrospective reviews, and meta-analyses consistently reported favorable SE clinical outcomes for the indications being reclassified by this final order. In addition, as part of the preparations for the 2011 Classification Panel Meeting, FDA conducted a systematic review of the scientific literature regarding the SE of ECT for a variety of psychiatric conditions. FDA conducted a meta-analysis of the data provided in all

studies that met criteria for inclusion in this systematic review. Based upon this review and meta-analysis, and the totality of evidence, FDA determined that there was reasonable assurance of the SE of ECT for the class II indications in this final order.

(Comment 20) Several concerns were raised about the process for the proposed order. Comments indicated the guidance should not be used or issued prior to finalization of the final order. Comments indicated there was inadequate time to comment on the proposed order due to timing of the comment period coinciding with holidays at the end of the year, and weekends being included in the 90-day response time. Comments indicated that two dockets (one for the proposed order and one for the draft guidance) on ECT made commenting more difficult. Commenters objected to elimination of mass mail in campaigns and duplicative or near-duplicative letters.

(Response 20) FDA agrees with the comment that guidance should not be used or issued prior to finalization of the final order. Final guidance will not be issued prior to issuance of the final order. FDA believes the correct process was followed for the proposed order issued for ECT. FDA determined it was beneficial to publish the proposed order and draft guidance on ECT concurrently to ensure that all relevant information pertinent to the potential reclassification of ECT, along with a recommended strategy for demonstrating substantial equivalence for ECT devices subject to 510(k), was available to the public at the same time. FDA believes that a 90-day comment period was ample time to allow the public to comment on the proposed order and concurrently released draft guidance and is consistent with the timeframes for other classification and reclassification efforts. Commenting on two dockets related to ECT rather than one docket does require additional effort by commenters. However, FDA had taken two different actions related to ECT (proposing a reclassification and issuing draft guidance), such that two dockets

were made available to provide the option of commenting on one or both of these proposed actions. Documents that are in "draft" form are not implemented by FDA unless and until finalized.

Information submitted as part of a mass campaign was also reviewed. However, while the content of these letters is considered and responded to, FDA does not individually respond to the same information contained in mass campaign letters and duplicative letters. This allows FDA to efficiently utilize resources when reviewing comments. As noted previously, although over 3,400 comments were received, comments were categorically grouped together so that responses are addressed by topic instead of responding independently to each individual comment.

(Comment 21) Several comments argue that the terms "treatment resistant" and "require rapid response" are vague, particularly to non-clinicians. Several comments asked for clarification on the number and types of treatments, as well as the duration of treatment that should be tried prior to being labeled treatment-resistant. Several comments indicated that there was not consensus from the literature and professional organizations on the meaning of treatment-resistant. A comment indicates that defining treatment-resistant depression as the failure of two antidepressants is not appropriate because antidepressants are not effective for every patient and there are other treatments that may be effective that should be used prior to ECT. Several comments indicated that psychotherapy or other non-medical treatments should be tried prior to ECT. Several comments were concerned that the lack of clarity of these terms would lead to misuse of ECT. Several other comments indicated that the terms "treatment-resistant" and "require rapid response" were well understood and described in applicable medical literature and the Diagnostic and Statistical Manual of Mental Disorders (Ref. 61).

(Response 21) FDA identifies the intended population in which ECT is classified in class II as patients who are treatment-resistant because ECT is not a currently established first-line treatment, except when rapid response is needed due to the severity of the patient's psychiatric or medical condition. FDA acknowledges that these terms may not be entirely clear to patients. However, comments by healthcare professionals generally indicated that the terms are well understood by the staff who would be prescribing or using this therapy. The need for rapid response and the criteria for treatment-resistant can be based on clinical judgment. The information on the intended patient population that, as part of the special controls, must be listed on the device label (§ 882.5940(b)(1)(viii)(D)) is directed toward the practitioner licensed by law to administer or use the device.

(Comment 22) A comment asks FDA to delete the recommendation in § 882.5940(b)(1)(viii)(B)(7) for "formal neuropsychological assessment" from the labeling because it is not the norm and would create barriers to the availability and timeliness of care in that such assessments are costly and difficult to access.

(Response 22) FDA recognizes that not all ECT practitioners have access to neuropsychologists who conduct formal neuropsychological assessment. However, FDA believes that the known risk of cognitive adverse events can be mitigated by the special controls that require user instructions recommending cognitive status monitoring prior to beginning ECT and throughout the course of treatment via a formal neuropsychological assessment. If cognitive abilities decline during the course of treatment, steps can be taken to avoid further decline.

(Comment 23) A comment stated depression is sometimes associated with cognitive problems and urges FDA to require that all providers of ECT assess patients' cognitive and

memory functioning when they first become patients before ECT begins, soon after ECT ends, and at longer term followup after ECT treatment.

(Response 23) FDA includes a special control (§ 882.5940(b)(1)(viii)(B)(7)) that requires user instructions that recommend cognitive status monitoring prior to beginning ECT and during the course of treatment via formal neuropsychological assessment for evaluating specific cognitive functions (e.g., orientation, attention, memory, and executive function). FDA acknowledges that autobiographical memory loss following ECT treatment can occur, so this adverse event has been included in the labeling for ECT. FDA also acknowledges that the "long-term safety and effectiveness of ECT treatment has not been demonstrated," and therefore has included this risk as a warning in the ECT device labeling that long-term followup may be needed.

E. Comments on Labeling Concerns

In this section, comments on labeling concerns in using ECT are categorically grouped together so that the responses could be addressed by topic instead of each comment considered independently.

(Comment 24) A comment requested that FDA delete the proposed warning in § 882.5940(b)(1)(viii)(J) and (ix)(G) ("When used as intended this device provides short-term relief of symptoms. The long-term safety and effectiveness of ECT treatment has not been demonstrated.") because it is understood that cessation of active treatment will be associated with cessation of treatment benefits.

(Response 24) Based upon all available evidence and FDA's own analysis of the published scientific literature, FDA concluded that the long-term SE of ECT has not been demonstrated. However, FDA recognizes that ECT healthcare professionals often conduct

longer term treatment strategies with ECT. The reclassification of ECT does not specifically address the issue of maintenance or continual ECT, which would be at the discretion of the healthcare professional. However, as described in the special controls, results from longer term performance data should be considered for inclusion in the healthcare professional and patient labeling, if warranted.

(Comment 25) A comment asks FDA to replace the word "contraindications" in proposed § 882.5940(b)(1)(ix)(A) with the phrase "conditions associated with substantially increased risk" because describing these conditions as contraindications is likely to restrict access to needed ECT in very rare but life-threatening situations.

(Response 25) The use of the word "contraindications" here refers specifically to medical conditions other than psychiatric disorders in which the use of ECT has been demonstrated to result in serious adverse events, some of which might be life-threatening. These include unstable cardiac and pulmonary conditions (e.g., recent heart attack, asthma, pneumonia) and history of neurological conditions (e.g., stroke, tumors, increased pressure in the brain). Contraindications are defined as situations in which the device should not be used because the risk of use clearly outweighs any benefit. (Ref. 62). Therefore, FDA believes it is appropriate to keep the language as initially written in the proposed order.

(Comment 26) A comment disagrees with definitions of short-term and long-term memory in § 882.5940(b)(1)(ix)(H)(1). The comment says equating short-term to anterograde memory loss and long-term to autobiographical memory loss is unusual in the psychiatric field and confusing for patients. The comment says short-term could mean: (1) lasting for a short period before returning; (2) affecting short-term memory, i.e. the type of memory where information is held onto for a few seconds to a few minutes; or (3) anterograde memory, which is

the ability to form new memories. The comment says this labeling does not clearly describe the range of deficits that patients might experience. The comment says there is a similar lack of clarity in the use of the term "long-term". The comment says long-term memory typically includes many different types of information storage, stored for an extended period of time that could range from more than a few minutes to years. The comment says many types of cognitive problems can occur following ECT in addition to anterograde verbal memory and retrograde autobiographical memory, including retrograde loss of non-personal, non-rote information (such as knowledge used in daily work tasks), and impairments in working memory, processing speed, attention, and executive function. The comment also indicates that there are discrepancies within the order on the definition of long-term, which is defined as 1 month in some instance and as 3 months in other instances.

(Response 26) FDA recognizes that there are a variety of terms used in the scientific literature with respect to memory function. The multiple descriptions and definitions of various memory functions such as "short-term" or "long-term" memory contributes to significant confusion both among healthcare professionals and lay persons. FDA will require the inclusion of the following in the labeling: "ECT treatment may be associated with disorientation, confusion and memory loss, including short-term (anterograde) and long-term (autobiographical) memory loss following treatment. These side effects tend to go away within a few days to a few months after the last treatment with ECT. However, some patients have reported a permanent loss of memories of personal life events (i.e., autobiographical memory)." In addition, because of the complexity of memory loss, cognitive status monitoring prior to beginning ECT and during the course of treatment via formal neuropsychological assessment for evaluating specific

cognitive functions (e.g., orientation, attention, memory, executive function) is included as a special control.

(Comment 27) A comment asks FDA to change the proposed labeling by deleting from the list of known risks the phrase, "a worsening of the psychiatric symptoms they are being treated for," in § 882.5940(b)(1)(ix)(H)(2). The comment notes symptoms may worsen if ECT is not effective but argues that this is not the same as saying that symptoms worsen as a known risk of ECT. The comment notes that the possibility of precipitating a manic episode with ECT treatment is documented in the scientific literature but is already included in the listing of potential risks.

(Response 27) FDA recognizes that worsening of an underlying medical condition can occur either by: (1) an ineffective treatment or (2) the treatment itself, particularly when it exacerbates the symptoms. Without additional scientific evidence to distinguish between these two causes for the use of ECT, this language is included as a potential risk.

(Comment 28) Several comments indicated that labeling was not a sufficient mitigation for the risks associated with ECT. Several comments indicated that labeling was not a sufficient mitigation because the label might not be read, understood, or followed.

(Response 28) FDA notes that regardless of the classification and the risk presented by medical devices, they have the potential to cause harm to patients if the labeling is not read, understood, or followed. FDA has purposefully included, per the special controls, specific mitigations in the required labeling to ensure patient protections and transparency related to the benefit-risk profile of ECT. Labeling directed to healthcare professionals and patients further help to mitigate the risks of ECT because it must include instructions for use and a description of the known risks.

(Comment 29) A comment asks FDA to delete in § 882.5940(b)(1)(ix)(H)(3)(v) the phrase "insufficient, or lack of breathing" as a pulmonary complication and add a new item "prolonged action of anesthetic agents associated with insufficient or lack of breathing." The comment says the proposed text implies that insufficient or lack of breathing may be a long-term complication of ECT, whereas apnea is an expected effect of neuromuscular blocking agents. The comment notes insufficient or lack of breathing may be prolonged in some individuals but can be addressed through continued ventilation and oxygenation by an anesthesia provider.

(Response 29) FDA agrees that the warnings related to pulmonary risks were unclear and has revised § 882.5940(b)(1)(ix)(H)(3)(v) to identify these pulmonary risks associated with the use of general anesthesia and neuromuscular blocking agents.

F. Comments Outside of the Scope of this Final Order

There were several comments submitted that were outside the scope of this Final Order and in this section we explain why. Also, in this section comments are categorically grouped together so that the responses are by topic.

(Comment 30) A number of comments recommended that FDA take action to not allow the American Psychiatric Association (APA) to use the phrase "safe, effective treatment" and to prevent the APA and the National Institute for Mental Health from explicitly using some of the claims on ECT treatment.

(Response 30) FDA generally does not have the authority to direct medical associations and other government agencies on how to phrase their scientific evaluation of medical devices. Therefore, the requests are outside the scope of this final order.

(Comment 31) Several comments raised concerns regarding insurance coverage with different indications in different regulatory classes. Several comments indicated that coverage issues may reduce patient options for treatment.

(Response 31) FDA has no authority over commercial health insurance carriers. Under section 513(e) 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 ECT treatment.

(Comment 32) Some comments claim that ECT devices for specific intended uses are being reclassified for financial reasons and the Agency was influenced by the pharmaceutical industry in making its determination. A comment also asked FDA to provide reparations for ECT patients.

(Response 32) As stated previously in this section, FDA based its determination of reclassification of ECT devices for use in treating catatonia or a severe MDE associated with MDD or BPD to class II (special controls) on valid scientific evidence, including the classification panel recommendations, evaluation of scientific literature, clinical practice guidelines, and comments submitted to the ECT public dockets. These comments and the request for reparations are outside the scope of this final order.

(Comment 33) A comment claimed that there is discriminatory use of ECT including in women, people of color, elderly, and economically struggling patients. Another comment stated that many people are receiving ECT treatment out of desperation.

(Response 33) FDA understands the concerns of possible discriminatory actions by sub-populations in the treatment of ECT and possible treatment out of desperation; however, these

comments are outside the scope of this final order in determining the classification of ECT devices.

(Comment 34) A comment stated that the advertising of ECT devices directed at consumers promotes "risk-taking behavior."

(Response 34) This is also outside the scope of this final order in determining the classification of ECT devices.

Under the FD&C Act, FDA has regulatory authority over the labeling of medical devices (21 CFR part 801). However, FDA's regulation of medical device advertising is limited to a subset of restricted medical devices, which ECT is not. The Federal Trade Commission regulates the advertising, as opposed to the labeling, of most medical devices under sections 12-15 of the Federal Trade Commission Act, which prohibit false or misleading advertising of certain products that FDA regulates (15 U.S.C. 52-55).

IV. The Final Order

Under section 515(b) and (i) of the FD&C Act, FDA is adopting, in part, its findings as published in the preamble to the proposed order. For the reasons described previously in section II, FDA has made revisions in this final order in response to comments submitted in the ECT public dockets and information received on the proposed order. The revisions modify the ECT class II classification to also reclassify ECT devices used for the treatment of catatonia into class II. The revisions further modify the ECT class II classification by changing the requirement that the patient be "18 years of age and older" to the requirement that the patient be "age 13 years and older." The revisions modify the ECT class III classification by removing the catatonia intended use.

In response to comments, FDA also made some changes to the patient labeling special control requirement that addresses statements on the physical risks of ECT and additional age-related precautions. The patient labeling provides a list of physical risks, including pulmonary (affecting lungs) complications. FDA removes "insufficient or lack of breathing" as a pulmonary complication and revised the complication list to include potential pulmonary complications of general anesthesia and neuromuscular blocking agents (muscle relaxants) given as part of ECT. FDA added language to clarify that the pulmonary risks of ECT include hypoxemia, hypoventilation, aspiration, and upper-airway obstruction (see § 882.5940(b)(1)(ix)(H)(3)(v)).

FDA separately considered the risk of the accessory electrodes as part of this classification (see § 882.5940(b)(1)(iii)). No other accessories are considered part of this classification.

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), if FDA determines that premarket notification is not necessary to provide reasonable assurance of the SE of the device. For these ECT devices classified as class II, FDA has determined that premarket notification is necessary to provide reasonable assurance of the SE 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.

Under section 515(i)(2) of the FD&C Act, FDA has the authority to issue an administrative order revising the classification of a device for which 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 class I or class II, after issuance of a proposed order, a meeting of a device classification panel, and consideration of the comments on a proposed order.

FDA published a proposed order to require the reclassification of ECT devices for intended uses specified in the proposed order and to require the filing of a PMA for ECT devices for other intended uses specified in the proposed order in the *Federal Register* of December 29, 2015. Moreover, as explained in section II of the proposed order, on January 27-28, 2011, FDA held a classification meeting of the 2011 Panel to discuss classification of ECT devices for treatment of several disorders. FDA received and has considered all the comments received in response to all the ECT public dockets, including the proposed order, as discussed in section II. Therefore, FDA has met the requirements under sections 515(b)(1) and 515(i)(2) of the FD&C Act.

V. Implementation Strategy

A. Date to File a PMA

In accordance with section 515(b) of the FD&C Act, ECT devices indicated for schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia or a severe MDE associated with MDD or BPD in patients under 13 years who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition must have a PMA or a notice of completion of a PDP filed with the Agency by [INSERT DATE 90 DAYS AFTER THE 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. 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."

Under § 812.2(d) (21 CFR 812.2(d)), the exemptions from the requirements of the IDE regulations for preamendments class III devices in § 812.2(c)(1) and (2) will cease to apply to ECT devices indicated for schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia or a severe MDE associated with MDD or BPD in patients that are under 13 years, or patients of any age who are not treatment-resistant or who do not require a rapid response due to the severity of their psychiatric or medical condition that are: (1) not legally on the market on or before [INSERT DATE 90 DAYS AFTER THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] or (2) legally on the market on or before [INSERT DATE 90 DAYS AFTER THE 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 THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], or for which PMA approval has been denied or withdrawn.

If a PMA for a class III device is not filed with FDA by [INSERT DATE 90 DAYS AFTER THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], the device will be deemed adulterated under section 501(f) of the FD&C Act. 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 THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to avoid interrupting investigations.

B. Compliance with Special Controls

Following the effective date of this final order, ECT devices intended for use in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition must comply with the special controls. FDA notes that a firm whose ECT 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 use in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition, 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*]. ECT devices intended for use in treating catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition must comply with the special controls following the effective date of this order. Manufacturers who wish to continue to legally market an ECT device for treatment of catatonia or a severe MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition must submit an amendment to their

previously cleared 510(k) that demonstrates compliance with the special controls by [INSERT DATE 180 DAYS AFTER THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Because FDA has modified the class II indications and the class II patient population from the proposed order, FDA is extending the time period for submitting an amendment to the 510(k), from 60 days to 180 days, to provide additional preparation time to submit a 510(k) amendment. 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 an ECT device is in compliance with the special controls. If a 510(k) amendment is not submitted by [INSERT DATE 180 DAYS AFTER THE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] or if FDA determines that the amendment does not demonstrate compliance with the special controls, the device may be considered adulterated under section 501(f)(1)(B) of the FD&C Act.

For ECT devices that are not in class III as designated in this final order, 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 21 CFR 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 this final order, before marketing the new or changed device.

VI. Codification of Orders

Section 515(b), as amended by FDASIA, and 515(i)(2) 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 section 515(i)(2) of the FD&C Act, as amended by FDASIA, in this final order, we are codifying the reclassification of ECT devices for use in treating catatonia or a MDE associated with MDD or BPD in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition into class II by amending § 882.5940. Further, we are codifying the requirement for approval of an application for premarket approval for ECT devices for the intended uses of schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform, and catatonia or a severe major depressive episode associated with MDD or BPD in patients under 13 years, or patients 13 years and older who are not treatment-resistant or who do not require a rapid response due to the severity of their psychiatric or medical condition, by amending the language in § 882.5940.

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. 3501-3520). 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 have been approved under OMB control number 0910-0231.

The collections of information in 21 CFR part 801 have been approved under OMB control number 0910-0485.

The device and patient warning labeling provisions in this final order are not subject to review by OMB because they do not constitute a "collection of information" under the PRA. Rather, the recommended labeling is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

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 § 882.5940 to read as follows:

§ 882.5940 Electroconvulsive therapy device.

(a) *Identification.* An electroconvulsive therapy device is a prescription device, including the pulse generator and its stimulation electrodes, used for treating severe psychiatric disturbances by inducing in the patient a major motor seizure by applying a brief intense electrical current to the patient's head.

(b) *Classification.* (1) Class II (special controls) when the device is intended to treat catatonia or a severe major depressive episode (MDE) associated with major depressive disorder (MDD) or bipolar disorder (BPD) in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. The special controls for this device are:

(i) The technical parameters of the device, including waveform, output mode, pulse duration, frequency, train delivery, maximum charge and energy, and the type of impedance monitoring system must be fully characterized to ensure that the device performance characteristics are consistent with existing clinical performance data.

(ii) Non-clinical testing data must confirm the electrical characteristics of the output waveform.

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

(iv) Performance data must demonstrate electrical and mechanical safety and the functioning of all safety features built into the device including the static and dynamic impedance monitoring system.

(v) Appropriate analysis/testing must validate electromagnetic compatibility.

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

(vii) Performance data must demonstrate electrical performance, adhesive integrity, and physical and chemical stability of the stimulation electrodes.

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

(A) Information related to generic adverse events associated with electroconvulsive therapy device (ECT) treatment;

(B) Instructions must contain the following specific recommendations to the user of the device:

(*1*) Conduct of pre-ECT medical and psychiatric assessment (including pertinent medical and psychiatric history, physical examination, anesthesia assessment, dental assessment, and other studies as clinically appropriate);

(*2*) Use of patient monitoring during the procedure;

(*3*) Use of general anesthesia and neuromuscular blocking agents;

(*4*) Use of mouth/dental protection during the procedure;

(*5*) Use of EEG monitoring until seizure termination;

(*6*) Instructions on electrode placement, including adequate skin preparation and use of conductive gel; and

(*7*) Cognitive status monitoring prior to beginning ECT and during the course of treatment via formal neuropsychological assessment for evaluating specific cognitive functions (e.g., orientation, attention, memory, executive function).

(C) Clinical training needed by users of the device;

(D) Information on the patient population in which the device is intended to be used;

(E) Information on how the device operates and the typical course of treatment;

(F) 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;

(G) A detailed summary of the device technical parameters;

(H) Where appropriate, validated methods and instructions for reprocessing of any reusable components;

(I) The following statement, prominently placed: "Warning: ECT device use may be associated with: disorientation, confusion, and memory problems"; and

(J) Absent performance data demonstrating a beneficial effect of longer term use, generally considered treatment in excess of 3 months, the following statement, prominently placed: "Warning: When used as intended this device provides short-term relief of symptoms. The long-term safety and effectiveness of ECT treatment has not been demonstrated."

(ix) Patient labeling must be provided and include:

(A) Relevant contraindications, warnings, precautions;

(B) A summation 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;

(C) Information on how the device operates and the typical course of treatment;

(D) The potential benefits;

(E) Alternative treatments;

(F) The following statement, prominently placed: "Warning: ECT device use may be associated with: disorientation, confusion, and memory problems";

(G) Absent performance data demonstrating a beneficial effect of longer term use, generally considered treatment in excess of 3 months, the following statement, prominently placed: "Warning: When used as intended this device provides short-term relief of symptoms. The long-term safety and effectiveness of ECT treatment has not been demonstrated"; and

(H) The following statements on known risks of ECT, absent performance data demonstrating that these risks do not apply:

(*1*) ECT treatment may be associated with disorientation, confusion and memory loss, including short-term (anterograde) and long-term (autobiographical) memory loss following treatment. Based on the majority of clinical evidence, these side effects tend to go away within a few days to a few months after the last treatment with ECT. Although the incidence of permanent cognitive memory loss was not supported by the clinical literature, some patients have reported a permanent loss of memories of personal life events (i.e., autobiographical memory);

(*2*) Patients treated with ECT may experience manic symptoms (including euphoria and/or irritability, impulsivity, racing thoughts, distractibility, grandiosity, increased activity, talkativeness, and decreased need for sleep) or a worsening of the psychiatric symptoms they are being treated for; and

(*3*) The physical risks of ECT may include the following (in order of frequency of occurrence):

(*i*) Pain/somatic discomfort (including headache, muscle soreness, and nausea);

(*ii*) Skin burns;

(*iii*) Physical trauma (including fractures, contusions, injury from falls, dental and oral injury);

(*iv*) Prolonged or delayed onset seizures;

(*v*) Pulmonary complications (hypoxemia, hypoventilation, aspiration, upper-airway obstruction);

(*vi*) Cardiovascular complications (cardiac arrhythmias, heart attack, high or low blood pressure, and stroke); and

(*vii*) Death.

(2) *Classification*: Class III (premarket approval) for the following intended uses: schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia or a severe MDE associated with MDD or BPD in:

(i) Patients under 13 years or

(ii) Patients 13 years and older who are not treatment-resistant or who do not require a rapid response due to the severity of their psychiatric or medical condition.

(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 FDA on or before [INSERT DATE 90 DAYS AFTER THE DATE OF PUBLICATION IN THE FEDERAL REGISTER], for any electroconvulsive therapy 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 THE DATE OF PUBLICATION IN THE FEDERAL REGISTER, been found to be

substantially equivalent to any electroconvulsive therapy device with an intended use described in paragraph (b)(2) of this section, that was in commercial distribution before May 28, 1976. Any other electroconvulsive therapy 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 18, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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