

Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses

Draft Guidance for Industry, Clinicians and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions regarding this document, contact Peter G. Como, Ph.D., at 301-796-6919 or peter.como@fda.hhs.gov



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Neurological and Physical Medicine Devices
Physical Medicine and Neurotherapeutic Devices Branch**

Preface

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Table of Contents

1	Introduction	1
2	Background	1
3	Scope	2
4	510(k) Submission Recommendations	2
4.1	Device Description	2
4.2	Comparison to Predicate Device	4
4.3	Technical Parameters	5
4.4	Biocompatibility	6
4.5	Electrical and Mechanical Safety	6
4.5.1	General Equipment Safety	7
4.5.2	Device Specific Safety Features	7
4.6	Electromagnetic Compatibility (EMC)	8
4.7	Software Life Cycle and Risk Management	8
4.8	Electrodes	9
4.8.1	Electrical Performance	9
4.8.2	Adhesive Performance	10
4.8.3	Stability	10
4.9	Labeling	10
4.9.1	Instructions for Use	10
4.9.1.1	Device Use	11
4.9.1.2	Intended Use	11
4.9.1.3	Contraindications	12
4.9.1.4	Warnings	13
4.9.1.5	Precautions	14
4.9.1.6	Procedure Cautions and Risk Mitigation	14
4.9.1.7	Clinical Testing and Reported Adverse Events	15
4.9.1.8	Reuse of the Device	16
4.9.1.9	Training	16
4.9.2	Patient Labeling	16
4.9.2.1	Purpose of the device and indications for use	17
4.9.2.2	Benefits and Risks of the Device	17
4.9.2.3	Alternative Treatments	19
5	Animal and Clinical Testing	19
5.1	Animal Testing	19
5.2	Clinical Evidence	19
5.3	Significant Risk and Investigational Device Exemption (IDE)	20
5.4	Clinical Protocol	20
5.5	Reporting of Statistical Outcomes for Clinical Study Results	23
5.5.1	Statistical Analysis Plan	24
5.6	Reporting Results from Journal Articles or Meta-analyses	25
	Appendix A. Definitions of Output Specifications	27

Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses

Draft Guidance for Industry, Clinicians and FDA Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1 Introduction

This draft guidance document provides draft recommendations for 510(k) submissions and compliance with special controls being proposed to support reclassification of Electroconvulsive Therapy (ECT) Devices into class II (special controls) for 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. An ECT device is an electrical device used for treating severe psychiatric disturbances by applying a brief intense electrical current to the patient's head to induce a major motor seizure. This guidance is issued for comment purposes only.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2 Background

FDA has issued a proposed administrative order to reclassify ECT devices for the treatment of severe MDE associated with MDD or BPD in patients 18 years of age or older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition, which are currently Class III devices, into Class II (special controls), subject to premarket notification. FDA is proposing this reclassification under the Federal Food, Drug and Cosmetic Act (FD&C Act) based on new information pertaining to the device. This draft guidance is intended to provide recommendations on how to comply with the special controls proposed in 21 CFR

36 882.5940(b)(1) and indicate what information is suggested for submission to FDA in a
37 510(k) to demonstrate that the special controls have been met.

38 The special controls proposed in 21 CFR 882.5940(b)(1) include a requirement that
39 devices marketed prior to the effective date of the final reclassification must submit an
40 amendment to their previously cleared 510(k) that demonstrates compliance with the
41 special controls within 60 days after the effective date of the final reclassification. The
42 recommendations in this guidance are also appropriate for submission in such
43 amendments.

44 **3 Scope**

45 An ECT device, as described in 21 CFR § 882.5940, is defined as:

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

50 The scope of this document is limited to ECT devices intended for the treatment of severe
51 MDE associated with MDD or BPD in patients 18 years of age and older who are treatment-
52 resistant or who require a rapid response due to the severity of their psychiatric or medical
53 condition, proposed § 882.5940(b)(1), product code GXC. ECT devices used outside of this
54 indication are not within the scope of this guidance.

55 **4 510(k) Submission Recommendations**

56 The sections below provide recommendations on information to include in a 510(k)
57 submission for an ECT device intended for the treatment of severe MDE associated with
58 MDD or BPD in patients 18 years of age and older who are treatment-resistant or who require
59 a rapid response due to the severity of their psychiatric or medical condition. The sections
60 below also include recommendations about how to comply with the proposed special
61 controls, and how to demonstrate such compliance within a 510(k) submission.

62 **4.1 Device Description**

63 You should identify your device by the regulation and product code described in **Section 3**
64 **(Scope)**. In addition, we recommend that your device description contain the following
65 information:

- 66 • **General Information:** You should identify classification name (e.g.,
67 electroconvulsive therapy device), the CFR classification regulation number under
68 which you believe the device and any components/accessories are regulated, common
69 name (e.g., electroconvulsive therapy device, (ECT)), trade or proprietary name,
70 including a listing of all model numbers, and a clear description of the proposed
71 device's intended use. In addition, you should specify whether this device has been
72 previously submitted to FDA and, if so, if it was for identical or different indications.

73 If the device has been previously cleared by FDA for different indications, specify for
74 which indications.

- 75 • **Device components and accessories.** You should provide a description of how the
76 ECT device interconnects (e.g., cables and connectors) with other components or
77 accessories.

78 Examples of components and accessories commonly used with ECT devices
79 including the following:

80
81 Stimulation Electrodes: You should specify the materials, construction, type (e.g.,
82 adhesive or hand-held), and dimensions of the electrodes provided with, or
83 recommended for use with, your device.

84
85 Electrode Lead Wires and Patient Cables: You should describe the length(s),
86 construction, materials, and connections between the stimulator device and the
87 electrodes.

88
89 Electrode Gel: Electroconductive media used with ECT devices are regulated as
90 class II devices under 21 CFR 882.1275.

91
92 Electroencephalography (EEG) Component: EEG components of ECT devices are
93 regulated as Class II devices under 21 CFR 882.1400.

94
95 Electrocardiography (ECG) Component: ECG components of ECT devices are regulated as
96 Class II devices under 21 CFR 870.2340.

97
98 For any devices labeled for use specifically with your ECT devices that have received
99 prior marketing clearance, you should identify the name of the manufacturer and, if
100 applicable, include reference to the 510(k) number through which marketing
101 clearance was obtained.

- 102 • **Photograph or engineering drawings of the device.** You should also provide a
103 photograph or engineering drawing of the device and a functional block diagram
104 (including all accessories).
- 105 • **User interface.** You should describe the user interface, including user controls,
106 displays and functions. You should describe how stimulation is initiated and controlled
107 and describe whether individual output stimulus parameters (e.g., amplitude, pulse
108 width, frequency, train duration) can be adjusted by the user or whether only the percent
109 maximum charge or energy can be adjusted. A description of all output displays should
110 be provided.
- 111 • **Programmability.** You should indicate any fixed or default programs and whether
112 the device can be custom programmed by the user. If programmable, the extent of the
113 device's programmability should be provided.
- 114 • **Technical specifications.** You should provide a detailed table summarizing the
115 device technical specifications (i.e., product specifications, such as the examples

- 116 below, including parameter ranges and accuracy, and any other functional, physical,
117 and environmental specifications of the device), including:
- 118 ○ Output stimulation specifications and operating limitations (See Sections 4.2
119 and 4.3 of this guidance);
 - 120 ○ Power source specifications:
 - 121 - For AC line-powered devices, you should specify the line voltage and
122 frequency, and the method of line current isolation
 - 123 - For battery powered devices, you should identify the number, size,
124 chemistry, and type (primary cell or rechargeable) of batteries to be used
125 with the device and the estimated longevity of the battery. You should also
126 provide a description of battery indicators (e.g., low battery and charging
127 indicators); and
 - 128 ○ A description of all possible device settings.
- 129 • **Patient contacting materials.** You should identify the components of the device that
130 are patient contacting. For each component, you should identify the generic material
131 of construction, the supplier, and the unique material identifier.
 - 132 • **Software.** You should provide a complete description of software and the appropriate
133 software documentation as described in Section 5.7 of this guidance.
- 134

135 **4.2 Comparison to Predicate Device**

136 You must provide information on how your device is similar to and different from the legally
137 marketed predicate device (“predicate device”) in accordance with 21 CFR 807.87(f). We
138 recommend that you provide a side-by-side comparison in a comparison table whenever
139 possible. You should provide a discussion elaborating on the similarities and differences
140 identified in the comparison table. Your discussion should include an explanation of how
141 your device is substantially equivalent, referencing performance data as necessary. If there
142 are technical differences between your device and the predicate device, you should also
143 provide a rationale for why such differences do not raise different questions of safety and
144 effectiveness .

145 Table 1 shows the minimum recommended comparison information to provide in your
146 submission.

147 **Table 1. Device Output Parameters (See Appendix A. Definitions of Output**
 148 **Specifications)**

Descriptive Information	Proposed Device	Predicate Device
Waveform(s) (e.g., pulsed monophasic, pulsed biphasic) ^a		
Shape		
Current or Voltage Regulated?		
Maximum Output Voltage (volts) (+/- ____%)		
Maximum Output Current (mA) (+/- ____%)		
Frequency (Hz)		
Pulse Duration (ms)		
Minimum Electrode Surface Area (cm ²)		
Pulse Delivery Mode		
Maximum Pulse Train Duration (seconds)		
Number of Trains per Activation		
Maximum Total Charge Delivered (mC) ^b (+/- ____%)		
Isolation Resistance from Ground (MΩ)		
Maximum Total Energy Delivered (J) ^c @ 220 Ω (+/- ____%)		
Impedance Monitor (static and/or dynamic)		
High/Low Impedance Shut Down Level(Ω) ^d		

149 ^a Output specifications should be provided for each different output waveform.

150 ^b The maximum total charge in predicate devices is 576.0 mC.

151 ^c The maximum total energy in predicate devices is 101.4 J into a 220 Ω load.

152 ^d Recommended allowable bounds for dynamic impedance is 100 to 600 Ω.

153 If the ECT device includes other components such as electrode gels (21 CFR 882.1275),
 154 EEG (21 CFR 882.1400), and ECG (21 CFR 870.2340), a comparison of the technical
 155 characteristics of the components should also be made to an appropriate legally marketed
 156 predicate device.

157 **4.3 Technical Parameters**

158 FDA is proposing to require as a special control that sponsors identify the technical
 159 parameters of the device, including waveform, output mode, pulse duration, frequency, train
 160 delivery, maximum charge and energy, and the type of impedance monitoring system
 161 necessary to characterize and compare the device performance. FDA is further proposing a
 162 special control that non-clinical testing confirm the electrical characteristics of the output

163 waveform. In order to adequately characterize your device output, the technical parameters
164 of the device, as listed in Table 1, should be provided. See Appendix A for definitions. You
165 should also provide the following documentation for each output waveform associated with
166 these output parameters:

- 167 a. Minimum and maximum output values;
- 168 b. Increments for increasing output value;
- 169 c. Accuracy (i.e., (+/- ____%));
- 170 d. Stimulus ramp up and down times;
- 171 e. A description of how the output values were verified, including the number of devices
172 tested (minimum of 10 devices is recommended)
- 173 f. For each output mode, you should provide an oscilloscope tracing (or an accurate
174 diagram) describing the electrical output waveform. For each output mode, we
175 recommend you provide tracings to describe the individual pulse output waveform
176 under loads of 100, 220, and 600 ohms. FDA also recommends you provide one
177 tracing showing the series of pulses into a 220 ohm load. With each tracing, we
178 recommend you include:
 - 179 i. name of the output mode
 - 180 ii. clearly labeled amplitude and time axes
 - 181 iii. identification of the amplitude baseline (i.e., with no output)
 - 182 iv. listing of all output parameter settings (e.g., amplitude, pulse width,
183 frequency).

184 **4.4 Biocompatibility**

185 FDA is proposing to require as a special control that components (and accessories) of the
186 device that come into human contact must be demonstrated to be biocompatible. You should
187 select biocompatibility tests appropriate for the duration and nature of contact with your
188 device. For stimulation electrodes, we recommend you conduct testing for external devices
189 in contact with the skin for a limited duration (i.e., less than 24 hours). If identical materials
190 and identical material processing are used in a predicate device with the same type and
191 duration of patient contact, you may identify the predicate device in lieu of providing
192 biocompatibility testing.

193 **4.5 Electrical and Mechanical Safety**

194 FDA is proposing to require as a special control that performance data must demonstrate
195 electrical and mechanical safety and the functioning of all safety features built into the device
196 including the static and dynamic impedance monitoring system. The sections below provide
197 recommendations regarding performance data for electrical and mechanical safety.

198 **4.5.1 General Equipment Safety**

199 We recommend that you demonstrate the electrical and mechanical safety of the device by
200 performing electrical and mechanical safety testing as described in the FDA-recognized
201 standard, IEC 60601-1, Medical Electrical Equipment – Part 1: General requirements for
202 basic safety and essential performance, or by an equivalent method.

203 You should provide a detailed discussion of the extent to which this standard was used to
204 guide the device design and protect against electrical and mechanical hazards. The
205 discussion should include specific criteria such as:

- 206 • power supply – supply type, rated voltage, rated current, frequency, etc.;
- 207 • accuracy of controls and protection from delivering hazardous outputs;
- 208 • protection under fault-conditions;
- 209 • protection against unwanted or excessive radiation;
- 210 • excessive temperature;
- 211 • environmental testing;
- 212 • mechanical hazards associated with moving parts and overall device construction; and
- 213 • protection from leakage current under normal and single-fault conditions.

214 If the device is intended for use with rechargeable batteries, we recommend that your 510(k)
215 identify the method used to isolate the user from AC line current, and that you follow IEC
216 60601-1, *Medical Electrical Equipment - Part 1: General Requirements for Safety*, or an
217 equivalent method to show that the levels of patient leakage current, measured under both
218 normal and single fault conditions, are acceptable. You should also specify whether the
219 device can be used during recharging.

220 **4.5.2 Device Specific Safety Features**

221 To demonstrate the functioning of safety features, FDA recommends you describe all such
222 features built into the device, including how they function (e.g., hardware and/or software),
223 and provide testing to demonstrate that they function as specified, including but not limited
224 to:

- 225 • disabling or limiting runaway pulse trains
- 226 • patient isolation from line currents
- 227 • preventing unintended DC current
- 228 • limiting maximum output

- 229 • providing shut-offs for high or low impedance with dynamic impedance monitoring
- 230 • visual and/or audible indicators for stimulus delivery
- 231 • manual abort treatment capability

232 **4.6 Electromagnetic Compatibility (EMC)**

233 FDA is proposing to require as a special control that appropriate analysis/testing must
234 validate electromagnetic compatibility (EMC). EMC encompasses both emissions
235 (interference with other electronic devices) and immunity (interference with device
236 performance created by emissions from other electronic devices). We recommend that you
237 evaluate the EMC of your device for all device output modes in accordance with IEC 60601-
238 1-2, *General requirements for basic safety and essential performance – Collateral standard:*
239 *Electromagnetic compatibility – Requirements and tests*. You should also provide:

- 240 • a clear summary of all EMC testing (emissions and immunity) of this device with the
241 test results and data to support any claims for immunity to electromagnetic
242 interference (EMI);
- 243 • a brief explanation of how each EMC test was performed and how the testing for each
244 mode addresses the risks for EMI and demonstrates EMC to the claimed levels;
- 245 • a brief explanation of how the testing addresses the timing of the device for therapy
246 delivery;
- 247 • explanations and justifications for any deviations from the referenced standards or
248 modifications to the device tested; and
- 249 • pass/fail criteria for each EMC tests, how these were quantified and measured, and
250 justifications for these criteria.

251 **4.7 Software Life Cycle and Risk Management**

252 FDA is proposing to require as a special control that appropriate software verification,
253 validation, and hazard analysis be performed. We recommend that you submit information
254 for software-controlled devices as described in [Guidance for the Content of Premarket](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)
255 [Submissions for Software Contained in Medical Devices](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)
256 [\(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/u](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)
257 [cm089543.htm\)](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm). As described in the Software Guidance, the documentation that FDA
258 recommends you submit is determined by the “level of concern” for your software device.
259 The level of concern is related to the risks associated with software failure. FDA believes
260 that the software used to operate an ECT device presents a “major level of concern” because
261 a failure or latent design flaw could either directly result in major injury to the patient or
262 could indirectly result in major injury to the patient through incorrect or delayed information
263 or through the action of a care provider.

264 We recommend that you provide a full description of the software/firmware supporting the
265 operation of the subject device following the Software Guidance, commensurate with a major
266 level of concern. This recommendation applies to original device/systems as well as to any
267 software/firmware changes made to already-marketed devices. Changes to software must be
268 revalidated and re-verified in accordance with Design Controls, 21 CFR 820.30, and
269 documented in the Design History File, per 21 CFR 820.30(j). Some software changes may
270 warrant the submission of a new 510(k).

271 We advise you to consider whether you can conform to any recognized software standards
272 and provide statements or declarations of conformity as described in the FDA Guidance, *Use*
273 *of*
274 *Standards in Substantial Equivalence Determinations* ([http://www.fda.gov/MedicalDevices/](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm)
275 [DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm)).¹ Please visit the
276 following website to search for the FDA-recognized standards involving medical devices
277 containing software: [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/G](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm)
278 [uidanceDocuments/ucm073752.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm).

279 If the device includes off-the-shelf software, you should provide additional information as
280 recommended in the FDA document titled *Guidance for Industry, FDA Reviewers and*
281 *Compliance on Off-the-Shelf Software Use in Medical Devices* ([http://www.fda.gov/Medical](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073778.htm)
282 [Devices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073778.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073778.htm)).

283 **4.8 Electrodes**

284 FDA is proposing to require as a special control that performance data must demonstrate
285 electrical performance, adhesive integrity, and physical and chemical stability of the
286 stimulation electrodes. To assure that the device performs as intended, we recommend that
287 you evaluate and document the electrodes' biocompatibility (see Section 4.4), electrical
288 performance, adhesive performance, stability, and, if applicable, suitability for reuse (see
289 Section 4.9.1.8).

290 **4.8.1 Electrical Performance**

291 The stimulation electrode design should ensure that the energy from the waveform/pulse
292 generator is efficiently transferred to the patient. For both recording and stimulation
293 applications, we recommend that you perform impedance testing to assure that the electrode
294 has conductive properties appropriate to the device's intended use. The construction of ECT
295 stimulation electrodes should ensure that the electrodes distribute electrical current
296 reasonably uniformly across the electrode-skin interface, and avoid "hot spots" that may
297 result in user discomfort or skin burns.

¹ In addition, FDA has developed updated draft guidance on the use of standards, *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices – Draft Guidance for Industry and Food and Drug Administration Staff* (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm396209.htm>). When final, this guidance will represent FDA's current thinking on this topic.

298 The electrode lead wires and patient cables intended for use with a medical device are subject
299 to the mandatory performance standard set forth in 21 CFR Part 898. The end of the lead
300 remote from the patient shall be constructed so that the lead cannot become connected to
301 earth ground via an exposed conductive surface or to mains power via direct connection to an
302 electrical outlet. The electrode lead wires and patient cables must be in compliance with the
303 test requirements and test methods of subclause 8.5.2.3 of IEC 60601-1 (2005), “*Medical*
304 *Electrical Equipment - Part 1: General Requirements for Safety*,” Amendment No. 1 (1991),
305 and Amendment No. 2 (1995), see 21 CFR 898.12(a). Your 510(k) should contain
306 information sufficient to demonstrate conformance to this standard.

307 **4.8.2 Adhesive Performance**

308 The electrode design should ensure that the electrodes will adhere to the patient’s skin for a
309 duration of use compatible with the intended use of the device. We recommend that you
310 perform testing to assure that the electrode’s adhesive performance meets the specified
311 design requirements and user needs.

312 **4.8.3 Stability**

313 ECT electrode materials should be stable and resist physical and chemical breakdown as a
314 result of conducting electrical current and extended periods of storage over a range of
315 environmental conditions. We recommend that you perform testing to establish, for labeling
316 purposes, the device’s shelf life and storage conditions, and in cases where the electrodes are
317 reusable, use life.

318 **4.9 Labeling**

319 FDA is proposing to require as a special control specific labeling requirements for both the
320 instructions for use and patient labeling. Premarket notification submissions must include
321 labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following
322 suggestions are aimed at assisting you in preparing labeling that satisfies the proposed special
323 control requirements, as well as the requirements of 21 CFR Part 801.

324 Labeling must include adequate information for practitioners to safely and correctly use the
325 device; this information should include indications, effects, routes, methods, frequency and
326 duration of administration and any relevant hazards, contraindications, side effects and
327 precautions (21 CFR 801.109(d)).

328 Proposed labels, labeling, and advertisements sufficient to describe the ECT device, its
329 intended use, and the directions for use should be provided with a specific intended use
330 statement and any warnings, contraindications, or limitations clearly displayed.

331 **4.9.1 Instructions for Use**

332 The labeling should include an operator’s manual (Instructions for Use) with clear and
333 concise instructions that delineate the technological features of the specific device and how
334 the ECT device is to be used. Instructions should encourage use of local/institutional training
335 programs approved by the relevant institutional and professional organizations.

336 FDA recommends that the operator’s manual for physician use include information in each
337 of the following categories:

338 *4.9.1.1 Device Use*

- 339 • Brief description of the device and its accessories, including illustrations, features,
340 functions, output modalities, and specifications
- 341 • Description of all user-accessible controls, including indicators, markings, labels on
342 the device, and accessories that provide information on the function or meaning of
343 each control, display, output jacks, etc.
- 344 • Directions for cleaning and maintenance, where appropriate
- 345 • Storage information
- 346 • Electrical safety requirements. Electrical safety requirements for the ECT device
347 should be stated clearly in the product labeling. A list of technical standards to which
348 the device has been tested and shown to comply should also be provided.

349 *4.9.1.2 Intended Use*

350 The labeling should include an intended use statement with specific indications of the
351 intended patient population meeting DSM-V² criteria for MDE associated with MDD or
352 BPD. In addition, the indications for use should specify that the device is indicated for
353 severe MDE in treatment-resistant patients. The indications for use should specify the
354 conditions of use and the patient population. For example, ECT devices are intended only
355 for use in patients 18 years of age and older who are treatment-resistant or who require a
356 rapid response due to the severity of their psychiatric or medical condition. In addition, you
357 should specify whether the device is intended to be used as sole therapy or as an adjunct to
358 other therapies, including medications in the specified population. The labeling should also
359 contain a description of the clinical trial population that identifies the population studied
360 according to treatment severity and resistance.

361 FDA recommends that physician labeling include a discussion of the benefits and risks to be
362 considered when choosing the proper stimulation parameter. Physician labeling should
363 include instructions to the physician to provide such labeling to the patient. Table 2
364 summarizes stimulation parameters, indicating preferred modalities of treatment and those
365 associated with increased cognitive and memory adverse events.

² American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

366 **Table 2. Stimulation Parameters and Effect of Cognitive/Memory Adverse Events**

Stimulation Parameter	Associated with Increased Cognitive/Memory Adverse Events	Preferred Modality of Treatment to Minimize Cognitive/Memory Adverse Events
Waveform	Sinusoidal	Brief pulse
Electrode Placement	Bitemporal, unilateral dominant	Unilateral non-dominant hemisphere
Stimulus intensity (especially with bilateral treatment)	Increased intensity of treatment	Decreased intensity of treatment (e.g., < 3 times seizure threshold, with bitemporal electrode placement)
Frequency of treatments	Increased frequency of treatment	Decreased frequency (e.g. 2 times per week or less) of treatment or holding treatment

367

368 **4.9.1.3 Contraindications**

369 Each contraindication in the labeling should describe the consequences of contraindicated
 370 use. Contraindications should include:

- 371 • Severe and unstable cardiovascular conditions (e.g. recent myocardial infarction,
 372 unstable angina, congestive heart failure, critical aortic stenosis, uncontrolled
 373 hypertension/hypotension)
- 374 • Cerebrovascular conditions (e.g. aneurysm, arteriovenous malformation)
- 375 • Increased intracranial pressure
- 376 • Space-occupying cerebral lesions (e.g. tumors)
- 377 • Recent stroke (hemorrhagic or ischemic)
- 378 • Severe and unstable pulmonary conditions (e.g. chronic obstructive pulmonary
 379 disease, asthma, pneumonia)³

³ American Psychiatric Association. 2001. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging—A Task Force Report, 2nd ed. American Psychiatric Press, Washington, DC. p. 30.

380 4.9.1.4 Warnings

381 FDA is proposing a special control that would require labeling for ECT devices to include a
382 prominently placed warning:

383 **Warning: ECT device use may be associated with: disorientation, confusion, and**
384 **memory problems.**

385 FDA is also proposing a special control that would require labeling for ECT devices to
386 include the following warning, prominently placed, unless performance data demonstrating a
387 beneficial effect of longer term use, generally considered treatment in excess of three
388 months, is provided:

389 **Warning: When used as intended this device provides short-term relief of symptoms.**
390 **The long-term safety and effectiveness of ECT treatment has not been demonstrated.**

391 Longer term use is generally considered treatment in excess of three months.

392 In addition, the warnings section of the operator's manual should address the concerns
393 described below.

394 • **Cognitive/Memory Decline.** Labeling must include a bolded warning regarding the
395 disorientation, confusion, and memory problems (see above).

396 The labeling should also provide additional information on cognitive/memory risks
397 including a warning that ECT device use may be associated with:

398 - Disorientation and confusion

399 - Anterograde (short-term) verbal memory

400 - Retrograde (long-term) autobiographical memory

401 • **Medical/Physical.** FDA recommends including a warning that ECT device use may
402 be associated with (in order of frequency of occurrence):

403 - Pain/somatic discomfort (including headache, muscle soreness, and nausea)

404 - Skin burns

405 - Physical trauma (including fractures, contusions, injury from falls, dental and oral
406 injury)

407 - Prolonged or delayed onset seizures

408 - Pulmonary complications (insufficient, or lack of breathing, or inhalation of
409 foreign substance into the lungs)

- 410 - Cardiovascular complications (heart attack, high or low blood pressure, and
411 stroke)
- 412 - Death
- 413 • **Psychiatric.** FDA recommends including a warning that ECT device use may be
414 associated with:
- 415 - **Risk of Ineffective Therapy:** The labeling should include appropriate warnings for
416 use in patient populations where efficacy has not been established and where
417 treatment may represent a risk to the patient. ECT device use may be associated
418 with ineffective treatment of your primary psychiatric condition, or may lead to
419 worsening of psychiatric symptomatology.
- 420 - **Treatment-emergent mania:** The labeling should include appropriate warnings
421 regarding the occurrence of manic symptoms (including euphoria and/or
422 irritability, impulsivity, racing thoughts, distractibility, grandiosity, increased
423 activity, talkativeness, and decreased need for sleep) following treatment.
- 424 - **Risk of Relapse:** The labeling should include appropriate warnings for use that
425 effectiveness greater than one month after treatment completion has not been
426 established.

427 4.9.1.5 Precautions

428 The following precautions should be provided.

- 429 • **Lack of Evidence for Efficacy or Safety in Specific Patient Populations.** Labeling
430 should include Precautions for the use of ECT devices in the treatment of patients
431 with psychiatric conditions where safety and efficacy has not been established. This
432 may include patients with:
- 433 - age less than 18
- 434 - schizophrenia
- 435 - schizophreniform disorder
- 436 - schizoaffective disorder
- 437 - bipolar mania or mixed states
- 438 • **Maintenance Treatment.** Labeling should include a precaution that describes the
439 limitations of available information on the safety and effectiveness of long-term
440 treatment with the ECT device, also known as maintenance ECT.

441 4.9.1.6 Procedure Cautions and Risk Mitigation

442 Specific procedural warnings and cautions for the use of the ECT device should be provided

443 in a separate section of the operator manual and should address concerns such as the risk of
444 inadvertent discharge or excessive stimulation discharge.

445 In addition, to mitigate the risks of ECT, FDA is proposing a special control that would
446 require labeling to include the following specific recommendations to the device user:

- 447 i. Conduct of a pre-ECT medical and psychiatric assessment (including pertinent
448 history, physical examination, anesthesia assessment, dental assessment, and other
449 studies as clinically appropriate)
- 450 ii. Use of patient monitoring during the procedure (i.e., electrocardiography, heart rate,
451 blood pressure, ventilation, oxygen saturation)
- 452 iii. The appropriate use of general anesthesia, including neuromuscular blocking agents,
453 by a licensed anesthesia provider during the ECT procedure
- 454 iv. pre-ECT dental assessment and the use of mouth protection (bite blocks) during the
455 procedure
- 456 v. Electroencephalography (EEG) monitoring until the continuous seizure has
457 terminated
- 458 vi. Instructions on electrode placement, including adequate skin preparation and the use
459 of conductivity gel during electrode placement
- 460 vii. Monitoring cognitive status
 - 461 • Cognitive function should be evaluated before beginning ECT and monitored
462 throughout the course of treatment via formal neuropsychological assessment
463 using validated psychometric instruments for evaluating specific cognitive
464 functions (e.g., attention, memory, executive function).
 - 465 • Assessment should also include patient self-report of perceived cognitive
466 difficulties via standardized self-report inventory and/or structured clinical
467 interview
 - 468 • All assessments should be conducted by a qualified, appropriately trained, mental
469 health professional licensed by the state
 - 470 • These results should be routinely reviewed during the course of treatment and
471 influence appropriate clinical decision-making (e.g., holding or terminating
472 treatment, changing ECT treatment parameters).

473 4.9.1.7 Clinical Testing and Reported Adverse Events

474 FDA is proposing a special control that would require labeling to include information related
475 to generic adverse events associated with ECT treatment, as well as a detailed summary of
476 the clinical testing, which includes the clinical outcomes associated with the use of the
477 device, and a summary of adverse events and complications that occurred with the device. A
478 specific section of the operator's manual should present a summary of adverse events and
479 complications that occurred with the ECT device in clinical studies as well as a summary of
480 the device effectiveness in clinical studies. Reports of cognitive and memory impairment
481 should be cited in number, type, and severity as these are frequently associated with ECT

482 treatment. In addition, the number and incidence of deaths, completed suicides, suicide
483 attempts, seizures or worsening of depression should be provided. Effects on cognitive
484 function using targeted measures of analysis should be reported.

485 *4.9.1.8 Reuse of the Device*

486 FDA is proposing a special control that would require labeling to include, where appropriate,
487 validated methods and instructions for reprocessing of any reusable components. If the
488 electrodes are not limited to single-patient use, we recommend that the labeling include
489 instructions for handling, transport, cleaning, and biological decontamination to ensure the
490 safety and protection of patients and health care or other personnel who perform these tasks.
491 You should evaluate the potential for skin reactions and disease transmission, as well as
492 demonstrate that the cleaning and biological decontamination of the electrodes provides
493 sufficient protection and does not impact their functional performance. In general, we
494 believe pre-gelled electrodes cannot be cleaned and decontaminated in a manner that assures
495 prevention of cross-contamination skin reactions or disease transmission; therefore, we
496 recommend that these electrodes be limited to single-patient use. For recommendations
497 regarding the development and validation of reprocessing instructions in your proposed
498 device labeling, please refer to the guidance [Processing/Reprocessing Medical Devices in
499 Health Care Settings: Validation Methods and Labeling](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf)
500 ([http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocu
501 ments/ucm253010.pdf](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf)).

502 *4.9.1.9 Training*

503 FDA is proposing a special control that would require device labeling to indicate the
504 appropriate training necessary for safe use of the device. Training recommendations may
505 include participation in a recognized device use training course, documented adequate
506 supervised device use (under a qualified clinician), or training as recommended by state
507 licensing boards and/or appropriate professional organizations.

508 **4.9.2 Patient Labeling**

509 FDA is proposing to require patient labeling as a special control for ECT devices. The
510 proposed special controls would require patient labeling provide prospective patients with
511 information that will assist them in understanding who may benefit from treatment with the
512 device, what those potential benefits are, relevant contraindications, warnings, precautions,
513 adverse effects/complications, how the device operates, the typical course of treatment, and
514 other available treatments. Providing such information to the patient prior to scheduling
515 treatment is an important tool to help ensure effective communication between the patient
516 and practitioner concerning the safe use of the device and the purposes for which it is
517 intended. Each patient should have access to clear information in plain language to assist
518 with forming realistic expectations of the treatment and its potential complications. Clearly
519 written patient labeling can help patients understand which types of potential side effects,
520 e.g., disorientation, confusion, memory problems, may be important to report to their health
521 care provider. The patient labeling should use terminology that is well known and understood
522 by the average layperson.

523 We recommend you follow the general format and relevant principles discussed in the
524 CDRH
525 guidance document entitled, [Guidance on Medical Device Patient Labeling](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm) (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm>)
526
527 In addition, we recommend patient labeling for ECT devices include the following
528 information specific to these devices and their intended uses:

529 *4.9.2.1 Purpose of the device and indications for use*

530 To demonstrate compliance with the special controls, patient labeling should contain a
531 description of the device, its intended use and intended patient population, as well as when
532 the device should not be used (contraindications). The labeling should also include
533 information from clinical studies describing appropriate candidates for the procedure.

534 Further, patient labeling should describe in lay terms how the device operates to achieve its
535 effects and the typical course of treatment, such as in the following suggested phrasing:

- 536 • “The device applies a controlled electric current and prevents the electrical current
537 (amplitude, waveform, duration of exposure) from exceeding limits specified by the
538 manufacturer. The treatment involves the application of a controlled electric current
539 that leads to a ‘convulsion’ or a ‘seizure’.
- 540 • For it to be effective, multiple treatments with ECT may be necessary.
- 541 • Patients should discuss the number of treatments and treatment schedule with their
542 physicians. It is important to continue with the recommended follow-up treatments to
543 help prevent the depression from returning.
- 544 • ECT device treatment effects are often temporary, and patients may need to continue
545 other forms of depression therapy.”

546 ECT informational material should be discussed with a designated and competent family
547 member or other individual who could also discuss any informed consent with the patient.

548 *4.9.2.2 Benefits and Risks of the Device*

549 FDA is proposing a special control that would require patient labeling to provide information on
550 potential device benefits. The labeling should provide patients and their caregivers with balanced,
551 accurate information about the expected benefits from using the device, and describe the
552 probability of such benefits based upon your clinical trial. The information provided should be
553 sufficient to help patients make informed treatment decisions based on accurate information
554 regarding the expected benefits of ECT treatment along with the risks involved.

555 FDA is also proposing a special control requiring patient labeling to describe the known risks
556 of ECT treatment. Absent performance data demonstrating that these risks do not apply, the
557 proposed special controls would require the following statements to be included in your
558 patient labeling::

559 • *ECT treatment may be associated with disorientation, confusion and memory loss,*
560 *including short-term (anterograde) and long-term (autobiographical) memory loss*
561 *following treatment. These side effects tend to go away within a few days to a few*
562 *months after the last treatment with ECT. However, some patients have reported a*
563 *permanent loss of memories of personal life events (i.e., autobiographical memory).*
564 *Improvements in the way ECT is applied to patients currently, with controlled electric*
565 *currents and electrode placement, can minimize but not completely eliminate, these*
566 *risks.*

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

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

573 • *Pain/somatic discomfort (including headache, muscle soreness, and nausea)*

574 • *Skin burns*

575 • *Physical trauma (including fractures, contusions, injury from falls, dental and*
576 *oral injury)*

577 • *Prolonged or delayed onset seizures*

578 • *Pulmonary complications (insufficient, or lack of breathing, or inhalation of*
579 *foreign substance into the lungs)*

580 • *Cardiovascular complications (heart attack, high or low blood pressure, and*
581 *stroke)*

582 • *Death*

583 FDA is proposing a special control to require that patient labeling include a summation of the
584 clinical testing, which includes the clinical outcomes associated with the use of the device,
585 and a summary of adverse events and complications that occurred with the device.

586 FDA is also proposing to require as a special control that patient labeling for ECT devices
587 include a prominently placed warning:

588 **Warning: ECT device use may be associated with: disorientation, confusion, and**
589 **memory problems.**

590 In addition, FDA is proposing a special control that would require labeling for ECT devices
591 to include the following warning, prominently placed, unless performance data
592 demonstrating a beneficial effect of longer term use, generally considered treatment in excess
593 of three months, is provided:

594 **Warning: When used as intended this device provides short-term relief of symptoms.**
595 **The long-term safety and effectiveness of ECT treatment has not been demonstrated.**

596 Longer term use is generally considered treatment in excess of three months.

597 4.9.2.3 Alternative Treatments

598 FDA is proposing a special control that would require patient labeling to describe currently-
599 available alternative treatments, including medications, devices and psychotherapy. FDA
600 recommends that patients speak with their health care providers to determine if they are
601 suitable alternatives for them.

602 **5 Animal and Clinical Testing**

603 ECT devices will generally not be subject to animal or clinical testing if they are similar to
604 legally marketed ECT devices in design and technology and are indicated for severe MDE
605 (associated with MDD or BPD) in patients 18 years of age and older who are treatment-
606 resistant or who require a rapid response due to the severity of their psychiatric or medical
607 condition. However, new or modified indications for use or technological characteristics
608 may require the submission of animal or clinical testing to demonstrate substantial
609 equivalence.

610 It is important to note that ECT devices for other indications are outside the scope of this
611 guidance but likely *would* require clinical testing.

612 **5.1 Animal Testing**

613 For devices with notable dissimilarity from legally marketed ECT devices (e.g., in design or
614 technology), nonclinical testing in animals may be appropriate to confirm the safety of the
615 procedure and evaluate the functional characteristics of the device design. Such testing must
616 comply with 21 CFR Part 58, which prescribes Good Laboratory Practices for nonclinical
617 studies. If you are considering animal testing, we encourage you to contact the review
618 branch early in the product development process to discuss your study design.

619 **5.2 Clinical Evidence**

620 Clinical testing will not generally be needed for new devices if the proposed device is
621 sufficiently similar to the predicate device in terms of indications, device specifications, and
622 energy output, such that reliance on bench and/or animal testing may be sufficient to
623 demonstrate substantial equivalence. In cases where clinical testing is needed, FDA
624 recommends that the clinical study be designed to demonstrate that your device is as safe and
625 effective as the predicate device when used as described in the Indications for Use statement.

626 Clinical evidence may be requested in situations such as the following:

- 627 • indications for use dissimilar from legally marketed devices of the same type;⁴⁵
- 628 • new technology, i.e., technology different from that used in legally marketed
- 629 devices of the same type, yet does not raise different questions of safety or
- 630 effectiveness; or
- 631 • cases where engineering and/or animal testing raise issues that warrant further
- 632 evaluation with clinical evidence to establish substantial equivalence.

633 FDA will consider alternatives to clinical testing when the proposed alternatives are

634 supported by an adequate scientific rationale.

635 FDA believes prospective clinical trials for ECT devices should support changes in

636 stimulation parameter outputs (i.e. current, voltage, frequency, phase duration, charge

637 density, and pulse width). If your device's electrical output to the patient exceeds that of

638 previously cleared predicate ECT devices, the 510(k) submission should include appropriate

639 supporting data to show that you have considered what consequences and effects this change

640 or new use might have on the safety and effectiveness of the device (21 CFR 807.87(g)). We

641 recommend a prospective clinical trial to provide the evidence of safety and effectiveness.

642 **5.3 Significant Risk and Investigational Device Exemption (IDE)**

643 FDA believes that ECT devices carry significant risks to patients,⁶ and therefore require the

644 filing of an IDE application, under 21 CFR 812.20(a)(1) when used for unapproved uses.

645 FDA believes any clinical investigation of an investigational ECT device in accordance with

646 the recommendations of section 5.2 of this guidance will generally constitute a significant

647 risk investigation as defined in 21 CFR 812.3(m)(4). Sponsors of clinical investigations of

648 devices must comply with the regulations governing institutional review boards (21 CFR Part

649 56) and informed consent (21 CFR Part 50).

650 **5.4 Clinical Protocol**

651 The clinical study should be designed to address the concerns provided below. To ensure

652 optimal study design, we recommend that you request the Agency's review of your protocols

653 prior to initiating clinical studies for your device through our pre-submission (pre-sub)

654 process. For information on the pre-sub process, see guidance [Requests for Feedback on](#)

⁴ ECT devices that are indicated for schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia are proposed to be classified as Class III devices, requiring PMAs.

⁵ Under section 513(i) of the FD&C Act, to be found substantially equivalent, a device must have the same intended use as a legally marketed device. If an indication for use is determined to be a new intended use, the device will be found not substantially equivalent.

⁶ See [Significant Risk and Nonsignificant Risk Medical Device Studies](#) at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>.

655 [Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)
656 ([http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceD](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)
657 [ocuments/UCM311176.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)).

658 **Indication for use:** The indication for use should identify the patient population for whom
659 the device is intended, including the age, DSM-V diagnosis, treatment severity, and level of
660 treatment resistance.

661 **Inclusion and Exclusion Criteria:** The inclusion and exclusion criteria should characterize
662 the population to be studied. Your inclusion and exclusion criteria should specify the DSM-
663 V diagnosis, medication resistance and treatment severity. Due to safety concerns, we
664 recommend you exclude subjects who have metal implanted in the head, excluding the mouth
665 (e.g., implanted brain stimulators), significant cardiovascular disease (including uncontrolled
666 hypertension, hypotension, arrhythmias or critical aortic stenosis), significant pulmonary
667 disease, history of adverse reaction to general anesthetic agents, history of seizure disorder,
668 cerebrovascular disease, dementia, delirium, head trauma, increased intracranial pressure, or
669 central nervous system (CNS) tumors.

670 In addition, you should address other subject characteristics, including:

- 671 • age
- 672 • comorbid psychiatric and neurological disorders
- 673 • pregnancy
- 674 • length of current episode, single or recurrent episode
- 675 • baseline depression severity, based on validated depression assessment tool
- 676 • risk of suicide, based on a validated suicide severity scale
- 677 • prior treatment with antidepressant therapies [Dose, duration and outcome of
678 antidepressant trials should be documented using a structured format, such as the
679 antidepressant treatment history form (ATHF)⁷
- 680 • the presence of neurostimulator devices
- 681 • significant heart disease, cerebrovascular disease, history of epilepsy, dementia, head
682 trauma, increased intracranial pressure, or central nervous system (CNS) tumors.

683 **Treatment parameters:** Treatment parameters should be standardized and should be
684 specified in detail in your protocol. You should include a description of the determination of

⁷ Oquendo M, et al. A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. J Clin Psychiatry 2003;64:825-33.

685 seizure threshold and determination of applied stimulation. In addition, you should specify
686 all the technical treatment parameters for stimulation, the site of electrode placement, the
687 number and frequency of treatments and overall duration of treatment exposure. FDA
688 recommends you provide details about whether treatment sessions will be individualized
689 (i.e., whether treatment parameters will be adjusted based on the study subject response, or
690 other variables).

691 **Study design:** For devices intended to treat neuropsychiatric indications (such as
692 depression) FDA recommends either a prospective randomized sham-controlled study or a
693 prospective randomized concurrent controlled trial comparing the device to a legally-
694 marketed predicate device for the same indications for use. We also recommend that you
695 perform the study in multiple centers to analyze for a treatment by site interaction.
696 Depending on the characteristics of the patient population, the randomized phase should be
697 of sufficient duration to demonstrate a clinically meaningful effect. If your study incorporates
698 a cross-over phase, (i.e., subjects originally receiving control treatment switched to receiving
699 investigational treatment or vice versa), you should provide detailed criteria pertaining to the
700 cross-over.

701 Due to the possible variation of neuropsychiatric symptoms over time, we recommend that
702 you incorporate a screening and/or baseline phase, prior to the randomized phase of the
703 study. During this phase, clinical indicators of symptomatology should be assessed to
704 provide assurance that the patient's depression has stabilized. During the baseline phase,
705 concurrent medication therapies may either be stabilized or withdrawn depending on how
706 you wish to study your device. The screening phase should be of sufficient duration to allow
707 stabilization of the patient's symptoms and, if appropriate, concurrent therapies.

708 If you plan to study patients on concurrent medications, you should describe how you plan to
709 deal with changes in medications or doses. If you plan to study your device on patients who
710 have been withdrawn from standard therapies, you should follow the drug manufacturer's
711 guidelines for the appropriate time period for each medication that will assure that the
712 medications have been washed out.

713 Given the inherent risks of ECT device use, we recommend you incorporate a prospective
714 lead-in phase design, in order to recruit only subjects who have demonstrated non-response
715 to medication therapy.

716 We also recommend that you design your study to incorporate a sufficient period of follow
717 up after the completion of the randomized phase of the study to evaluate the durability of
718 effect. FDA recommends a post treatment follow-up period to assess patient response or
719 remission, the incidence of suicide, and any long-lasting adverse effects. We recommend
720 that the follow-up include assessment of both the active and control groups when feasible, for
721 example, if both groups are receiving best medical therapy.

722 **Device effectiveness:** You should specify the primary and secondary effectiveness
723 endpoints for the study. Endpoints should be chosen to assure a clinically meaningful effect.

724 Validated assessment scales should be used as the primary endpoint. FDA recommends that a
725 comparison of the proportion of subjects who meet the criteria of response and remission in

726 both the active and control groups be performed. In addition, FDA recommends that you
727 assess a patient reported outcome such as quality of life as one of your secondary endpoints.
728 Additional outcome measures should include patient global impression of improvement and
729 clinician global impressions of improvement and severity.

730 **Device safety:** Clinical studies conducted in the US must comply with the applicable
731 reporting requirements of 21 CFR 812.150(b).⁸ For clinical studies of ECT devices, device
732 safety data should include the incidence of serious adverse events (e.g., medical/physical
733 complications such as adverse reaction to anesthetic agents/neuromuscular blocking agents,
734 cardiovascular complications, death, physical trauma, prolonged (or tardive) seizures,
735 pulmonary complications, or stroke), cognitive/memory dysfunction (i.e., global cognitive
736 function global memory function, anterograde verbal memory, retrograde impersonal
737 memory, and retrograde personal (autobiographical) memory, subjective memory), and
738 device malfunction resulting in patient or operator injury. For depression, due to the
739 possibility of suicidal ideation or behavior in the study population, FDA recommends that the
740 protocol include a suicide severity rating scale, such as the Columbia Suicide Severity Rating
741 Scale⁹, to assess both suicide intent and behavior. You should also collect incidence of
742 common adverse events such as alterations in blood pressure, physical trauma, dental/oral
743 trauma, headache, muscle soreness, nausea and vomiting, application site skin burns or
744 pain/discomfort, and discontinuation rate due to adverse events.

745 If possible, you should collect systematic safety outcomes data for cognitive/memory
746 dysfunction (i.e., global cognitive function global memory function, anterograde verbal
747 memory, retrograde impersonal memory, and retrograde personal (autobiographical)
748 memory, subjective memory) using validated and standardized assessment tools,
749 administered by appropriately trained and licensed personnel. These assessments should be
750 conducted for at least 12 months after ECT treatment.

751 You should also determine the severity and duration of each adverse event. To achieve that
752 goal, your data should include information about any intervention that was performed,
753 whether and when the event was resolved, and whether the event was device related.

754 **Training:** You should describe any training provided to study investigators, including both
755 training on the use of the device and on any assessment tools. Supporting information to
756 substantiate an adequate level of training should be stated, such as a pre-study reliability
757 certification program and reliability assessment for clinical raters during the study.

758 **5.5 Reporting of Statistical Outcomes for Clinical Study Results**

759 The following study design features should be stated clearly in the study protocol document.

⁸ Studies conducted under an approved IDE must meet all recordkeeping and reporting requirements described in 21 CFR 812.150. Studies allowed under the abbreviated IDE requirements (as defined in 21 CFR 812.3(m)(4)) must comply with the recordkeeping and reporting requirements described in 812.2(b).

⁹ See <http://www.cssrs.columbia.edu>

760 **Sample Size Estimation:** FDA recommends you provide justification for your sample size
761 estimates. We recommend you provide clearly defined null and alternative hypotheses, pre-
762 specified type I and II error rates, clinically acceptable differences to be detected in the
763 superiority trial, or non-inferiority margin in the non-inferiority trial, and an estimation of
764 sample size that accounts for study subject loss to follow-up and drop-out. FDA also
765 recommends you discuss how to adjust for a type I error rate in any interim analyses based
766 upon a clearly defined group sequential trial design, if applicable.

767 **Hypotheses:** You should specify your null and alternative hypotheses. Your statistical
768 hypothesis should describe the specific statistical model proposed for the main analysis and
769 any relevant secondary analyses.

770 **Randomization and Blinding:** You should describe an *a priori* method of randomization
771 and provide a method to ensure integrity of the study blind in detail. We recommend you
772 include an assessment of the effectiveness of the blinding, such as asking patients to guess
773 their treatment group. In addition, we recommend that you perform sensitivity analyses, such
774 as examining the correlation between adverse events and the observed treatment effect to
775 examine the possibility of unblinding due to adverse events.

776 **Effectiveness Assessments:** You should include an overall assessment of safety and
777 effectiveness. In your assessment, you should report:

- 778 • the primary efficacy endpoint which should be based on a validated assessment tool;
- 779 • the secondary efficacy endpoints which should also be based on validated assessment
780 tools (Your secondary endpoints should assess any benefits for which you plan to
781 claim effectiveness.); and
- 782 • the standardized effect size for continuous outcome measures and/or the number-
783 needed-to-treat (NNT) for categorical endpoints (whichever measure or endpoint you
784 report, you should include it for the study population and the control group).

785 **5.5.1 Statistical Analysis Plan**

786 **Analysis populations:** The preferred analysis population for a superiority study is the intent-
787 to-treat population, consisting of all patients as originally randomized. For non-inferiority
788 studies with an active control, you should base the determination of effectiveness on the
789 collective results from per-protocol, intent-to-treat, and as-treated analysis populations. A
790 per-protocol population refers to patients with no protocol violations and complete follow-up.
791 As-treated, although similar to intent-to-treat, refers to all patients, but is grouped according
792 to the treatment actually received not the randomization assignment.

793 **Primary and secondary endpoints:** You should report the primary and secondary
794 endpoints, comparing the results of the active group to the control group. For depression
795 studies, we recommend that you report change as a continuous measure, as well as the rate of
796 response, defined as a 50% reduction on the assessment scale, and also the rate of remission.

797 If you wish to make any labeling claims based on your secondary endpoints, you should
798 prespecify a statistical method to control multiplicity, such as a hierarchical testing order or
799 the step-down method of Holm.

800 **Missing data:** Your study analysis plan should include methods for handling missing data.
801 This includes imputation methods, such as multiple imputation, and sensitivity analyses, such
802 as imputing various proportions of missing outcomes (of a binary endpoint) as “successes” or
803 “failures.”

804 **Covariate Analysis:** We recommend you specify methods for handling significant
805 covariates in the statistical model. For any covariate term included in the proposed
806 statistical model to evaluate effectiveness, we recommend you investigate a treatment group
807 by covariate interaction. If such an interaction term is found to be statistically significant,
808 your statistical summary should include a discussion of the implication of the statistically
809 significant interaction on the overall interpretation of the study results.

810 **Treatment by site interactions:** Multicenter studies should include a measure to assess any
811 significant treatment by center interaction on the primary effectiveness measure. We
812 recommend both treatment and control groups be studied at the same site(s). We also
813 recommend you apply an appropriate randomization blocking procedure to balance the
814 number of subjects in each participating center between control and treatment groups in order
815 to facilitate an assessment of the poolability of data across centers. In addition, your
816 statistical analysis section should include a discussion of the importance of any statistically
817 significant treatment-by-site interaction to the overall interpretation of the study results.

818 **Bayesian Methods:** If Bayesian statistical methods are used, we recommend you specify the
819 prior information and conduct simulation analysis to estimate the probability of Type I error
820 rate and the required sample size.

821 FDA recommends you identify the type of patient population (e.g., intent-to-treat, per
822 protocol, evaluable, complete, or others) used in each statistical analysis.

823 **5.6 Reporting Results from Journal Articles or Meta-analyses**

824 If applicable, safety results obtained with the ECT device that were reported in the medical
825 literature should be summarized and included in the 510(k). In addition, effectiveness data for
826 your ECT device for your indications for use that are available from journal articles or meta-
827 analyses may be submitted as supportive information. FDA recommends you provide a
828 comprehensive analysis of the available current, peer-reviewed literature that relates to the
829 advantages and disadvantages of your device. Because the body of literature on ECT is
830 expansive, and varies in scientific quality, we recommend that your analysis rate the strength
831 of the scientific evidence in each study¹⁰. We also suggest that your review focus on recently

¹⁰ An example of a method of evaluating literature is by methods described by the Agency for Healthcare Research and Quality, “*Evidence Report/Technology Assessment, Number 47, Systems to Rate the Strength of Scientific Evidence*” (West, et al. 2002).

832 conducted studies, utilizing more current standard of practice techniques and stimulation
833 parameters.

834 For each reviewed publication, the following information should be reported:

- 835 • indication for use and intended use
- 836 • patient population studied, including age, summary of psychiatric disorder(s),
837 antidepressant or other medications, any prior ECT treatment, duration and frequency
838 of previous treatments, and relevant baseline psychiatric characteristics
- 839 • use or non-use of drugs during the study
- 840 • electrode placement, and stimulation used for treatment
- 841 • nature of and type of control group (e.g., concurrent, patients as own control,
842 historical control, randomization, sham treatment, double masking)
- 843 • patient assessments used (pre- and post-treatment)
- 844 • statistical analyses used and results
- 845 • duration of patient follow-up
- 846 • adverse events and treatment-emergent pathologies reported, and how this
847 information was obtained
- 848 • long-term effects on retrograde memory and cognitive function and the assessment
849 measures used
- 850 • safety and effectiveness results of study and conclusion.

Appendix A. Definitions of Output Specifications

851
852
853 For the purposes of this guidance document, the following definitions of output specifications are
854 used:

- 855 • **Brief Pulse:** A rectangular pulse with a pulse duration of 0.5 to 2.0 milliseconds.
856
- 857 • **Charge:** The total charge is the integral of the current magnitude over the duration of the
858 stimulus train. For constant-current, rectangular-pulse trains the total charge is equal to the
859 product of the pulse current amplitude, width, pulse repetition frequency, and train duration.

860
861 Total Charge = Current Amplitude x Pulse Width x Train Duration x Frequency x 2 [only
862 multiply by 2 for biphasic waveforms to account for pulse-pairs (see Figure A2)]
863

- 864 • **Charge Density:** Charge referred to the unit area of the electrode. It is calculated by dividing
865 the charge by the electrode surface area.
866

- 867 • **Dynamic Impedance:** The impedance during delivery of the output stimulus. It is measured
868 during the delivery of energy by monitoring voltage and current. Dynamic monitoring helps
869 to ensure safety since impedances may change during stimulus delivery.
870

- 871 • **Energy:** The total energy is the integral of the power delivered during the stimulus train,
872 which for constant current rectangular pulses is equal to the product of the total charge, the
873 current amplitude, and the dynamic impedance. For reporting purposes the Energy should be
874 calculated using a dynamic impedance of 220 Ω .

875 Energy = Charge x Current Amplitude x Dynamic Impedance
876

- 877 • **Frequency:** For *monophasic* waveforms the frequency is the number of pulses per second
878 (see Figure A1). For *biphasic* waveforms the frequency is the number of pulse-pairs per
879 second (see Figure A2). The unit of measure is Hertz (Hz).
880

- 881 • **Impedance Monitor.** Devices can make static electrode impedance measurements,
882 which are made before or after the delivery of energy, and/or dynamic electrode impedance
883 measurements, which are made during the delivery of energy by monitored voltage and
884 current. Dynamic monitoring is safer when impedances change during shock delivery.
885

- 886 • **Number of Pulses in a Train:** The number of pulses in a train can be calculated as follows,
887

887 *Monophasic Waveform:* Train Duration x Pulse Frequency

888 *Biphasic Waveform:* Train Duration x 2 x Pulse-pair Frequency

- 889 • **Pulse:** A rapid, transient change in the amplitude of a signal from a baseline value to a
890 higher or lower value, followed by a rapid return to the baseline value. (see Figures A1 and
891 A2)
892

- 893 • **Pulse-pairs:** Symmetrical biphasic pulses are referred to as pulse-pairs (see Figure A2).
894
- 895 • **Pulse Width:** The time elapsed from the beginning to the end of all phases plus the
896 interphase interval within one pulse (see Figures A1 and A2).
897
- 898 • **Static Impedance:** The impedance before or after the delivery of energy. It is measured
899 during self-test procedures.
900
- 901 • **Train Duration:** A train is a finite series of pulses and the train duration is the time period
902 in which these finite series of pulses are delivered (See Figures A1 and A2).
903
- 904 • **Ultra Brief Pulse:** A rectangular pulse with a pulse duration of less than 0.5 milliseconds.
905
- 906 • **Waveform:** Shape of the shortest repetitive component of the output wave (e.g., rectangular).
907 The waveform can be *monophasic* (See Figure A1 below) or *biphasic* (See Figure A2
908 below). A monophasic waveform can have either positive or negative pulses. A biphasic
909 waveform has a positive and a negative pulse and is *symmetrical* if the positive and negative
910 pulses of stimulation are of the same duration, magnitude and shape. Alternating current
911 sinusoidal waveforms are a specific type of biphasic waveform.
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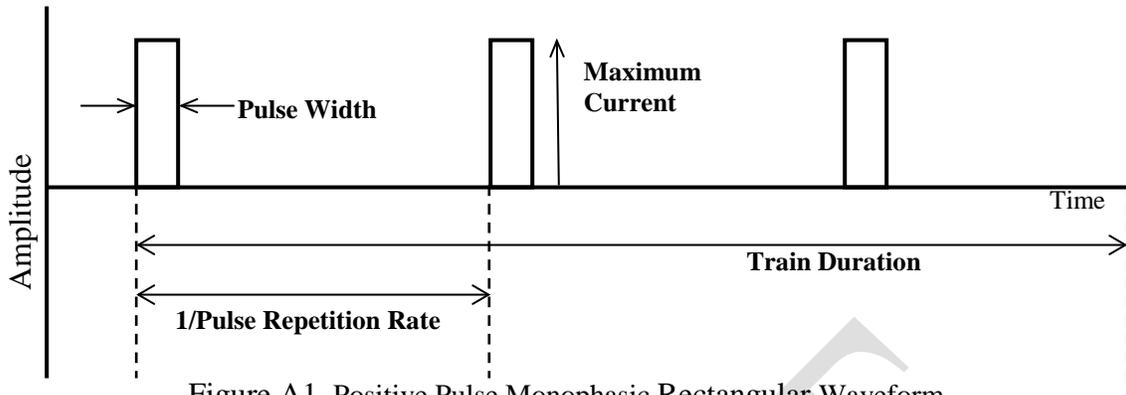


Figure A1. Positive Pulse Monophasic Rectangular Waveform

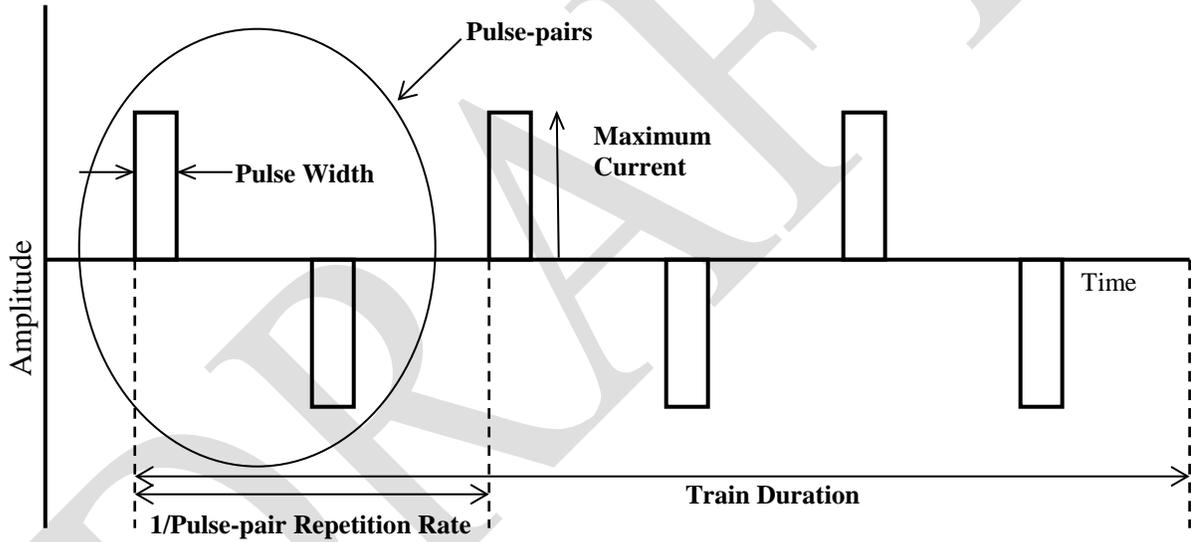


Figure A2. Biphasic Rectangular Waveform