[Federal Register Volume 80, Number 249 (Tuesday, December 29, 2015)]
[Proposed Rules]
[Pages 81223-81233]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2015-32592]

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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 Intended for Use in Treating Severe Major Depressive Episode in Patients 18 Years of Age and Older Who Are Treatment Resistant or Require a Rapid Response; Effective Date of Requirement for Premarket Approval for Electroconvulsive Therapy for Certain Specified Intended Uses

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed administrative order to reclassify the electroconvulsive therapy (ECT) device for use in treating severe major depressive episode (MDE) associated with major depressive disorder (MDD) or bipolar disorder (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, which is a preamendments class III device, into class II (special controls) based on new information. FDA is also proposing to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for ECT devices for other intended uses specified in this proposed order. The Agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the devices to meet the statute's approval requirements for other intended uses specified in this proposed order. In addition, FDA is announcing the opportunity for interested persons to request that the Agency change the classification of any of the devices mentioned in this document based on new information. This action implements certain statutory requirements.

DATES: Submit either electronic or written comments on this proposed order by March 28, 2016. See section XVII of this document for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

Federal eRulemaking Portal: http://www.regulations.gov.

Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to http://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party

may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on http://www.regulations.gov.

If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ``Written/Paper Submissions'' and ``Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ``Instructions.''

Instructions: All submissions received must include the Docket No. 2014-N-1210 for ``Neurological Devices; Reclassification of Electroconvulsive Therapy Devices Intended for Use in Treating Severe Major Depressive Episode in Patients 18 Years of Age and Older Who Are Treatment-Resistant or Require a Rapid Response; Effective Date of Requirement for Premarket Approval for Electroconvulsive Therapy Devices for Certain Specified Intended Uses''. Received comments will be placed in the docket and, except for those submitted as ``Confidential Submissions,'' publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ``THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION''. The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on http://www.regulations.gov. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ``confidential.'' Any information marked as ``confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: http://www.fda.gov/regulatoryinformation/dockets/default.htm.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the ``Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Michael J. Ryan, Center for Devices and

[[Page 81224]]

Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1615, Silver Spring, MD 20993, 301-796-6283, michael.ryan@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. 101-629), Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval). One type of general control provided by the FD&C Act is a restriction on the sale, distribution, or use of a device under section 520(e) of the FD&C Act (21 U.S.C. 360j(e)). A restriction under section 520(e) of the FD&C Act must be implemented through rulemaking procedures, unlike the administrative order procedures that apply to this proposed reclassification under section 513(e) of the FD&C Act, as amended by FDASIA.

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) 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).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type may be marketed without submission of a 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 or until the device is subsequently reclassified into class I or class II.

Although, under the FD&C Act, the 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. For simplicity, although corresponding requirements for PDPs remain available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing and receiving approval of a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act, changing the process for reclassifying a device from rulemaking to an administrative

order. Section 608(b) of FDASIA amended section 515(b) of the FD&C Act changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

A. Reclassification

FDA is publishing this document to propose the reclassification of ECT devices for use in treating 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 from class III to class II.

Section 513(e) of the FD&C Act governs reclassification of classified preamendments devices. This section provides that FDA may, by administrative order, reclassify a device based upon ``new information.'' FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term ``new information,'' as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland Rantos Co. v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see Bell, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F. Supp. 382, 388-391 (D.D.C. 1991)) or in light of changes in ``medical science'' (see Upjohn, 422 F.2d at 951). Whether data before the Agency are old or new data, the ``new information'' to support reclassification under section 513(e) must be ``valid scientific evidence,'' as defined in section 513(a)(3) of the FD&C Act and Sec. 860.7(c)(2) (21 CFR 860.7(c)(2)). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Mfrs. Assoc. v. FDA, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

FDA relies upon ``valid scientific evidence'' in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the ``valid scientific evidence'' upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act .) Section 520(h)(4) of the FD&C Act, added by FDAMA, provides that FDA may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This includes information from clinical and preclinical tests or studies that demonstrate the safety or effectiveness of the device but does not include descriptions of methods of manufacture or product composition and other trade secrets.



Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order for reclassifying a device. Specifically, prior to the issuance of a final order reclassifying a 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 to a public docket. 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, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act.

FDAMA added a section 510(m) to the FD&C Act. Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C

Act if the Agency determines that premarket notification is not necessary to assure the safety and effectiveness of the device.

B. Requirement for Premarket Approval Application

FDA is proposing to require PMAs for ECT devices for the intended uses listed in section IX of this proposed order. For the purposes of this proposed order, the term, ``Certain Specified Intended Uses,'' refers to the listing of the intended uses in section IX of this proposed order and includes the following: schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order requiring PMAs. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers. 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, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or a declared completed PDP and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order and the proposed findings, and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

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. For ECT devices, the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since these devices were classified in 1979, the 30-month period has expired (44 FR 51776, September 4, 1979). Therefore, if the proposal to require premarket approval for ECT devices for Certain Specified Intended Uses is finalized, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such device be filed within 90 days of the date of issuance of the final order. If a PMA is not filed for such device within 90 days after the issuance of a final order, the device would 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 by the later of the two dates, 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). In the past, FDA has requested that manufacturers take action to prevent the further use of devices for which no PMA has been filed and may determine that such a request is appropriate for the class III devices that are the subject of this proposed order, if finalized.

In accordance with section 515(b)(2)(D) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of ECT devices for Certain Specified Intended Uses.

## II. Regulatory History of the Device

In the preamble to the proposed rule (43 FR 55729, November 28, 1978), FDA described the recommendation of the Neurological Device Classification Panel (the Panel) that ECT be classified into class II because: ``Although the use of this device involves a substantial risk to the patient, the Panel believes that the benefit of the treatment outweighs the risks involved if the patients are selected carefully and the devices are designed and used properly. The Panel believes that a standard will provide reasonable assurance of the safety and effectiveness of the device and that there is sufficient information to establish a standard to provide such assurance.'' However, in 1979 (44 FR 51776, September 4, 1979), FDA classified ECT into class III after receiving several comments on the proposed rule, and reconvening the Panel to discuss these comments (May 29, 1979). The Panel discussed whether there was sufficient evidence to establish a performance standard for ECT. Several panel members expressed doubt that such information was available, and the Panel voted to recommend that ECT be classified into class III. FDA agreed with the Panel stating that FDA did not believe that the characteristics of ECT devices had been



identified precisely enough such that special controls could be established that would provide reasonable assurance of the safety and effectiveness of the device.

On August 13, 1982, the American Psychiatric Association (APA) submitted a reclassification petition to FDA requesting that ECT be classified into class II. The reclassification petition was discussed at a Panel meeting on November 4, 1982 (47 FR 44611, October 8, 1982). The Panel recommended that ECT be reclassified from class III to class II. FDA tentatively agreed that there was sufficient evidence to reclassify to class II for severe depression and schizophrenia and published a notice of intent to reclassify (48 FR 14758, April 5, 1983). Several comments received by the Agency argued that research and data did not support that ECT is an effective therapy for schizophrenia, and after careful review of the scientific literature and the APA's petition, FDA agreed with the comments. In the subsequent proposed rule (55 FR 36578, September 5, 1990), FDA determined that the evidence of effectiveness for schizophrenia was inconclusive, and proposed that ECT be reclassified to class II only for severe depression and remain class III for all other indications. In 1995, FDA published an order for the submission of safety and effectiveness information on ECT devices (60 FR 41986, August 14, 1995). In 2003, FDA published an intent to withdraw the 1990 proposed rule (68 FR 19766,

April 22, 2003) followed by withdrawal in 2004 (69 FR 68831, November 26, 2004) of the proposed rule for reclassification of ECT, along with other FDA proposed rules that had been outstanding for more than 5 years because the proposals were no longer considered viable candidates for final action. Thus, ECT devices remain in class III for all indications.

In 2009, FDA published an order for the submission of safety and effectiveness information on ECT devices by August 7, 2009 (74 FR 16214, April 9, 2009). In response to that order, FDA received two submissions from ECT manufacturers suggesting that ECT devices could be reclassified to class II. The manufacturers stated that safety and effectiveness of these devices may be assured by reducing the frequency of treatments, temporary or permanent interruption of treatments, reduction of stimulus dose, electrode placement, dosage or type of anesthetic (or other) medications, including minimizing psychotropic medications, brief pulse or ultra-brief pulse waveform stimulus, EEG monitoring, proper preparation (including conductive gel) and contact of the electrodes to the skin, changing anesthetic medications or doses, and changing concurrent medications.

In 2009, FDA also opened a public docket to receive information and comments regarding the current classification process for ECT by January 8, 2010 (74 FR 46607, September 10, 2009). FDA received over 3,000 submissions to the docket, with the majority of respondents, approximately 80 percent, opposing reclassification of ECT. The majority of those opposing reclassification of ECT cited adverse events from ECT treatment as the basis for their opposition. The most common type of adverse event mentioned in the public docket were memory adverse events, followed by other cognitive complaints, brain damage, and death.

On January 27-28, 2011, a meeting of the Neurological Devices Panel was held to discuss the classification of ECT devices for treatment of several disorders. There was panel consensus recommending class III for Schizophrenia, Bipolar manic states, Schizoaffective, and Schizophreniform disorder. The Panel did not reach consensus on the classification of ECT for depression (unipolar and bipolar) and catatonia. The Panel transcript and other meeting materials are available on FDA's Web site (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm240924.htm).

## III. Device Description

The ECT device consists of an electrical generator and a pair of electrodes that apply a brief intense electrical current to the head in order to induce a generalized seizure. In addition to generating and modulating the electrical functions of the stimulus, the box enclosing the generator also has capabilities and displays for physiological monitoring. The device parameters such as voltage, pulse width, frequency, and treatment (train) duration are adjustable. The typical display may provide information such as Electroencephalograph (EEG) activity, stimulus administration, total charge, energy, and impedance. These devices are currently regulated under Sec. 882.5940 (21 CFR 882.5940), product code GXC.

FDA is proposing in this order to modify the identification language from how it is presently written in Sec. 882.5940(a). FDA is clarifying in the identification that these are prescription devices and clarifying that this device type includes the ECT pulse generator and its stimulation electrodes and accessories.

## IV. Proposed Reclassification

FDA is proposing that ECT devices intended for 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 be reclassified from class III to class II. In this proposed order, the Agency has

identified special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls applicable to the devices, would provide reasonable assurance of safety and effectiveness. Absent the special controls identified in this proposed order, general controls applicable to the device are insufficient to provide reasonable assurance of the safety and effectiveness of the device.

Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and21 CFR 860.130, based on new information with respect to the devices and taking into account the public health benefit of the use of the device and the nature and known incidence of the risk of the device, FDA, on its own initiative, is proposing to reclassify this preamendments class III device into class II when the device is intended to treat 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. FDA believes that this new information is sufficient to demonstrate that the proposed special controls can effectively mitigate the risks to health identified in the next section, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness for ECT devices intended for 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.

Section 510(m) of the FD&C Act authorizes the Agency to exempt class II devices from premarket notification (510(k)) submission. FDA has considered ECT devices intended for 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 and decided that the device does require premarket notification. Therefore, the Agency does not intend to exempt this

[[Page 81227]]

proposed class II device from premarket notification (510(k)) submission.

## V. Risks to Health

After considering the available information from the reports and recommendations of the advisory committees (panels) for the classification of these devices, FDA has evaluated the risks to health associated with the use of ECT devices and determined that the following risks to health are associated with its use:

Adverse reaction to anesthetic agents/neuromuscular blocking agents. The muscle relaxing and sedating (or sleep inducing) drugs that are a part of the procedure may hamper the patient's ability to breathe spontaneously.

Adverse skin reactions. The patient-contacting materials of the device may cause an adverse immunological or allergic reaction in a patient.

Cardiovascular complications. The therapeutic convulsions may be accompanied by arrhythmias (irregular heartbeat) or ischemia/infarction (i.e., heart attack). Hypertension (high blood pressure) as well as hypotension (low blood pressure) may be associated with ECT treatment. ECT treatment may also result in stroke (impairment of blood flow to the brain or bleeding in the brain).

Cognition and memory impairment. ECT treatment may result in memory impairment, specifically immediate post-treatment disorientation, anterograde memory impairment and retrograde personal (autobiographical) memory impairment.

Death. Death may result from various complications of ECT such as reactions to anesthesia, cardiovascular complications, pulmonary complications, or stroke.

Dental/oral trauma. Dental fractures, dislocations,

lacerations, and prosthetic damage may occur as a result of strong muscle contractions during treatment.

Device malfunction. Faulty hardware, software or accessories (electrodes) or improper use may cause electrical hazards, such as the risk of excessive dose administration, prolonged seizures, and skin burns.

Manic symptoms. ECT treatment may result in the development of hypomanic or manic symptoms.

Pain/discomfort. The patient may experience mild to moderate pain following the motor seizure induced by ECT treatment.

Physical trauma. Inadequate supportive drug treatment may allow the patient to be injured from unconscious violent movements during convulsions.

Prolonged or tardive seizures. ECT treatment may result in prolonged or delayed seizures, and status epilepticus (continuous unremittent seizure) may ensue if prolonged seizures are not properly treated.

Pulmonary complications. ECT treatment may result in prolonged apnea (no breathing) or inhalation of foreign material, such as regurgitated stomach contents.

Skin burns. Excessive electrical current or improperly designed electrodes may cause the patient's skin under the electrodes to be burned.

Worsening of psychiatric symptoms. ECT treatment may be ineffective and therefore may result in worsening psychiatric symptoms.

## VI. Summary of Reasons for Reclassification

FDA believes that ECT devices indicated for 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 should be reclassified from class III to class II because, in light of new information about the effectiveness of these devices, special controls, in addition to general controls, can be established to provide reasonable assurance of safety and effectiveness of the device, and because general controls themselves are insufficient to provide reasonable assurance of its safety and effectiveness. FDA believes that in the specified patient population, and with the application of general and special controls as described in this document, the probable benefit to health from use of the device outweighs the probable injury or illness from such use. FDA acknowledges significant risks associated with ECT but believes that for the specified population--patients age 18 years of age and older experiencing a severe MDE associated with MDD or BPD for whom other treatment options have not been successful or for whom rapid, definitive response is needed due the severity of a psychiatric or medical condition--the probable benefit of ECT outweighs these risks. FDA is inviting comments on whether the term ``treatment resistant'' and the phrase ``require rapid response'' provide sufficient clarity to the population for which ECT benefits outweigh risks.

## VII. Summary of Data Upon Which the Reclassification Is Based

Since the time of the original ECT device classification, sufficient evidence has been developed to support a reclassification of ECT to class II with special controls for 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. FDA's review of the clinical literature has been previously summarized in the Executive Summary to the January 27-28, 2011, Neurological Device Panel meeting to discuss ECT classification (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM240933.pdf). The largest body of evidence for ECT effectiveness exists for MDE associated with MDD and BPD in patients 18 years of age

and older. Based on this review, FDA concluded that ECT demonstrated effectiveness in the acute phase (less than 3 months after treatment); however, the Panel members had various scientific opinions regarding the long-term effectiveness of ECT for the treatment of depression, but agreed that it was effective in the acute phase. Panel members indicated that controlled clinical trials are lacking regarding the effectiveness of ECT beyond the acute phase, in part, due to the fact that many patients have an initial improvement in the depressive symptoms following an acute course of ECT and are able to return to alternative treatments for managing depression such as medications and psychotherapy. The findings from FDA's review are consistent with other recently conducted, comprehensive, high quality systematic reviews, including the American Psychiatric Association (APA) recommendations/ guidelines (Ref. 1), the Third report of the Royal College of Psychiatrists' Special Committee on ECT (2004) (Ref. 2), the United Kingdom National Institute for Health and Clinical Excellence (NICE 2003; NICE 2009) (Refs. 3, 4), the Surgeon General's report on mental health (Ref. 5), systematic reviews by Semkovska and McLoughlin (Ref. 6), and Greenhalgh et al (Ref. 7). These findings from the FDA review included examining the results of over 60 randomized controlled clinical trials comparing ECT with either placebo (sham) or antidepressant therapy in which ECT was superior for patients 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. In addition, FDA conducted a systematic meta-analysis of these



studies which supported a robust effect of ECT in the short-term (e.g. 3 months) (Ref. 11).

FDA also examined other conditions, including bipolar mania, schizophrenia, schizoaffective disorder, schizophreniform disorder, and catatonia, but there were insufficient clinical data to support effectiveness for these conditions. FDA relied upon literature describing clinical study data collected largely in patients age 18 and older. Data on the use of ECT in children and adolescents is limited and hence the recommended reclassification is limited to patients 18 years of age and older. Most of the published literature FDA is aware of and reviewed focused on subject populations that did not receive benefit from prior treatments; therefore, the recommended reclassification is limited to treatment resistant populations as well as those patients who require a rapid response due to the severity of their psychiatric or medical condition. Further, practice guidelines published by the APA task force on ECT and the NICE in the United Kingdom recommend that ECT be considered for primary use (i.e., prior to medications) when there is a need for rapid, definitive response due to the severity of a psychiatric or medical condition. Conventional treatments such as medications and psychotherapy are likely to be less effective for a rapid definitive response, thus the recommended reclassification for ECT includes patients who require a rapid response because of the severity of their psychiatric or medical condition.

Panel deliberations focused heavily on ECT versus sham meta-analysis for treatment of depression. Discussion focused on the clinical meaningfulness of the effect size, the wide confidence interval which included 0 (i.e., the possibility of no effect), and the sources of variability in the dataset. Compared with other approved treatments for depression, the data suggest that the effect size of ECT is at least as large as, or larger than, that of other treatments (i.e., antidepressant medications) (Refs. 8, 9). In addition, other sources of evidence supported the effectiveness claim of ECT, including the FDA effectiveness systematic review, the meta-analysis demonstrating ECT favorability over placebo, and meta-analyses demonstrating ECT effectiveness being equal to or better than some antidepressant medications (see FDA Executive Summary from the panel meeting, Ref. 11).

While medical/physical risks may occur with ECT, they vary in frequency, with the most severe risks being quite rare. Death associated with ECT appears to occur at a very low rate comparable to that of minor surgical procedures. Recent estimates of the mortality rate associated with ECT treatment are 1 per 10,000 patients or 1 per 80,000 treatments (Refs. 1, 10).

The risks of greatest concern to clinicians and patients remain cognitive and memory impairment. Both the FDA review of literature and the meta-analyses of the randomized controlled studies indicate that while post-procedure disorientation occurs frequently, it is transient, typically resolving within minutes after the procedure is complete. The systematic meta-analyses of the randomized controlled clinical trials data by FDA revealed that there is no evidence that disorientation following ECT is long-term or persistent. The primary areas of concern for persistent changes are anterograde and retrograde autobiographical memory. While rates of occurrence are difficult to estimate, it appears that both types of memory impairment are not uncommon. The literature review suggests that anterograde memory declines immediately post-ECT and then returns to baseline within 3 months post-ECT. Retrograde autobiographical memory declines immediately post-ECT and then appears to improve over time. It is important to note that while improvement is seen, impairment may persist past 6 months post-ECT. Data on persistent retrograde autobiographical memory deficits beyond 6 months is lacking in the scientific literature. Therefore, it cannot be concluded that retrograde autobiographical memory returns to baseline over time. (See tables 6 and 7 and Figures 2-24 from FDA's Executive Summary, Ref. 11.)

Despite the occurrence and uncertainty of duration of memory impairment, FDA believes that the potential benefits of ECT outweigh the risks in patients 18 years of age or older for 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.

## VIII. Proposed Special Controls

FDA believes that special controls, in addition to the general controls, are necessary to provide a reasonable assurance of safety and effectiveness for ECT devices indicated for 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. FDA believes that the risks to health identified in section V associated with ECT devices indicated for 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 can be mitigated with general and special controls.

Several of the risks associated with ECT, including adverse reaction to anesthetic agents/neuromuscular blocking agents, cardiovascular complications, death, and pulmonary complications, are medical/physical risks related to the procedure involving use of the device. For these risks, safe use of the device is based on appropriate directions for use. FDA believes that labeling provisions are adequate to mitigate these risks, including:

- Disclosure of contraindications, precautions, warnings, and potential adverse effects/complications in both physician and patient labeling so that users and patients can be advised of conditions under which ECT treatment should not proceed, and
- Specific device use instructions including information regarding conduct of pre-ECT patient assessments; and information on appropriate patient monitoring during an ECT procedure) to minimize potential ECT procedural complications.

Other ECT risks are specific to the medical/physical effects of the induced seizure and potentially severe muscle contractions that result from use of the device (dental/oral trauma, physical trauma, prolonged or tardive seizures, pain/discomfort). FDA believes that appropriate labeling provisions are adequate to mitigate these risks, including:

Disclosure of contraindications, precautions, warnings, and adverse effects/complications in both physician and patient labeling so that users and patients can be advised of conditions under which ECT treatment should not proceed and are aware of potential adverse effects associated with ECT treatment, and

Specific device use instructions including information regarding conduct of pre-ECT assessments, use of mouth protection during the procedure, use of general anesthetic agents and neuromuscular blocking agents, and information on appropriate patient monitoring during the procedure to minimize potential post-ECT complications.

The risks of skin burns can be mitigated by performance testing of the device to demonstrate safe electrical performance, adhesive integrity, and physical and chemical stability of the



stimulation electrodes. This risk is further mitigated by providing specific user instructions regarding proper electrode placement, including instructions for adequate skin preparation and use of conductivity gel in placing the electrodes.

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 to ensure that the device performance characteristics are consistent with existing clinical performance data that supports a reasonable assurance of safety and effectiveness (see information on review of clinical performance data in section VII). This risk is further mitigated by providing information to both the user and patient 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 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 providers to make informed choices about how and when to use ECT to maximize benefits and minimize potential adverse effects.

The risks associated with malfunction of the device can be mitigated by data demonstrating electrical and mechanical safety and the functioning of all safety features built into the device (including the static and dynamic impedance monitoring system); appropriate analysis/testing of electromagnetic compatibility such that electromagnetic interference does not cause device malfunction; and appropriate software verification, validation, and hazard analysis to ensure that any device software has been adequately designed.

The potential for manic symptoms or worsening of the condition being treated can be mitigated by labeling provisions, including:

The clinical training needed by users of the device to ensure appropriate use of ECT and appropriate ongoing medical management of the patient, and

Information on the patient population in which the device is intended to be used, including a detailed summary of the clinical testing pertinent to use of the device, information on the potential adverse effects of treatment, and information on the typical course of treatment such that users and patients can make informed decisions regarding the appropriate use of ECT.

The risks of adverse skin reactions can be mitigated with biocompatibility testing to ensure that the materials used in patient-contacting components of the device are safe for skin contact as well as labeling that provides information on validated methods for reprocessing any reusable components between uses.

Specifically, FDA believes that special controls in Sec. 882.5940(b)(1), together with general controls, are sufficient to mitigate the risks to health described in section V:

Table 1 shows how FDA believes that the risks to health identified

in section V can be mitigated by the proposed special controls.

Table 1--Health Risks and Mitigation Measures for ECT

| Identified risk | Special controls |
|---|---|
| Adverse reaction to anesthetic agents/ neuromuscular blocking agents. | Labeling. |
| Adverse skin reactions | Biocompatibility<br>Labeling. |
| Cardiovascular complications | Labeling. |
| Cognitive and memory impairment | Technical parameters<br>Non-clinical test data.<br>Labeling. |
| Death | Labeling. |
| Dental/oral trauma | Labeling. |
| Device malfunction | Performance data.<br>Electromagnetic compatibility.<br>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.<br>Labeling. |
| Worsening of psychiatric symptoms | Labeling. |

In addition, FDA is proposing to limit this reclassification to prescription use devices under 21 CFR 801.109. Under 21 CFR 807.81, the device would continue to be subject to 510(k) notification requirements. Elsewhere in this issue of the Federal Register, FDA is announcing the availability of a draft guidance document entitled ``Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses,'' that, when finalized, would provide recommendations on how to comply with the special controls proposed in this order, if FDA reclassifies this device.

## IX. Dates New Requirements Apply

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency within 90 days after issuance of any final order based on this proposal for ECT devices intended for Certain Specified Intended Uses. 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.''

FDA intends that under Sec. 812.2(d), the preamble to any final order based on this proposal will state that, as of the date on which the filing of a PMA or a notice of completion of a PDP is required to be filed, the exemptions from the requirements of the IDE regulations for preamendments class III devices in Sec. 812.2(c)(1) and (2) will cease to apply to any device that is: (1) Not legally on the market on

or before that date or (2) legally on the market on or before that date but for which a PMA or notice of completion of a PDP is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA for a class III device is not filed with FDA within 90 days after the date of issuance of any final order requiring premarket approval for the device, the device would be deemed adulterated under section 501(f) of the FD&C Act (21 U.S.C. 351(f)). 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 Sec. 812.30. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before the end of the 90-day period after the issuance of the final order to avoid interrupting investigations.

FDA proposes that following the effective date of any final order, ECT devices intended for 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 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 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, may remove such intended uses from the device's labeling. FDA proposes that such ECT devices must comply with the special controls, and, as part of the special controls, anyone who wishes to continue to market an ECT device for these uses must submit an amendment to their previously cleared premarket notification (510(k)) that demonstrates compliance with the special controls within 60 days after the effective date of the final order. 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 within 60 days after the effective date 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

## X. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring that this device have an approved PMA or a declared completed PDP when intended for use in treating any condition other than 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 (2) the benefits to the public from the use of ECT devices for other specified intended uses.

These findings are based on the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted in response to the 515(i) Order (74 FR 16214), the public docket (74 FR 46607) and any additional information that FDA has obtained. Additional information regarding the risks as well as classification associated with this device type can be found in 43 FR 55729, 44 FR 51776, 48 FR 14758, and 55 FR 36578.

## XI. Device Subject to the Proposal To Require a PMA--ECT Devices for Certain Specified Intended Uses (Sec. 882.5940(c))

### A. Identification

An electroconvulsive therapy device is a device 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. Summary of Data

For intended uses other than the treatment of 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, FDA concludes that the safety and effectiveness of ECT devices have not been established by adequate scientific evidence. Given the FDA analysis and the advisory panel deliberations (see http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm240924.htm), there is insufficient evidence of effectiveness for indications including: schizophrenia, bipolar mania (and mixed states), schizoaffective disorder, schizophreniform disorder, and catatonia. The panel recommended Class III designation for schizophrenia, bipolar mania (and mixed states), schizoaffective disorder, and schizophreniform disorder; however, the panel did not reach consensus on the classification of ECT in treatment of catatonia and a review of the literature for use of ECT in catatonia yielded only one randomized control trial (Ref. 11). The body of evidence is not sufficiently robust for FDA to determine that there is a reasonable assurance of safety and effectiveness for ECT treatment of catatonia. Catatonia is a potentially life-threatening condition for patients unresponsive to the current standard of care treatment. FDA encourages collection of additional data that may support future reclassification of ECT for this use.

FDA believes that insufficient information exists regarding the risks and benefits of the device in order for FDA to determine that general and/or special controls will provide reasonable assurance of the safety and effectiveness of ECT for Certain Specified Intended Uses. 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 safety and effectiveness and the device is purported or represented to be for a use that is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. FDA believes that the risks to health identified in section V for the use of ECT devices for Certain Specified

[[Page 81231]]

Intended Uses, in the absence of an established positive benefit-risk profile, presents a potential unreasonable risk of illness or injury.

C. Risks to Health

The risks to health for ECT devices for intended uses other than the treatment of 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 are the same as outlined in section V.

D. Benefits of ECT Devices

As discussed previously, there is limited scientific evidence regarding the effectiveness of ECT devices for intended uses other than the treatment of 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. Because the benefits of these devices for such uses are unknown, it is impossible to estimate the direct effect of the devices on patient outcomes. However, based on claims made about the devices, the devices have the potential to benefit the public by providing additional treatment options for schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia.

## XII. PMA Requirements

A PMA for ECT devices Certain Specified Intended Uses must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see Sec. 860.7(c)(1)). Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. (Sec. 860.7(c)(2)).

## XIII. Opportunity To Request a Change in Classification

Before requiring the filing of a PMA or notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of ECT devices is to be in the form of a reclassification petition containing the information required by 21 CFR 860.123, including new information relevant to the classification of the device.

## XIV. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices and section 515(b) of the FD&C Act provided for FDA to issue regulations to require approval of an application for premarket approval for preamendments devices or devices found to be substantially equivalent to preamendments devices. Because sections 513(e) and 515(b) of the FD&C Act as amended require FDA to issue final orders rather than regulations, 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 (CFR). Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this proposed order, we are proposing to codify the reclassification of ECT devices for use in treating severe Major Depressive Episode (MDE) associated with Major Depressive Disorder (MDD) or Bipolar Disorder (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 into class II by amending Sec. 882.5940.

## XV. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) 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.

## XVI. Paperwork Reduction Act of 1995

This proposed 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 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120. The collections of information in 21 CFR 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 device and patient warning labeling provisions in this proposed rule 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)).

## XVII. Proposed Effective Date

FDA is proposing that any final order based on this proposal become effective 90 days after the date of publication in the Federal Register.

## XVIII. Specific Questions for Comment

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). FDA is explicitly seeking 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.

[[Page 81232]]

## XIX. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at http://www.regulations.gov. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

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10. Girish, K., N.S. Gill, ``Electroconvulsive Therapy in Lorazepam Non-Responsive Catatonia.'' Indian Journal of Psychiatry: 45(1):21-25, 2003.
11. FDA Executive Summary, Prepared for the January 27-28, 2011 meeting of the Neurological Devices Panel, Meeting to Discuss the Classification of Electroconvulsive Therapy Devices (ECT), available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm240924.htm.

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, it is proposed that 21 CFR part 882 be amended as follows:

PART 882--NEUROLOGICAL DEVICES

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1. The authority citation for 21 CFR part 882 continues to read as follows:

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

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2. Revise Sec.  882.5940 to read as follows:

Sec.  882.5940  Electroconvulsive therapy device.

(a) Identification. An electroconvulsive therapy device is a

prescription device, including the pulse generator and its stimulation electrodes and accessories, 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 severe major depressive episodes (associated with major depressive disorder or bipolar disorder) 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. 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.

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

(iii) Components (and accessories) 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 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 conductivity 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.''

(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.''

(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. 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). Improvements in the way ECT is applied to patients currently, with controlled electric currents and electrode placement, can minimize but not completely eliminate, these risks.

(2) Patients treated with ECT may also 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.

(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 (insufficient, or lack of breathing, or inhalation of foreign substance into the lungs).

(vi) Cardiovascular complications (heart attack, high or low blood pressure, and stroke).

(vii) Death.

(viii) Devices marketed prior to the effective date of this reclassification must have an amendment submitted to their previously cleared premarket notification (510(k)) that demonstrates compliance with these special controls within 60 days after the effective date of this reclassification.

(2) Classification: Class III (premarket approval) for the following intended uses: schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia.

(c) Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER 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 [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER 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, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-32592 Filed 12-28-15; 8:45 am]

BILLING CODE 4164-01-P