de novo Program
Evaluation of Automatic Class III Designation

FDA Small Business
Regulatory Education for Industry (REdI)
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Case Study: Electrogastrogram (EGG) System

• gastric motility monitoring system: measure the electrical activity of stomach muscle

• 3 surface leads are placed on the surface of the peritoneum (abdominal region)

• similar concept to the cardiac ECG lead systems
EGG System
Device Output
Regulatory History

• principles of device technology in clinical practice for decades (practice of medicine)

• no legally marketed EGG devices

• primary purpose: to determine motility effect of gastric drugs, usually in research
Regulatory Conundrum: no appropriate predicate device

Gastric Motility Monitoring System

– 21 CFR 876.1725
– Class II Medical Device

– **description**: measure peristaltic activity or pressure using **pressure** transducers
– closest existing predicate/regulation, but not suitable for this new, novel device
Regulatory Conundrum: only one option

If not equivalent to a Class I or II medical device, then:

Premarket Approval (Class III)

Is this the appropriate level of regulatory burden for a device that is not high risk?
Outline of Presentation

• What is a de novo?
• Regulatory Background
• Submission Process
• Content of de novo request
• Examples
• What happens after a de novo is granted
• Best Practices/Helpful Hints
• Q&A
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What is a de novo?

A process:

- using a risk-based strategy
- for new, novel devices whose type has not previously been classified
- would be classified into Class III due to no predicate
- to reclassify into Class I or II if general and/or special controls provide a reasonable assurance of safety and effectiveness
What is a de novo?

• the submission of a request by a medical device sponsor to FDA

• involves the establishment of a new classification, regulation, and “device type”

• upon completion, may serve as a predicate for new medical devices (where appropriate)
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Regulatory Background


Section 513

• classification of medical devices
• risk-based approach:
  – 513(a)(1)(A): Class I, general controls
  – 513(a)(1)(B): Class II, special controls
  – 513(a)(1)(C): Class III, premarket approval
Regulatory Background


Section 513(a)(1)(C): “high risk devices”

• Class III, require Premarket Approval
• Devices which:
  – Support/sustain human life, are of substantial importance in preventing impairment of human health, or present potential unreasonable risk of illness or injury AND
  – For with insufficient information exists to determine the application of general or special controls provides a reasonable assurance of safety and effectiveness
Regulatory Background


Section 513(f)(1): “new devices”

• a device not equivalent to a Class I or II device is classified into Class III automatically: a “new device”
• regardless of risk
• post-Amendments Class III devices
Regulatory Background

FD&C Act – modified in 1997
Food and Drug Administration Modernization Act (FDAMA)

Section 513(f)(2): established de novo classification process
- also known as “Evaluation of Automatic Class III Designation”
- provided regulatory authority for FDA to reclassify devices that were classified into Class III per Section 513(f)(1) (new devices)
- to Class I or II using criteria of Section 513(a)(1)(A-B)
Regulatory Background

de novo Process, post-FDAMA: 4-step process

1. Sponsor submits premarket notification (510(k))

2. FDA issues final 510(k) decision of not substantially equivalent due to no predicate
   – i.e., new intended use and/or technological characteristics that raise different types of safety and effectiveness questions
   – does not apply to NSE decisions due to lack of data
Regulatory Background

**de novo Process, post-FDAMA: 4-step process**

3. Sponsor submits de novo request

4. FDA evaluates whether the device can be classified into Class I or Class II:
   - if Class II: also identify special controls
Regulatory Background

FD&C Act, further modified - 2012
Food and Drug Administration Safety and Innovation Act (FDASIA)

Section 513(f)(2) - modified

– created alternative de novo pathway
– goal to streamline and increase efficiency in de novo process
– removed requirement for sponsor to receive NSE decision prior to submission of de novo request
– still only applies to Section 513(f)(1) (new devices)
– pathway per FDAMA still an option
– intent and decision-making threshold for de novo eligibility unchanged
Regulatory Background

de novo Process, post-FDASIA:
2-step process

1. Sponsor submits de novo request

2. FDA evaluates whether the device can be classified into Class I or Class II:
   • if Class II: also identify special controls

or...
Regulatory Background

de novo Process, post-FDASIA:
4-step process

1. 510(k) submission
2. NSE decision
3. de novo request
4. FDA evaluates whether the device can be classified into Class I or Class II
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Submission Process: Two Methods

1. **Method #1:** 510(k) ➔ de novo

2. **Method #2:** de novo only
Submission Process:
Method #1: 510(k) ➔ de novo

1. Sponsor submits 510(k) submission
   • should be complete submission consistent with 510(k) requirements

2. FDA reviews 510(k) submission; makes NSE finding due to lack of appropriate predicate
   • may also resolve safety and effectiveness issues during review of 510(k)
   • FDA may choose to indicate in NSE letter that new device may be appropriate de novo candidate (based on benefit-risk profile, not adequacy of data submitted)
     ➢ FDA’s suggestion for de novo is not binding
     ➢ sponsor may pursue de novo without FDA’s suggestion
Submission Process

Method #1: 510(k) → de novo

3. Sponsor submits de novo request

- reference prior 510(k)
- address any differences between prior 510(k) and de novo request; provide added testing, S&E information as needed
- characterize risks to health of the new device
- characterize how the risks may be mitigated
- if propose to reclassify to Class II, then identify the special controls necessary to provide a reasonable assurance of safety and effectiveness
Submission Process

Method #1: 510(k) → de novo

4. FDA reviews de novo request

- may interact with sponsor (especially near latter stages of FDA review)
- request for additional information
- render final de novo decision: grant or deny
- if grant de novo, then also:
  - issue written order (e.g., letter to the de novo requester) granting de novo: device is legally marketed
  - publish Federal Register Notice:
    - new classification - Class I or II
    - special controls (if Class II)
Submission Process

Method #2: de novo only

1. Sponsor submits de novo request:
   - evidence that provides a reasonable assurance of safety and effectiveness of new device
     - device description
     - labeling
     - performance testing (bench, animal, clinical)
     - etc.
   - characterize risks to health of the new device
   - characterize how the risks may be mitigated
   - if propose to reclassify to Class II, then identify the special controls necessary to provide a reasonable assurance of safety and effectiveness
Submission Process

Method #2: de novo only

2. FDA reviews de novo request

- may interact with sponsor (especially near latter stages of FDA review)
- ask for additional information
- render final de novo decision: grant or deny
- if grant, then also:
  - issue written order granting de novo (e.g., letter to the de novo requester): device is legally marketed
  - publish Federal Register Notice:
    - new classification - Class I or II
    - special controls (if Class II)
Submission Process

Informal Advice (Pre-Submission)

**FDA encourages use of Pre-Submissions (Pre-Subs) for candidate de novo applications!**

- after device design and intended use are established
- after sufficient information has been collected regarding safety and effectiveness (e.g., test methods)
- useful for novel devices with no FDA regulatory history, based on your research

Pre-Submission Program Draft Guidance

**Reference:**

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Content of De Novo Request
(suggested)

1. Administrative Information:
   – applicant name
   – contact name
   – address
   – phone
   – fax
   – email
Content of De Novo Request

(suggested)

2. Regulatory History:
   - prior submissions to FDA for same device
     • prior 510(k)s and related NSE decisions
     • IDEs
     • Pre-Submissions (Pre-Subs)
     • previously withdrawn/declined de novos
Content of De Novo Request
(suggested)

3. Device Information and Summary
   – device name
   – device description
   – intended use/indications for use statement
   – technological characteristics
   – labeling (directions for use)
Content of De Novo Request
(suggested)

4. Classification Summary
   – review of FDA classifications, regulations, and approved PMAs to confirm that your device has not already been classified
     • in other words, confirmation that this is a “new device”

5. Classification Recommendation
   – recommended Class (i.e., either Class I or II)
   – exempt or not-exempt
   – justification for recommended classification, controls, and exemption (as applicable)
Content of De Novo Request
(suggested)

6. Supportive Evidence
   – summary of performance testing:
     • methods, data, results
     • testing to include: pre-clinical, animal, clinical, where appropriate
     • correlation between evidence and classification recommendation

7. Summary of Benefits and Known/Potential Risks to Health
Content of De Novo Request
(suggested)

8. Risk and Mitigation Information
   – discussion of each risk, mitigation measure, and evidence
   – mitigation to include general and/or special controls

9. Device Labeling
   – per Section 201(m) of FD&C Act

Consideration of Benefit-Risk Profile

Reference: Factors to Consider When Making Benefit-Risk Determinations in...De Novo Classifications:
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Neuropsychiatric EEG-Based Assessment Aid for ADHD System: background

Original 510(k) Submission: K112711

- interpretive electroencephalograph (EEG) assessment aid

- compact EEG recording system, EEG data archive and communications system, and analysis system

- uses patient’s EEG (theta/beta ratio) to provide interpretation of neuropsychiatric condition

- for patients between ages 6 and 17 years old
# Neuropsychiatric EEG-Based Assessment Aid for ADHD System: risks to health

<table>
<thead>
<tr>
<th>Identified Risk</th>
<th>Mitigation Measure</th>
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<tbody>
<tr>
<td>adverse tissue reaction</td>
<td>biocompatibility; labeling</td>
</tr>
<tr>
<td>electromagnetic incompatibility</td>
<td>electromagnetic compatibility testing</td>
</tr>
<tr>
<td>equipment malfunction leading to injury to user/patient (shock, burn, or mechanical failure)</td>
<td>electrical safety, thermal, and mechanical testing; labeling</td>
</tr>
<tr>
<td>false result leading to delay in treatment or unnecessary treatment due to hardware failure</td>
<td>performance testing; hardware/software verification, validation and hazard analysis; technical parameters; labeling</td>
</tr>
<tr>
<td>false result due to incorrect artifact reduction</td>
<td>operator training; software verification and validation; labeling</td>
</tr>
<tr>
<td>false result due to incorrect placement of electrodes</td>
<td>operator training; clinical performance testing; labeling</td>
</tr>
<tr>
<td>false result when a neuropsychiatric interpretive EEG assessment aid is used for confirmatory support or support for further testing</td>
<td>clinical performance testing; device design characteristics; labeling</td>
</tr>
<tr>
<td>use error</td>
<td>clinical performance testing; labeling</td>
</tr>
</tbody>
</table>
Neuropsychiatric EEG-Based Assessment Aid for ADHD System: **classification**

de novo granted July 15, 2013

21 CFR 882.1440

- Neuropsychiatric Interpretive Electroencephalograph Assessment Aid
- Class II
- Product Code: NCG
- **Identification:**
  
  “... a prescription device that uses a patient’s electroencephalograph (EEG) to provide an interpretation of the patient’s neuropsychiatric condition. The [device type] is used only as an assessment aid for a medical condition for which there exists other valid methods of diagnosis.”
Neuropsychiatric EEG-Based Assessment Aid for ADHD System: special controls

- **technical parameters** of the device, hardware and software must be fully characterized and must demonstrate a reasonable assurance of safety and effectiveness.

- **device parts** that contact the patient must be demonstrated to be **biocompatible**.

- **device** must be **designed and tested** for electrical safety, EMC, thermal and mechanical safety.

- **clinical performance testing** must demonstrate the accuracy, precision, reproducibility of determining the EEG-based interpretation, including any specified equivocal zones (cut-offs).
Neuropsychiatric EEG-Based Assessment Aid for ADHD System: special controls

- **clinical performance testing** must demonstrate ability of device to function as an assessment aid for the indicated medical condition.
  - **performance measures** must demonstrate device performance characteristics per intended use and environment.
  - **performance measurements** must include sensitivity, specificity, positive predictive value and negative predictive value.
  - demonstrate **repeatability of measurements** using interclass correlation coefficients and qualitative scatter plot(s).

- **device design** must include safeguards to prevent use of the device as a stand-alone diagnostic

- **labeling** must bear all information required for the safe and effective use of the device:
  - Warning that the device is not to be used as stand-alone diagnostic; detailed summary of clinical performance testing; qualifications and training requirements for users; intended use (specifying patient population); instructions that should be given by technicians to patients regarding data collection; information for clinicians; validated methods and instructions to reprocess any reusable components (where appropriate)
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After de novo is granted

- **New Device is Legally Marketed**
  - subject to post-market requirements applicable to that device and class (including general controls, special controls as applicable)

- **New Device Establishes New Classification**
  - future similar devices may attempt to use that device as predicate
    - follows standard 510(k) process

- **FDA publishes order announcing new classification, controls**
After de novo is granted

- FDA publishes summary of de novo review
  - submission number
  - approval order
  - decision summary

Transparency Initiative

Reference:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparencyucm232269.htm
After de novo is granted

Evaluation of Automatic Class III Designation (De Novo) Summaries

The Food and Drug Administration Modernization Act of 1997 (FDAMA) added the "De Novo" classification option as an alternate pathway to classify certain new devices that had automatically been placed in Class III due to lack of a predicate.

The De Novo process applies to low and moderate risk devices that have been classified as class III because they were found not substantially equivalent (NSE) to existing devices. Applicants who receive this determination may request a risk-based evaluation for reclassification into class I or II within 30 days of receipt of an NSE determination. Devices that are classified through the De Novo process may be marketed and used as a predicate for future Premarket Notification [510(k)] submissions.

FDA has begun releasing De Novo Summary documents for devices granted market authority through the De Novo process. The De Novo Summary is intended to present an objective and balanced summary of the scientific evidence that served as the basis of the decision to grant a de novo petition. The Summary outlines how FDA determined that the device for which a petition is granted is low to moderate risk and that general and/or special controls provide reasonable assurance of safety and effectiveness. The De Novo Summary also serves as a resource on the types of information necessary to support substantial equivalence for device manufacturers that may wish to use the de novo device as a predicate for future 510(k) submissions.

Links to all available De Novo Summary documents can be found in the table below.

<table>
<thead>
<tr>
<th>Device Name</th>
<th>510(k) Number</th>
<th>Approval Letter</th>
<th>Decision Summary</th>
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</thead>
<tbody>
<tr>
<td>Infrascanner Model 1000</td>
<td>K080377</td>
<td>Approval Letter</td>
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<tr>
<td>Zeltiq™ Dermal Cooling Device</td>
<td>K080521</td>
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<td>Erchonia ML Scanner</td>
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<tr>
<td>NuMED NuCLEUS and NuCLEUS-X BAV Catheters</td>
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<tr>
<td>Hem-Avert Perianal Stabilizer</td>
<td>K083692</td>
<td>Approval Letter</td>
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After de novo is granted

Approval Order
(1st page)
After de novo is granted

**Decision Summary**

(1st page)
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• **Best Practices/Helpful Hints**
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1. Do your homework and regulatory research to show your new device is de novo eligible.

- Verify that your product is not already classified
- Research all available databases (510(k), PMA, classification) and prior decisions
2. Be specific with the device description and indications for use.

- The specifics of the device description and intended use will determine whether the device has a predicate to which it may be compared.
Best Practices/Helpful Hints

3. Complete all required performance testing prior to submission of de novo.

– Testing may include bench, animal, in vivo, in vitro, clinical.
– Each de novo will need the level of testing to characterize level of risk of device, demonstrate reasonable assurance of safety and effectiveness, and (as applicable), the appropriateness of special controls.
– Clinical testing may not always be required, but is likely in many cases.
4. Correlate each risk to health with a mitigation measure.

- Consider similarities of new device risk with mitigation used for similar devices (i.e., consider special controls for other de novos and existing Class II devices)
- Make sure to address each risk to health with at least one mitigation measure.
5. Being Low Risk helps support de novo eligibility, but isn’t sufficient.

- A new device that is low risk may be eligible for a de novo, **only** if one may characterize the risks to health and establish general and/or special controls to manage those risks.
Case Study revisited: Electrogastrogram (EGG) System

• de novo program implemented prior to resolution of 510(k) submission.

• determined that device was eligible for de novo program
Case Study revisited: EEG System

21 CFR 876.1735

- Electrogastrography System
- Class II
- Product Code: MYE
- Identification:

  “... a device used to measure gastric myoelectrical activity as an aid in the diagnosis of gastric motility disorders. The device system includes the external recorder, amplifier, skin electrodes, strip chart, cables, analytical software, and other accessories.”

64 FR 51444, published September 23, 1999
Case Study revisited: EEG System

**special controls**

- **labeling requirements:**
  - proper instructions for use, placement of electrodes
  - description of collection of background data, elimination of artifact
  - description of test protocol to obtain EGG signal
  - explanation of how to interpret test results

- device design to ensure that EGG signal is distinguishable from background noise that may interfere with true gastric myoelectric signal

- data to demonstrate that device has adequate precision and the EGG signal is reproducible and interpretable
Questions?
For Further Assistance
Contact Us!

Email: dsmica@fda.hhs.gov

Phone: (800) 638-2041 or (301) 846-8149
   Monday - Friday, 8 am – 5 pm, EST

Medical Device Specialists at your service!