Summary
Goal

- Obtain panel feedback regarding classification of Electroconvulsive Therapy (ECT) devices for each of the currently cleared indications

  » Should ECT devices remain Class III devices and require premarket approval (PMA)?

  » Should ECT devices be reclassified to Class II and require premarket notification (510(k))?
1. Regulatory Considerations:
   Marjorie Shulman, Program Operations Staff, ODE
2. ECT Clinical and Regulatory Background
   Bradley Cunningham, LCDR, USPHS, Branch Chief
3. FDA Assessment of ECT
   Strategy and Methodology: Anna Georgiopoulos, MD
4. FDA Safety Review
   Public docket, manufacturer docket, MAUDE database: Anna Georgiopoulos, MD
   Identification of all potential adverse events, adverse events subject to focused review, and key risks: Anna Georgiopoulos, MD
   Cognitive and Memory Adverse Events Systematic Review: Peter Como, PhD
   Cognitive Meta-Analyses: Cara Krulewitch, CNM, PhD, FACNM
   Neuropathological Changes and Death: Allison Komiyama, PhD
5. FDA Effectiveness Review
   Lawrence Park, MD
6. Key Risk Identification and Mitigation Factors
   Lawrence Park, MD
All Reported Adverse Events (from all sources; by approximate frequency of report)

- Memory dysfunction\(^1,2\)
- Cognitive dysfunction\(^1,2\)
- Neuropathological changes (brain damage) \(^1,2\)
- Death/reduced life span\(^1,2\)
- Onset/exacerbation of psychiatric symptoms
- General motor dysfunction
- General functional disability
- Pain/discomfort\(^2\)
- Prolonged seizures\(^2\)

\(^1\) Focus of FDA literature review
\(^2\) Identified key risk, mitigation factors proposed
All Reported Adverse Events (continued)

- Physical trauma\(^2\)
- Skin burns\(^2\)
- Neurological symptoms
- Pulmonary complications\(^2\)
- Sleep disturbance
- Visual disturbance
- Nausea
- Alterations in blood pressure\(^2\)
- Cardiovascular complications\(^2\)
- Stroke\(^2\)
- Auditory complications
- Dental/oral trauma\(^2\)
- Suicidality
- Homicidality
- Substance abuse
- Urinary complaints
- Coma
- Adverse reaction to anesthetic/neuromuscular blocking agents\(^2\)

\(^1\) Focus of FDA literature review
\(^2\) Identified key risk, mitigation factors proposed
Key Risks

- **Medical/Physical**
  - Adverse reaction to anesthetic agents/neuromuscular blocking agents
  - Alterations in blood pressure
  - Cardiovascular complications
  - Death
  - Dental/oral trauma
  - Pain/discomfort
  - Physical trauma
  - Prolonged seizures
  - Pulmonary complications
  - Skin Burns
  - Stroke

- **Cognition and Memory Dysfunction**

- **Device Malfunction**
<table>
<thead>
<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction to anesthesia</td>
<td>Anesthetic agents, neuromuscular blockers</td>
<td>-Pre-ECT assessment</td>
</tr>
<tr>
<td></td>
<td>Frequency: rare</td>
<td>-Appropriate procedure monitoring</td>
</tr>
<tr>
<td></td>
<td>Severity: severe</td>
<td>-Appropriate clinical management</td>
</tr>
<tr>
<td>Alterations in blood pressure</td>
<td>Hypertension or hypotension</td>
<td>-Pre-ECT assessment (EKG, echocardiogram)</td>
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<tr>
<td></td>
<td>Frequency: common</td>
<td>-Appropriate procedure monitoring</td>
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<tr>
<td></td>
<td>Severity: mild-severe</td>
<td>-Appropriate clinical management</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>Arrhythmias or Ischemia</td>
<td>-Pre-ECT assessment</td>
</tr>
<tr>
<td></td>
<td>Frequency: uncommon</td>
<td>-Appropriate procedure monitoring</td>
</tr>
<tr>
<td></td>
<td>Severity: severe</td>
<td>-Appropriate clinical management</td>
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<tr>
<td></td>
<td>Known common risk of ECT.</td>
<td></td>
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<tr>
<td>Death</td>
<td>Resulting from other pathophysiological processes</td>
<td>-Medical work-up and management</td>
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<tr>
<td></td>
<td>Frequency: rare</td>
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<tr>
<td></td>
<td>Severity: severe</td>
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<tr>
<td>Key Risk</td>
<td>Risk Characterized</td>
<td>Potential Mitigation Factors</td>
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<tr>
<td>Dental/oral trauma</td>
<td>Dental fractures, dislocations, lacerations, prosthetic damage</td>
<td>- Use of general anesthetic agents and neuromuscular blocking agents</td>
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<tr>
<td></td>
<td>Frequency: uncommon</td>
<td>- Pre-ECT dental assessment</td>
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<tr>
<td></td>
<td>Severity: mild-moderate</td>
<td>- Use of mouth protection (bite blocks)</td>
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<tr>
<td>Pain/discomfort</td>
<td>Frequency: common</td>
<td>- Use of analgesic medications</td>
</tr>
<tr>
<td></td>
<td>Severity: mild-moderate</td>
<td></td>
</tr>
<tr>
<td>Physical trauma</td>
<td>Fractures, contusions</td>
<td>- Use of general anesthetic agents and neuromuscular blocking agents</td>
</tr>
<tr>
<td></td>
<td>Frequency: uncommon</td>
<td></td>
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<tr>
<td></td>
<td>Severity: mild-severe</td>
<td></td>
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<tr>
<td>Prolonged seizures</td>
<td>Frequency: uncommon</td>
<td>- Pre-ECT evaluation</td>
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<tr>
<td></td>
<td>Severity: moderate-severe</td>
<td>- EEG monitoring</td>
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# Key Risks: Medical/Physical

<table>
<thead>
<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary complications</td>
<td>Apnea, aspiration</td>
<td>- Pre-ECT assessment (e.g. lab tests, chest x-ray, pulmonary function tests)</td>
</tr>
<tr>
<td></td>
<td>Frequency: rare</td>
<td>- Appropriate procedure monitoring</td>
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<tr>
<td></td>
<td>Severity: high</td>
<td>- Appropriate clinical management</td>
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<tr>
<td>Skin burns</td>
<td>Burns at electrode site</td>
<td>- Skin preparation and electrode contact</td>
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<tr>
<td></td>
<td>Frequency: uncommon</td>
<td>- Use of conductivity gel</td>
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<tr>
<td></td>
<td>Severity: mild</td>
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<tr>
<td>Stroke</td>
<td>Frequency: rare</td>
<td>- Pre-ECT assessment (neuroimaging)</td>
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<tr>
<td></td>
<td>Severity: high</td>
<td>- Appropriate procedure monitoring</td>
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<td></td>
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<td>- Appropriate clinical management</td>
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## Potential Mitigating Factors: Cognitive and Memory Dysfunction

<table>
<thead>
<tr>
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<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
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| Cognition | Disorientation generally occurs post-treatment, but typically resolves minutes after completion of treatment.                                                                                                        | -Exclusive use of square wave, direct current, brief pulse waveform stimulus  
-Use of ultrabrief pulse (0.3 msec) stimulus  
-Exclusive use of unilateral nondominant electrode placement  
-Use of bifrontal electrode placement  
-Frequency of treatment no greater than twice weekly during a course of ECT                                                                                                                                 |
Potential Mitigating Factors: Acceptance of Risk and Informed Decision Agreement

- Written Informed Consent
- Inclusion of checklist of risks of treatment
- Checklist elements
  - All known risks of ECT
  - Likelihood of occurrence
  - Potential severity
- Review by treating physician and patient
- Initialing of each risk by both physician and patient to acknowledge review of the risk
- Documentation to be kept with standard written informed consent documentation
- Criteria for patient capacity to consent for treatment unchanged
Panel Classification Recommendation for ECT

- **Class II**
  » Reasonable assurance of safety and effectiveness provided by general and special controls

- **Class III**
  » High risk devices for which general and special controls are inadequate to assure safety and effectiveness
  » PMA required
Panel Questions
To inform the FDA’s decision on reclassification, the key risks presented by ECT must be identified, and a determination must be made regarding how and whether sufficient information exists to establish controls to mitigate those risks. The FDA has identified the following key risks of ECT (in alphabetical order) in the FDA’s review of the Public Docket, the Manufacturer Docket, the Manufacturer and User Facility Device Experience (MAUDE) Database, and in FDA’s literature review:
Panel Question (continued)

a. Adverse reaction to anesthetic agents/neuromuscular blocking agents
b. Alterations in blood pressure
c. Cardiovascular complications
d. Cognition (disorientation and confusion)
e. Death
f. Dental/oral trauma
g. Device malfunction
h. Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
i. Pain/somatic discomfort
j. Physical trauma
k. Prolonged seizures
l. Pulmonary complications
m. Skin burns
n. Stroke
Panel Question (continued)

Is this a complete and accurate list of the key risks presented by ECT?

Comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks are among the key risks presented by ECT.
2. Below are potential regulatory controls FDA could apply to ECT to mitigate medical/physical risks of ECT (i.e. adverse reaction to anesthetic agents/neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, death, dental/oral trauma, pain/somatic discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, stroke):
Panel Question (continued)

a. Restricting ECT device use to physicians with specific training and/or experience with the administration of ECT;

b. Physician labeling recommendations for:
   i. pre-ECT assessment (including pertinent history, physical examination, EKG, echocardiogram, chest x-ray, pulmonary function tests, lab tests, and neuroimaging)
   ii. ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)
Panel Question (continued)

iii. The appropriate use of general anesthesia, neuromuscular blocking agents by a licensed anesthesiologist during the ECT procedure
iv. pre-ECT dental assessment and the use of mouth protection (bite blocks)
v. Electroencephalography (EEG) monitoring during and after the procedure
vi. Adequate skin preparation and the use of conductivity gel during electrode placement
Panel Question (continued)

c. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment

d. Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new indications for use (IFU)
Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the medical/physical risks of ECT.
3. Below are potential regulatory controls FDA could apply to ECT to mitigate risks of adverse cognitive and memory effects (especially with respect to anterograde and retrograde memory functioning):

   a. Physician labeling recommendations for:
      i. Exclusive use of brief pulse (1-1.5 msec) waveform stimulus
      ii. Use of ultrabrief pulse (0.3 msec) stimulus
      iii. Exclusive use of unilateral nondominant electrode placement
      iv. Use of bifrontal electrode placement
      v. Limiting frequency of treatment to a maximum of twice weekly during a course of ECT
      vi. Monitoring cognitive status prior to ECT and throughout the course of treatment
b. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment.

c. Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new IFU.

Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the cognitive and memory risks of ECT.
4. Regarding neuropathological changes, the manufacturer and public dockets both indicated “brain damage” as a potential risk associated with ECT. However, FDA’s review of the literature did not identify evidence of gross anatomical, histological, or immunohistochemical evidence, or evidence from biomarkers of injury, to support this association. Please discuss whether the existing clinical data support brain damage as a potential risk of ECT and if so, how this risk can be mitigated.
Panel Question

5. Currently cleared indications for use (IFUs) for ECT devices include the following:
   a. Depression (unipolar and bipolar)
   b. Schizophrenia
   c. Bipolar manic (and mixed) states
   d. Schizoaffective disorder
   e. Schizophreniform disorder
   f. Catatonia

Please provide your overall recommendation for the classification (Class II or III) of the ECT device for each of the above indications.