

Welcome to today's FDA/CDRH Webinar

*Thank you for your patience while we register all of today's
participants.*

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**REGULATORY OVERVIEW FOR DEVELOPERS
AND SPONSORS OF NEUROLOGICAL and
PHYSICAL MEDICINE DEVICES:
*An Introduction to the De Novo Pathway***

**Thursday, August 27, 2020
1:00PM-2:30PM**

What We'll Discuss Today

- **Introduction to the Review of Neurological and Physical Medicine Devices under the De Novo Pathway**
- **The De Novo Pathway**
- **Benefit-Risk Analysis**
- **Case Study**
- **Engaging with the FDA through the Pre-submission process**
- **Closing Remarks**



Introduction

Carlos Peña, PhD, MS

Director

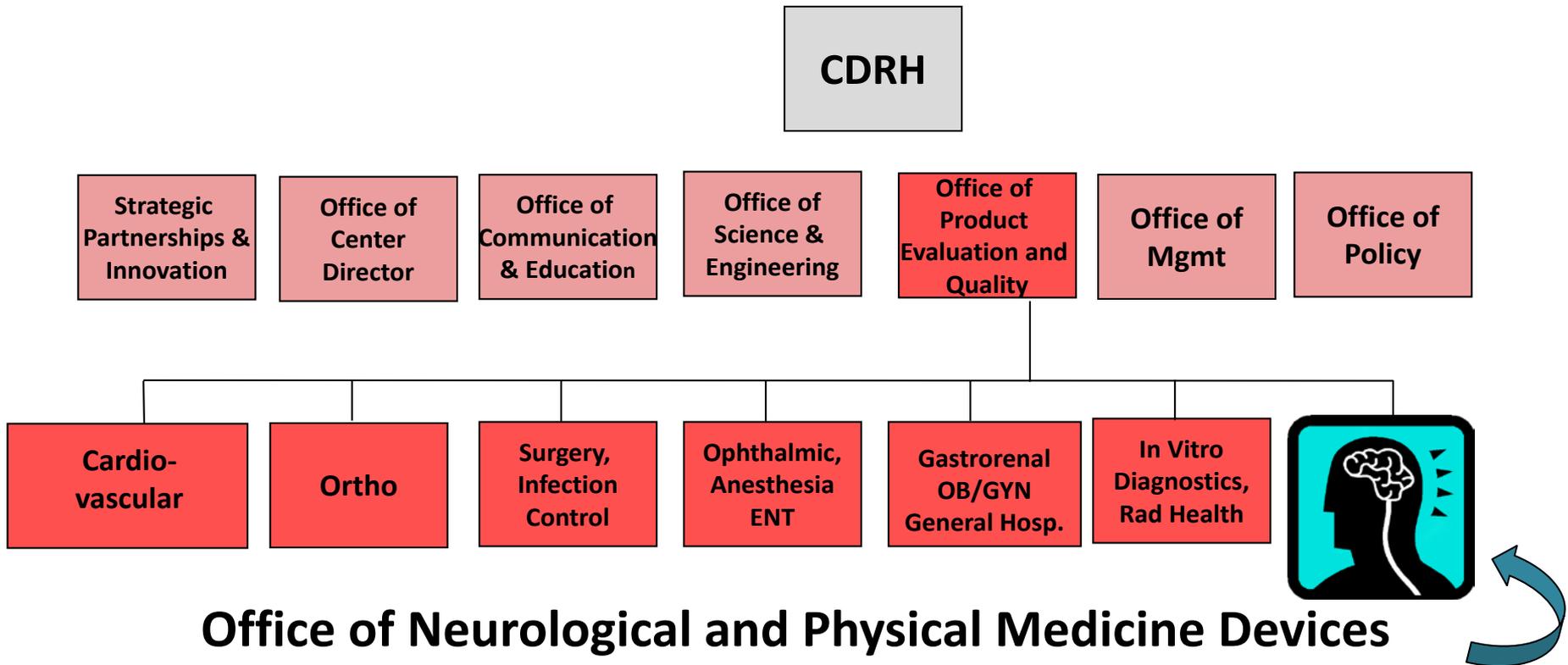
Office of Neurological & Physical Medicine Devices

Office of Product Evaluation and Quality

Center for Devices and Radiological Health

Investing in Review

Center for Devices and Radiological Health (CDRH) Organization Pathway for Neurological and Physical Medicine Regulatory Submissions





CDRH Vision

- Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.
- The U.S. is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.
- U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance.
- Devices are legally marketed in the U.S. and remain safe, effective, and of high-quality.
- Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.

Medical Device Definition

Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) states, in part:

- “Device... means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...”
- “...intended for use in the **diagnosis** of disease or other conditions, or in the **cure, mitigation, treatment, or prevention** of disease, in man...” or
- “...intended to affect the structure or any function of the body of man and which does not achieve any of its primary intended purposes through chemical action....”

Experience in Moving Neurological Medical Devices From **Bench to Market**



Clot Retriever for Ischemic Stroke



Ablation Therapy



Cognitive Function following concussion



Prosthetic Arm



Medical Device For Migraine



Microcatheters for the neurovasculature

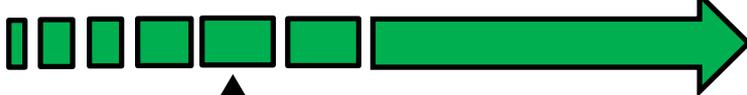
Regulatory Pathways for Medical Devices

Sponsors Apply to FDA to Market Device

FDA Decision Points

NonClinical & Clinical Study Phase

May occur over multiple years of development



Sponsors may submit a pre-submission to the FDA to start early regulatory discussions and develop a path forward

PreMarket Approval (PMA) Submission



180* Days

De Novo Submission



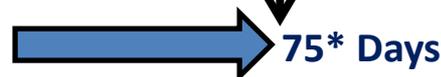
150* Days

Premarket Notification 510(k)



90* Days

Humanitarian Device Exemption



75* Days

**Stamp
Legally
Marketed
in the
United
States**

*Number of days noted is days the submission is under review by the FDA, not the total time that it may take to get the device technology to market or through the review process. In some cases, the review process may take longer depending upon the particular device, technology, indication for use, user, and risk of the device.

Classifications & Regulatory Pathways

- Class III: generally PMA (Premarket Approval)
- Class II: 510(k) (premarket notification), if the intended use and technology are similar to something already classified
- Class I: Low risk, general controls are typically sufficient; generally exempt from 510(k)



The De Novo Pathway

Sergio M. de del Castillo, RAC

De Novo Program Lead

Office of Regulatory Programs

Office of Product Evaluation and Quality

Center for Devices and Radiological Health

What Is a De Novo Classification Request?

De Novo Classification

- **New device type**
 - Intended for devices that are automatically classified into Class III
- **Risk-based classification**
 - Request to FDA to classify new device into Class I or Class II

De Novo Classification

- **Granted De Novo request**
 - Creates new classification regulation
 - Regulates new device type through 510(k) pathway, when De Novo granted as a Class II device
 - Authorizes marketing in U.S.A.

Is Your Product a New Device Type?

- **Must be a medical device (Section 201(h) of FD&C Act)**
- **Must not fit into any existing classification regulation**
 - No predicate device
 - Doesn't fit into existing Class III classification regulation
- **No approved PMA(s) for same device type**

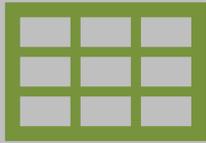
De Novo Classification Goals

1. Determine if the probable benefits outweigh the probable risks to health
2. Identify probable risks to health
3. Determine level of control needed to mitigate risks:
 - general controls only = *Class I*
 - general controls + special controls = *Class II*

De Novo Classification Elements



Benefit-Risk Assessment



Risk/Mitigation Table



Special Controls (Class II)



New Classification Regulation

Benefit-Risk Assessment

- Based on totality of evidence (primarily clinical)
- Assessment of probable benefits and probable risks
- Assessment of additional factors, for example:
 - Uncertainty
 - Patient perspectives
 - Addressing unmet medical need

See [“Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications”](#)



Preparing a De Novo Request

Suggested Resources

- [CDRH Device Advice – De Novo Classification Request](#)
- [De Novo Classification Process \(Evaluation of Automatic Class III Designation\)](#)
- [Acceptance Review for De Novo Classification Requests](#)



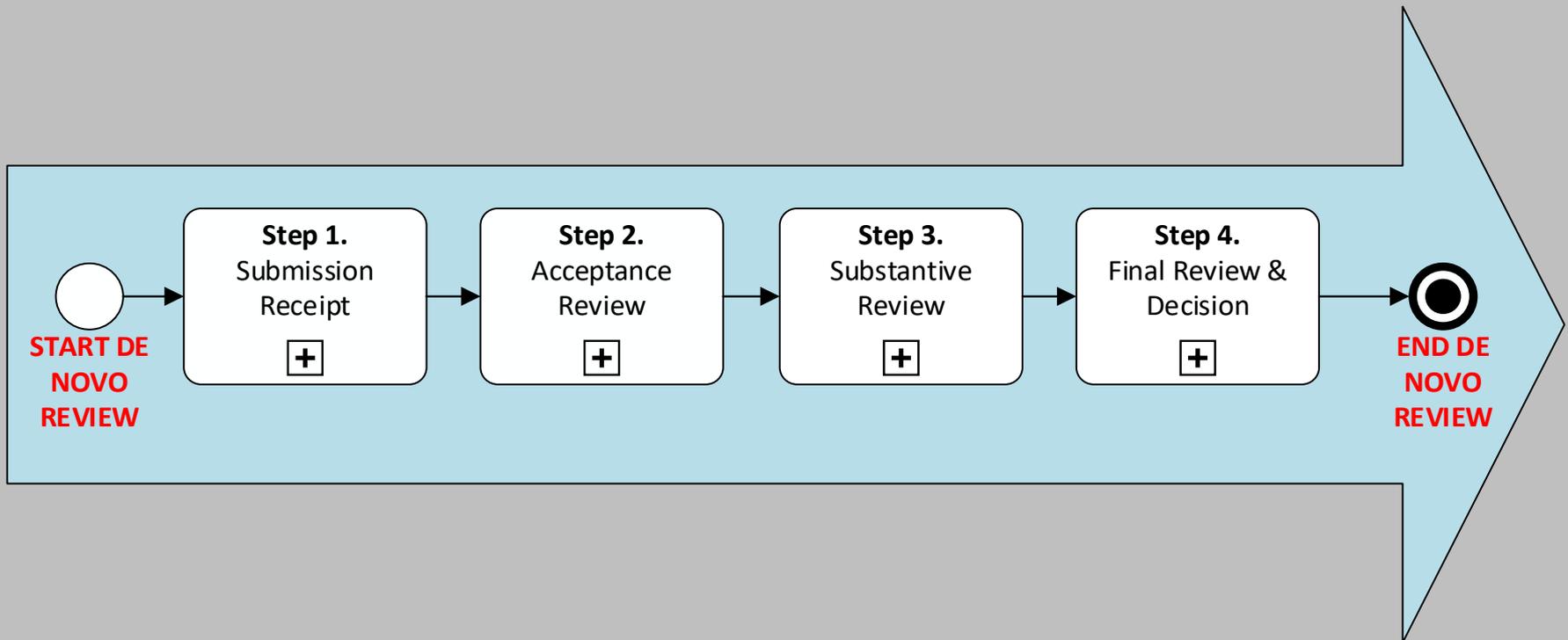
De Novo Review Process

Overall Process and Timeline

Goal → Final decision by FDA Day 150

- Typically two separate review cycles (75 days each)
 - 1st cycle: issue request for Additional Information, when necessary
 - 2nd cycle: render final decision (**grant** or **decline**)

De Novo Review Process



Submission Receipt

- De Novo sent to Document Control Center (DCC)
- DCC verifies following criteria are met:
 - Applicable user fee is paid
 - Valid electronic copy (eCopy) is provided
- If above criteria are met, De Novo is assigned to lead reviewer

Acceptance Review

- Determine if De Novo is administratively complete
- Intend to complete review within 15 calendar days of receiving original De Novo
- Once accepted, proceed to substantive review

See [“Acceptance Review for De Novo Classification Requests”](#)

Substantive Review

- Classification summary – verify device is eligible
- If eligible:
 - review all information/data in the De Novo
 - Includes benefit-risk assessment
 - identify any questions (deficiencies)
 - interactive review (where feasible)

Substantive Review

- When appropriate, FDA will send request for Additional Information (AI), which stops review clock
- Submitter has 180 days to provide complete responses to AI letter

Final Review & Decision

- Submitter provides responses to AI letter
- If FDA determines complete responses provided, the review clock resumes
- FDA reviews responses, including any new data
 - Includes updated benefit-risk assessment
- FDA renders final decision: **grant** or **decline**

Decline Decision

- Typical reasons for a **decline** decision:
 - Benefits do not outweigh risks
 - Cannot develop/determine if special controls mitigate risks
 - Ineligible (1st review cycle)
- Decline order will be issued to requester
- Decline order will identify all outstanding deficiencies

Granting Decision

- ✓ Determine probable benefits outweigh probable risks
- ✓ Identify probable risks to health
- ✓ Determine level of control needed to mitigate risks to health
 - General controls only = *Class I*
 - General controls + special controls = *Class II*

After a De Novo Is Granted

- FDA sends granting order
- De Novo device may be legally marketed
 - Subject to applicable requirements, including special controls
- New classification regulation is established
- De Novo device may be used as a predicate device

After A De Novo Is Granted

- FDA updates [De Novo Database](#)
 - Granting order
 - Decision Summary
- FDA publishes notice in Federal Register
 - Mechanism for updating Code of Federal Regulations

Summary

- De Novo pathway is intended for new device types.
- A granted De Novo creates a new classification regulation.
- Classification is determined by benefit-risk assessment and controls needed to mitigate risk.

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 30, 2019.

Document originally issued on March 28, 2012.

This document supersedes “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications” issued August 24, 2016.

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf>

Benefit-Risk Determinations

- Balance considerations of **probable benefits** and **probable risks** as part of determination of a **reasonable assurance of safety and effectiveness** for the device for its intended use
- Both clinical and non-clinical data can play a role in benefit-risk determinations
- Probable risks and probable benefits supported by valid scientific evidence

Benefit-Risk Determinations

- A **reasonable assurance of safety** occurs when “it can be determined, based upon valid scientific evidence, that the probable benefits ... outweigh any probable risks,” and can be demonstrated by establishing “the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.” (21 CFR 860.7(d)(1)).

Benefit-Risk Determinations

- A reasonable assurance of effectiveness of a device shall consist principally of well-controlled investigations, as defined in [21 CFR 860.7(f)], unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations. The Commissioner may make such a determination where the requirement of well-controlled investigations in [21 CFR 860.7(f)] is not reasonably applicable to the device. 21 CFR 860.7(e)(2).

Benefit-Risk: Factors the FDA Considers

Benefits	Risks
<p>Extent of the probable benefit(s):</p> <ul style="list-style-type: none"> • Type of benefit(s) • Magnitude of the benefit(s) • Probability of the patient experiencing one or more benefit(s) • Duration of effect(s) • Degree of Uncertainty 	<p>Extent of the probable risk(s)/harm(s):</p> <ul style="list-style-type: none"> • Severity, types, number and rates of harmful events associated with the use of the device <ul style="list-style-type: none"> - Device related serious adverse events - Device related non-serious adverse events - Procedure related complications • Probability of a harmful event • Duration of harmful events • Risk from false-positive or false-negative results for diagnostics • Degree of Uncertainty

Benefit Considerations

Factors	Questions to Consider?
Type of benefit	<ul style="list-style-type: none"> • What benefit was evaluated? • What value do patients place on the benefit?
Magnitude of the benefit(s)	<ul style="list-style-type: none"> • What was the magnitude of each treatment effect? • How did the benefit rank on the scale used to measure benefit?
Probability of the patient experiencing one or more benefit(s)	<ul style="list-style-type: none"> • Was the study able to predict which patients will experience a benefit? • What is the probability that a patient for whom the device is intended will experience a benefit? • How did the benefits evaluated vary across sub-populations? • Was there a variation in public health benefit for different populations? • Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?
Duration of effect(s)	<ul style="list-style-type: none"> • Could the duration, if relevant, of each treatment effect be determined? If so, what was it? • Is the duration of the benefit achieved of value to patients?

Risk Considerations

Factors	Questions to Consider?
Severity, types, number and rates of harmful events	<ul style="list-style-type: none"> • What are the device related serious adverse events? • What are the device related non-serious adverse events? • What are other procedure related complications?
Probability of a harmful event	<ul style="list-style-type: none"> • What percent of the intended patient population would expect to experience a harmful event? • What is the incidence of each harmful event in the study population? • How does the incidence of harmful events vary by sub-population (if applicable)? • Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?
Duration of harmful events	<ul style="list-style-type: none"> • How long does the harmful event last? • Is the harmful event reversible? • What type of intervention is required to address the harmful event?
Risks from false-positive or false-negative results for diagnostics	<ul style="list-style-type: none"> • What are consequences of a false-positive, or false-negative? • Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?

Benefit-Risk: Additional Factors

- Uncertainty
- Patient-centric assessments and patient-reported outcomes (PROs)
- Characterization of the disease
- Patient perspectives
- Availability of alternative treatments or diagnostics
- Risk mitigation
- Post-market data
- Novel technology addressing unmet medical need

Hypothetical Case Study

**Using the De Novo Process to Classify
and Bring to Market an Innovative, Low-
Risk Device**

Step 1

Define Technology and Intended Use

“B-Stim” Device

Intended Use

Treat acute pain of headache caused by bruxism

Technology

- wearable (forearm), battery-powered device
- low energy electrical pulses
- controlled by a mobile app
- 45 minutes per treatment
- turns off automatically

Step 2

Is the “B-Stim” a medical device?

[201(h) of the FD&C Act (21 U.S.C. 321)]

- “...an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...”
- “...intended for use in the **diagnosis** of disease or other conditions, or in the **cure, mitigation, treatment, or prevention** of disease, in man...” or
- “...intended to affect the structure or any function of the body of man and which does not achieve any of its primary intended purposes through chemical action....”

Step 3

Is this Device eligible for De Novo Classification?

- Is there a predicate Class II or Class I device?
- Is there a similar Class III PMA device?

FDA website “Classify Your Medical Device”:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm>

Is a Non-Invasive Stimulation Device an Appropriate Predicate Device?

- Decision 1: Is there a legally marketed similar device?
- Decision 2: Does the “B-Stim” have the same intended use?
- Decision 3: Does the “B-Stim” have the same technological characteristics?
- Decision 4: Do the different technological characteristics raise different questions of safety and effectiveness?

*Also see Fig. 1 of FDA Case Study or 510(k) Guidance Document: “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notification [510(k)]”

Is “B-Stim” Similar to TENS for Pain Relief Devices?

- Same Intended Use?

No

Step 4

Assess the risks and mitigations

Can general controls or general and special controls provide reasonable assurance of safety and effectiveness?



Step 5

Obtain FDA Feedback?

[Optional and recommended]

- Section 513(g) Request
- Pre-submission (informal feedback on specific questions)

Neither of these submissions represent final FDA decisions with regard to legally marketing the medical device in the United States.



Step 6

Submit the De Novo to the FDA

The FDA performs

- classification review
- Benefit-risk review
- substantive review

Step 7

Benefit-Risk Assessment

- Based on totality of evidence (primarily clinical)
- Assessment of **probable** benefits and **probable** risks
- Assessment of additional factors, for example:
 - Uncertainty
 - Patient perspectives
 - Addressing unmet medical need

See [“Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications”](#)

PRE-SUBMISSION BEST PRACTICES

Patrick Antkowiak, PhD

Team Lead, Neurodiagnostic Devices Team
Office of Neurological & Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Q-Submission Guidance

- “Requests for Feedback on Medical Device Submissions: The Q-Submission Program and Meetings with Food and Drug Administration Staff”:

<https://www.fda.gov/media/114034/download>

- The guidance covers multiple types of interactions, but this webinar focuses on the “Pre-Submission”

Timeframe for Review

- Per the guidance, the FDA strives to hold a meeting (if requested) within 75-90 days of acknowledged receipt
 - If you request a meeting, we will aim to provide written feedback 5 days in advance of the scheduled date of the meeting
- Feedback is typically provided 70 days after receipt of a submission
- If a meeting is requested, they typically last approximately 1 hour and should be planned accordingly

Why Engage As Early As You Can?

- Pre-submission interactions allow potential issues to be identified earlier, and we can work through them with you as appropriate
 - Particularly useful if there are concerns related to novel technology, testing, or the need for a clinical study
- If needed, you can submit a supplement to get additional feedback

Common Issues: eCopy

- Make sure you comply with the eCopy guidance
 - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions>
- Your submission will NOT be officially logged in, the review clock will not start until FDA receives a valid eCopy
- Questions: cdRh-eCopyinfo@fda.hhs.gov

Submission Contents

- Cover Letter
- Background information, which can include:
 - Device description
 - Proposed indications for use
 - Bench/animal testing protocols
 - Clinical study protocols
- Specific Questions
- Submission should NOT contain data

Submission Contents

- Additional information for Pre-Submissions regarding potential future De Novo submissions
 - Proposed Class (I or II)
 - Discussion of relevant existing classification regulations
 - Benefit - risk analysis
 - Proposed special controls, if relevant
 - Prior regulatory history

Common Issue: Not Enough Information Provided Upfront

- We recommend you first identify the proposed intended use and key aspects of the device design before submission
- Lack of Device Description information, especially for devices we have not previously reviewed, may hinder meaningful discussion

How This Impacts the Review Process

- Without enough information to understand the device, CDRH ends up asking a lot of clarifying questions.
- Providing complete responses to such questions takes time, and extends the overall length of the review process.

What You Can Do

- Remember, **YOU** as the applicant know the most about your device technology, not the FDA
- The more you can explain your rationale and provide justification when submitting a Pre-Submission, the more we can focus on the substance and give you better feedback

Best Practices: Background Information

- It's OK to err on the side of including what you think may be more information than we may need
 - Make sure information is organized and easy to follow
- If you cite literature articles, please provide copies in the submission
- There is such a thing as too much information. We don't need:
 - Circuit diagrams
 - Lines of software code
 - A copy of your entire grant

Best Practices: Background Information

- Avoid assumptions:
 - Unless there is an applicable guidance, standard, or other regulatory precedent you can cite, identify the most appropriate approach for **YOUR** needs and justify it
 - Example: not every animal study needs to use a non-human primate model. Some other model and protocol may be better suited to your particular situation

Common Issue: “Specific” Questions

- Not providing your own proposal for us to review:
 - “What animal model should we use?”
 - “What should our clinical control group be?”
- Wanting the FDA to review data:
 - “Does the FDA have any comments on the nonclinical test results?”

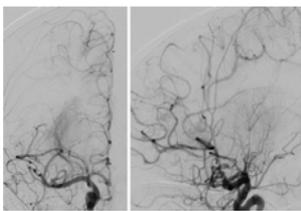
Best Practices: Specific Questions

- The questions should build on the background information you have provided
 - Good question: “What concerns do you have with our proposed animal model to support device safety?”
 - Good question: “Based on the intended use, is the selected control group in our proposed clinical trial appropriate?”

Best Practices: Specific Questions for a De Novo

- “Based on the information provided (device description, indications for use, predicate analysis), does FDA agree that my device is eligible for a De Novo submission?”
- “Does FDA believe that there are risks, other than the ones we have identified, that must be mitigated?”
- “Are there other special controls that should be considered to provide a reasonable assurance of safety and effectiveness?”

It's About the Patients



Questions?

Division of Industry and Consumer Education:
DICE@fda.hhs.gov

Slide Presentation, Transcript and Webinar
Recording will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under the Heading: Specialty Technical
Topics; Subheading: Neurological Devices

Please complete a short survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/CDRHWebinar immediately following the conclusion of the live webinar

Resources

Slide Number	Cited Resource	URL
5	CDRH Device Advice – Classify Your Device	https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device
12	CDRH Device Advice – De Novo Classification Requests	https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request
12	De Novo Classification Process (Evaluation of Automatic Class III Designation)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation
12, 19	Acceptance Review for De Novo Classification Requests	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-review-de-novo-classification-requests

Resources

Slide Number	Cited Resource	URL
13	Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
14	Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de
25	DEN160062 – Decision Summary	https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160062.pdf
31	De Novo Database	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm