



Welcome to today's **FDA/CDRH Webinar**

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

If you have not connected to the audio portion of the webinar, please do so now:

Dial: 888-790-3347

International: 1-517-308-9381

Passcode: 1687624

Conference Number: PW9776650



**REGULATORY OVERVIEW FOR INVESTIGATORS
AND SPONSORS OF NEUROLOGICAL DEVICES AND
A PATH TO INITIATING HUMAN STUDIES**

**Wednesday, September 14, 2016
10:00AM-11:30AM**

Webinar Goal

- **Introduction to the FDA's Review of Neurological Devices, Nonclinical Testing**
- **Early Feasibility Studies**
- **FDA Engagement and the Q-Sub Process**
- **Points of Contact**

In Support of the White House BRAIN Initiative



Introduction

Carlos Peña, PhD, MS

Director

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health



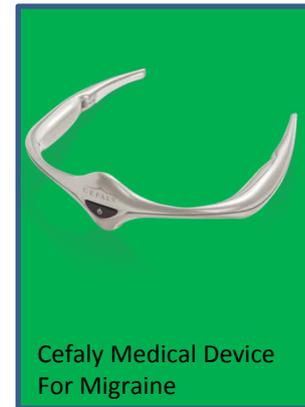
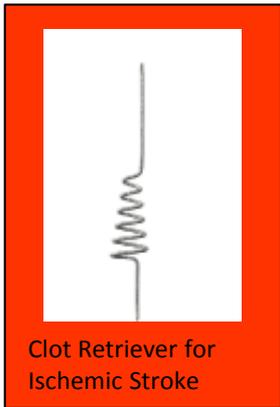
CDRH Vision

- 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

- Definition of a medical device is specified in section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) *
- Section 201(h) states in part:
 - The term “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**



A Risk Based Approach for Medical Devices since 1976

Increasing Risk

Classification determines extent of regulatory control (Risk Based)

Class I

- General Controls

Class II

- General controls
- Special controls

Class III

- General controls
- Premarket approval (PMA)

General Controls

- Electronic Establishment Registration
- Electronic Device Listing
- Quality Systems
- Labeling
- Medical Device Reporting (MDR)
- Premarket Notification [510(k)] (unless exempt)

Special Controls (addressing Risk)

- Guidelines (e.g., Glove Manual)
- Mandatory Performance Standard
- Performance testing, such as biocompatibility, engineering, animal, etc.
- Special Labeling

Classifications & Regulatory Pathways

- Class III: generally PMA (Premarket Approval)
- Class II: 510(k) (or premarket notification), if the intended use and technology are similar to something already classified
- De Novo: devices that aren't comparable enough to something on the market. This generates a new device classification regulation, and will typically (but not always) be Class II

When is **Clinical Data** Needed?

- PMA: typically needed
- De novo: typically needed, but not always
- 510(k): typically not needed

You can request feedback on any protocols through a Q-sub, preferably before starting the study

Increasing Regulatory Transparency

NEW Targeted Guidance for Sponsors (and Developers & Innovators)

- Presubmission Guidance
- IDEs for Early Feasibility Clinical Studies Guidance Document
- Design Considerations for Pivotal Clinical Investigations
- Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

NEW Draft Guidance-March, 2016-Not for Implementation

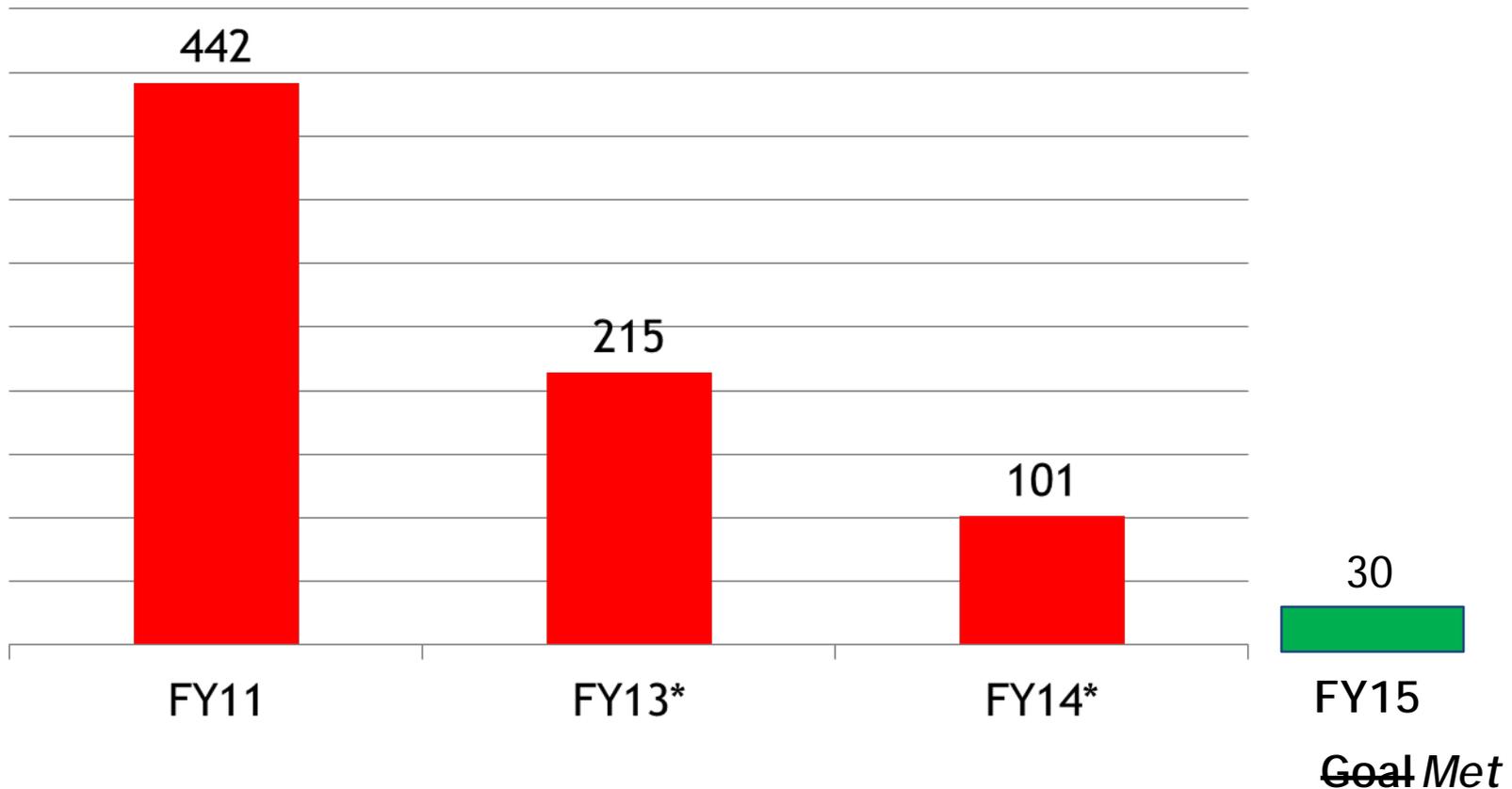
- Clinical Considerations for IDEs for Neurological Devices Targeting Disease Progression and Clinical Outcomes

Investigational Device Exemption (IDE)

- Pertains to devices that have not been approved or cleared for marketing OR that are being tested for a new indication
- IDE allows an investigational device to be used in a clinical study in order to collect safety and/or effectiveness data necessary to support a marketing application (e.g., 510(k), PMA, or HDE)
- Sponsors/investigators may submit a Q-sub to obtain preliminary feedback from the FDA (e.g., risk determination, feedback on proposed study design, etc.)

Reducing FDA Review Timelines

Median Days to Full IDE Study Approval

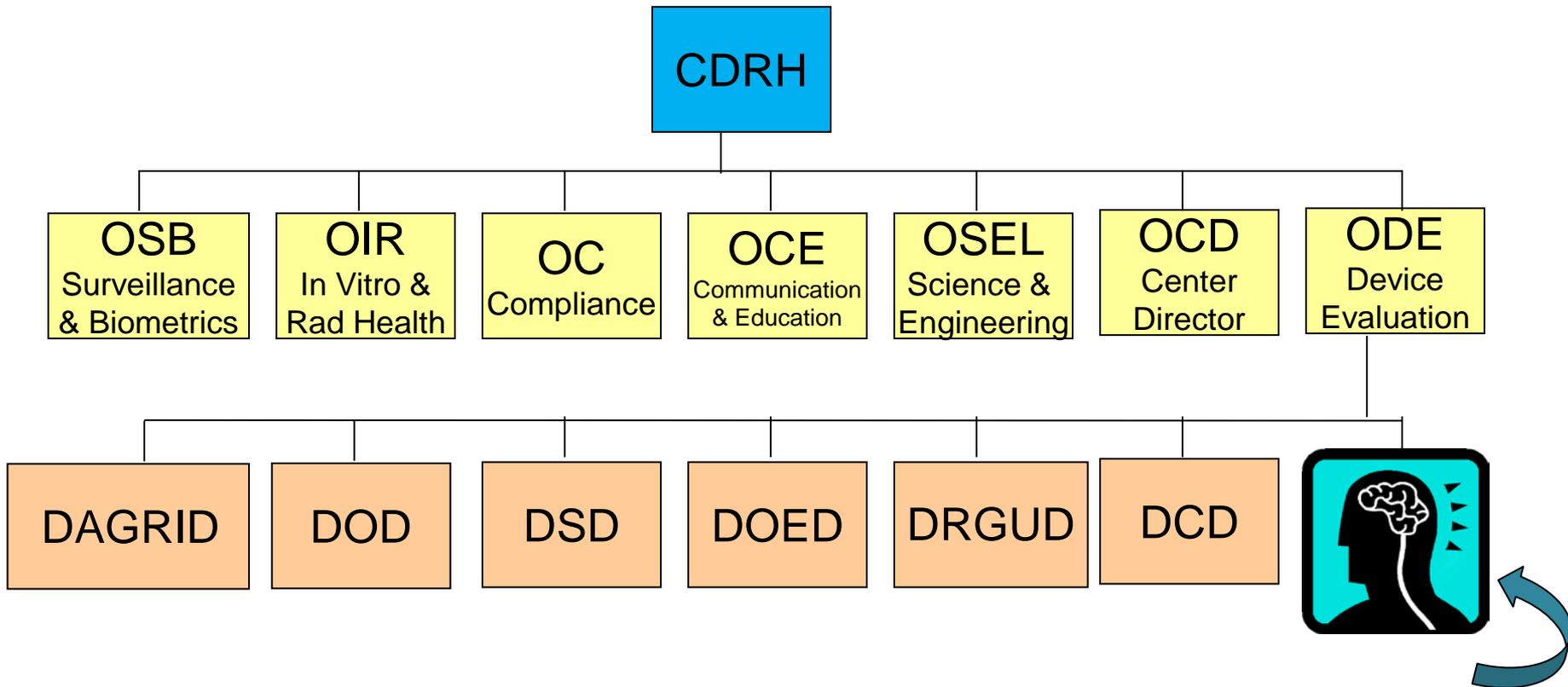


* Values calculated on 10/31/13 and 10/31/14 respectively

Investing in Review-A New Division at FDA

Center for Devices and Radiological Health (CDRH) Organization

Pathway for Neurological and Physical Medicine Regulatory Submissions



Division of Neurological and Physical Medicine Devices

Division of Neurological and Physical Medicine Devices

Coming Soon-New Branch Organization

Neurodiagnostic and Neurosurgical Devices

- Cranial Materials & Other Sealants
- EEG & Non-EEG Diagnostic Devices
- Neurocognitive Diagnostic Devices
- Surgical Instruments & Tools for the Neurovasculature
- Stereotactic Systems for the Neurovasculature

Neurointerventional Devices

- Embolization Coils
- Flow Diverters
- Guidewires & Catheters for the Neurovasculature
- Neurothrombectomy Devices
- Neurovascular & Cerebral Interventional Devices
- Cerebrospinal Fluid Shunts

Neurostimulation Devices Neurology Branch

- Stimulation Devices for Movement Disorders, Epilepsy, Alzheimer’s Disease, Headache, and Traumatic Brain Injury
- Devices may include cortical stimulation devices and deep brain stimulation devices

Neurostimulation Devices Psychiatry Branch

- Stimulation Devices for Major Depression, Obsessive Compulsive Disorder, and Post Traumatic Stress Disorder
- Devices may include cranial electrical stimulation devices, electroconvulsive therapy, and transcranial magnetic stimulation devices

Physical Medicine & Rehabilitation Devices

- Brain Computer Interfaces
- Diathermy
- Functional Electrical Stimulators
- Iontophoresis Devices
- Massagers/Vibrators
- Orthoses, Exoskeletons
- Powered Muscle Stimulators
- Rehabilitation Equipment
- Wheelchairs, Walkers



Nonclinical Testing

Biocompatibility Evaluation

Chandramallika (Molly) Ghosh, PhD, DABT
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Presentation Outline

- Safety assessment of medical devices
 - Biocompatibility
 - ISO 10993 series of standards
 - FDA guidance
- Considerations for safety assessment of neurological devices
 - Special consideration for neurological devices
 - Direct contact with brain and CSF
 - Limitations of chemical characterization approach for neurotoxicity assessment of devices in direct contact with neural tissue
 - Biocompatibility assessment of brain implants

Nonclinical Review Considerations

- **Performance Characteristics**
 - Does the device provide appropriate performance characteristics over the device use life?
- **Biocompatibility**
 - Is the final product biocompatible?

What is Biocompatibility?

Biocompatibility of a medical device refers to the ability of the device to elicit the desired biological response without causing adverse effects in the body. Biocompatibility depends on the body's responses to the device as well as the device's responses to the physiological environment inside the human body.

Why do we ask for biocompatibility assessment?

- Don't always know everything in a final product
- CDRH regulates medical devices, not materials
 - CDRH doesn't clear/approve materials (vs. CDER - e.g., drugs, excipients)
- CDRH recommends biocompatibility assessment on final, sterilized (if applicable) product unless otherwise justified
- Toxicological activity of a medical device
 - Leachable chemicals / manufacturing residuals
 - Response to surface geometry/chemistry
 - Potential degradation products
 - Interactions

Safety Evaluation of a Medical Device

- Effects of leachable chemicals from the device (classical toxicological testing);
- Biological response to surface properties (e.g., bound chemicals, surface properties, and/or device micro/macro geometric features) (testing specific for devices – not applicable for drugs/biologics); plus
- Consideration of how biological response affects device performance (testing specific for devices – not applicable for drugs/biologics).

ISO 10993 Series

Biological Evaluation of Medical Devices

- International Standards Organization (ISO) 10993 series – Biological evaluation of medical devices
- ISO 10993 has different parts
- Some parts are specific in testing methods, while others are very general
- ISO 10993-1 provides guidance on biocompatibility assessment strategy
 - Device categorization
 - Recommends assessment of biocompatibility endpoints based on the category of the device

FDA Guidance and ISO 10993 Standards

- FDA Guidance: Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1 : Evaluation and testing within a risk management process”
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>
 - Final guidance issued on June 16, 2016
 - Guidance implemented on September 14, 2016
- CDRH Standards Program
 - Guidance on the recognition and use of consensus standards
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf>

Device Categorization (ISO 10993-1)

Selection of Biocompatibility Endpoints for Assessment

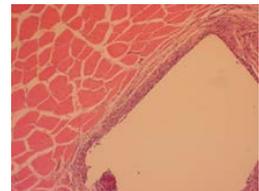
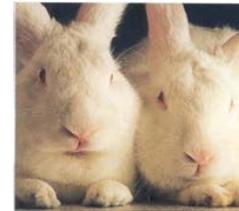
- **Device categorization is based on**
 - **Nature of Tissue contact**
 - Surface contacting device
 - External communicating device
 - Implant device
 - **Duration of Tissue contact**
 - A: Limited (≤ 24 hours)
 - B: Prolonged (> 24 hours to 30 days)
 - C: Permanent (> 30 days)
- **Assessment is based on the category of the device**

Biocompatibility Assessment

- Biocompatibility Endpoints
- Chemical characterization / risk assessment approach to evaluate some biocompatibility endpoints (subchronic/chronic tox, carcinogenicity etc.)

Biocompatibility Endpoints

- Cytotoxicity
- Sensitization
- Irritation/Intracutaneous reactivity
- Acute Systemic Toxicity
- Pyrogenicity
- Subchronic & Chronic Toxicity
- Hemocompatibility
- Genotoxicity
- Neurotoxicity
- Implantation
- Carcinogenicity
- Reproductive/Developmental Toxicity
- Immunotoxicity
- Biodegradation



Some Examples of Neurological Devices

- Deep Brain Stimulator (DBS) leads (polyurethane, PT/IR, epoxy)
- Dura Substitutes (biological & synthetic substitutes)
- Cortical Electrodes (PT/IR, polymer coatings, epoxy)
- Intracranial Stents (Nitinol)
- Ventricular Catheters (silicone elastomer, polymer coatings)

A Few Considerations for Neurological Devices

- Neurological implants in direct contact with neural tissue and CSF bypass the protective function of BBB
- Need for animal implant testing in relevant neural tissue to assess neurotoxic effects
- We recommend devices in contact with neural tissue and CSF be non-pyrogenic with confirmatory LAL endotoxin testing (2.15 EU/device limit) and material-mediated pyrogenicity testing

Challenges for Using Chemical Characterization/Risk Assessment Approach for Neurotoxicity Assessment

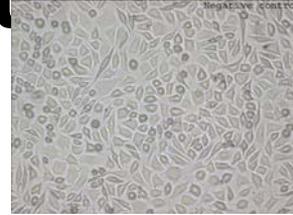
- Chemical characterization/risk assessment approach may not be relevant for assessing local tissue response
- Chemical characterization/risk assessment approach may only be used to assess the potential neurotoxicity of chemicals from neural implants if toxicological data on the chemicals are available from clinically relevant route of exposure studies (for example, intracerebroventricular)

One Example of a Biocompatibility Assessment of a Brain Implant

Permanent implant with neural tissue, CSF, and blood (indirect contact through CSF) contact:

- Biocompatibility assessment per ISO 10993-1/
FDA Biocompatibility Guidance, June 16, 2016
(Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity, Acute systemic toxicity, Material-mediated pyrogenicity, Subchronic toxicity, Genotoxicity, Implantation, Hemolysis, Chronic toxicity, and Carcinogenicity)
- Neurotoxicity assessment due to brain contact
 - Neuroimplantation study
(Clinically relevant implant site study per ISO 10993-6)
- LAL Testing (2.15 EU/device) per FDA Guidance issued on January 21, 2016: “Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile”

<http://www.fda.gov/downloads/MedicalDevices/.../ucm109897.pdf>



One Example of a Neurotoxicity Assessment of a Brain Implant

- Currently, no standard protocol for brain implantation study (ISO 10993-6 Annex in development)
- Some Considerations for neurotoxicity assessment of brain implants:
 - Brain implantation study (e.g. rabbit model for passive DBS lead implant)
 - Separate test and control (e.g. biomaterial control like HDPE) groups
 - Equal number of male and female animals
 - Implantation period – Acute and chronic responses
 - Clinical observations
 - Neurobehavioral assessment
 - Body weight change, food consumption, clinical chemistry, hematological parameters
 - Gross necropsy
 - Histopathology – Neurodegeneration, gliosis, and myelinopathy

Neurotoxicity Assessment from a Functional Study: Theoretical Case Study

- Large animal study (e.g. pig) with active DBS leads
- Test groups to evaluate different stimulation parameters
- Control groups
 - Sham surgical control (passive leads implanted and immediately withdrawn to control for the effect of surgical procedure)
 - Control group with passive implant
- Different time points
- Clinical observation and behavioral assessment
- Blood work (CBC, clinical chemistry pre- and post-implant and pre-termination), Body weight, food consumption
- Gross necropsy
- Histopathology (H & E, Fluoro-Jade B, Luxol fast blue, GFAP)



Nonclinical Testing

Animal Studies

Dhanya K. Williams, M.S.

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

What is the purpose of conducting an Animal Study?

Animal studies are intended to demonstrate that the device under study is sufficiently safe for early human experience [e.g., to support an investigational device exemption (IDE) application] or to demonstrate device safety in support of a marketing application, while incorporating modern animal care and use strategies.

Good Laboratory Practice Requirements

- Good Laboratory Practice (GLP), as outlined in 21 CFR Part 58 (GLP Regulations), applies to nonclinical animal studies.
- Non-GLP studies may be acceptable in some submissions, however, sponsors should provide adequate justification why GLP provisions were not met, how the study deviated from GLP, and why these deviations would not impact the study outcome.

Considerations in Designing a Nonclinical Animal Study

- Animal Model
- Study design (study size and duration)
- Study Endpoints

Animal Model

Provide scientific justification for the animal model used.

- An animal model should be generally accepted for the study of the device type
- Clinical relevance of implant/treatment site
- Address limitations to the selected animal model
- Diversity in animal models used for neurological devices
 - Rats, Rabbits, Sheep, Swine, Canine

Study Design

Use the minimum number of animals necessary to generate valid and meaningful scientific data to demonstrate reasonable safety and performance.

- Include appropriate treatment and control animals to evaluate safety and performance
- Include animal cohorts to evaluate tissue responses over the course of the study based on expected duration of clinical use
- Animal loss

Study Endpoints

- **Safety**
 - Clinical observations
 - Histopathology
- **Performance**
 - Device condition following use
 - Device specific functional endpoints
 - Labeling claims need to be substantiated
- **Consider methods to minimize bias (e.g., blinding, multiple evaluators, randomization, etc.)**

Q-subs

The FDA will review proposed biocompatibility evaluation strategies and animal study rationale, design and protocols, however please note that data cannot be reviewed in the Pre-submission process.

Available Resources

Biocompatibility Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (June 16, 2016)

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>

21 CFR PART 58 GLP FOR NONCLINICAL LABORATORY STUDIES:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58>

Recognized Consensus Standards:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/Search.cfm>

FDA Guidance Documents:

<http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

Early Feasibility Studies

A Valuable Regulatory Tool for Neurological and Physical Medicine Device Development

Erin Keegan, MS and Devjani Saha, PhD

Early Feasibility Study Representatives

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

Agenda

- What is an EFS?
- How can an EFS benefit you?
- Stages of an EFS Pathway to IDE
- Key EFS Principals and DNPMD Examples
- Tips
- Initiating your EFS

What is an EFS?

IDE - Investigational Device Exemption

- An IDE submission allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data

EFS IDE - A standard IDE except...

- Small number of subjects (< 10) in the clinical investigation
- Device is generally early in development
- Device iterations are expected
- Limited non-clinical data may be available
- Enhanced clinical mitigations may be required

EFS is an informal designation

How can an EFS benefit you?

Permits A More Efficient Pathway to US Commercialization

- FDA feedback early in product development may help you improve your development strategy and reduce unnecessary testing
- Data collection in the US patient population may be easier to leverage to support later studies or marketing applications

Enables collection of high quality clinical data for:

- Optimizing device design or operator technique
- Refining the intended use population
- Refining nonclinical test plans
- Developing subsequent clinical study protocols

Stages of an EFS Pathway to IDE

- **Stage 1:** Informal discussion with EFS representatives
- **Stage 2 (optional):** Informational meeting pre-submission
- **Stage 3:** Initial pre-submission as outlined in the EFS guidance
- **Stage 4:** Additional pre-submissions as needed (e.g., if test requirements are uncertain/discussion of clinical protocol)
- **Stage 5:** IDE submission

Key Principles of EFS and DNPMD Examples

Just-In-Time Testing (JITT)

Concern: Comprehensive testing during early phases of device development may add cost without significant return

EFS Approach:

- Doing the right testing at the right time
- EFS should not take the place of informative nonclinical testing

DNPMD Examples:

- Long term durability testing may be deferred given criticality of short term benefit (e.g. glioblastoma, SCI, severe psychiatric disorders)
- Limiting use of a device to the hospital instead of a patient's home may change testing strategy (e.g. EMC for electronic based assistive devices)
- Small number of devices may rely on single lot Ethylene Oxide (EO) sterilization versus full EO sterility validation (e.g. novel leads for spinal cord stimulation)

Enhanced Risk Mitigation Strategies

Concern: An EFS may carry greater unknown risks as compared to traditional feasibility and pivotal studies

EFS Approach:

- Enhanced clinical monitoring specified in the protocol
- More frequent/detailed reporting to the FDA
- Informed consent should highlight greater unforeseeable risk

DNPMD Examples:

Risks	Mitigations
Stimulation related adverse events	<ul style="list-style-type: none"> • Titrating therapy • Turn device off and revert to standard of care
Novel endovascular stroke intervention	<ul style="list-style-type: none"> • Surgery performed at select sites with expert surgical and clinical team
Infection caused by lead implantation	<ul style="list-style-type: none"> • Ongoing monitoring of implantation sites and body temperature

Leveraging Existing Data

Concern: Applicable data may already exist in non-traditional formats (e.g., testing or literature from marketed products or earlier prototypes)

EFS Approach:

- Leveraged data can be used to provide information without unnecessary burden
- You should provide a leveraging rationale and a detailed discussion of differences (e.g., material, design, manufacturing) between the leveraged data and the proposed device

DNPMD Examples:

- Some biocompatibility endpoints could be leveraged from an animal study
- Data from published literature could support device safety (e.g. approved SCS parameters for novel PNS)

Timely Device & Clinical Protocol Changes

Concern: Devices studied under EFS are expected to change throughout the study and require timely device iterations.

EFS Approach:

- Contingent approval: device changes that are anticipated during the study may be executed without additional FDA action if the proposed change, supporting test plans, and acceptance criteria were agreed upon in an IDE or IDE Supplement
- Broader implementation of 5-day notice IDE supplements

DNPMD Examples:

- 5-Day notice: device changes that do not constitute significant changes to the design or principal of operation (e.g. ergonomic modifications)
- Contingent Approval: adjust stimulation parameters, interchange prosthetic devices/components

Tips

If you are making design modifications:

- record device modifications with rationale
- record testing completed with each device iteration
- keep samples of previous generation to help for leveraging in future submissions (e.g. biocompatibility)

If you would like to use test results that were not obtained per standard FDA recommendations:

- provide an explanation for why the data is sufficient
e.g. if your animal study deviates from 21 CFR 58 (GLP) tabulate each part of the regulations, list how the study deviates and how you will ensure data integrity and minimize bias

Tips

If you would like to use short-term animal studies to support EFS initiation of a device intended for long-term use, please note the following:

- providing supporting evidence that short-term results are predictive of long-term safety
- applying additional clinical mitigation strategies (e.g., longer-term follow-ups)
- conducting additional nonclinical testing (e.g., mechanical integrity testing under exaggerated conditions, computational modeling)

Please also note that additional long-term animal study data may be needed to support a larger clinical study

When are you ready for an EFS?

You can:

- describe why additional nonclinical testing will not be informative and therefore a human clinical study is needed;
- justify how any leveraged information supports your clinical trial; and
- identify potential risks and how they will be adequately mitigated

The Device Evaluation Strategy as described in the EFS guidance is a useful regulatory tool to support initiation of your study

- See Appendix 2 in the EFS Guidance available online:
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

When is a good time to talk to the FDA about an EFS?

After...

- You have established your general device design, intended use, and what information you would like to gather from the EFS

Before...

- Expensive and time consuming non-clinical testing has been started

We recommend that you reach out to DNPMD EFS representatives informally to discuss submission strategy

PRE-SUBMISSION BEST PRACTICES

Tim Marjenin

Branch Chief

Neurostimulation Devices Neurology Branch

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

Q-Sub Guidance

- “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff”:
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>
- While the guidance covers multiple types of interactions, today we will focus 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 provide written feedback about 3 days in advance of the scheduled date of the meeting
- You should generally plan to meet with us or receive written feedback 75-90 days after receipt, due to workload considerations of review staff
- Make sure you budget your time 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
 - This is particularly useful if there are concerns related to novel technology or testing
- If needed, you can submit a supplement to get additional feedback

Common Issue: eCopy

- Make sure you comply with the eCopy guidance
 - <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm313794.pdf>
- Your submission will NOT be officially logged in, the review clock will not start, and nothing else will happen until we receive a valid eCopy
- Questions: cdrh-eCopyinfo@fda.hhs.gov

Submission Contents

- Cover Letter
- Background information, which can include:
 - Device description
 - Bench/animal testing protocols
 - Clinical study protocols
- Specific Questions

Common Issue: Not Enough Information Provided Upfront

- An analysis of a number of Investigational Device Exemption (IDE) letters showed that the area generating the most questions was “Device Description”:
 - What the device is and does
 - Instructions for use
 - Hazard Analysis
- We encounter similar issues across other submission types

How This Impacts the Review Process

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

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 thought processes when you submit a pre-submission, the more we can focus on the substance and give you better feedback

Understand the Existing Landscape

- Search for and review applicable guidance documents and standards (if there are any), such as:
 - Biocompatibility, if you are not using an approved device (ISO 10993)
 - “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”
- Explain the relationship of what you’re proposing compared to what’s been done in the past

Best Practices: Background Information

- It's ok to err on the side of including what you think may be more information than we would need
 - Make sure it's 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:
 - 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?”
 - “How large should the sample size 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?”
 - Good question: “Are the proposed sample size calculation method and related elements of the statistical analysis plan appropriate for the proposed clinical study?”

Risk Determinations

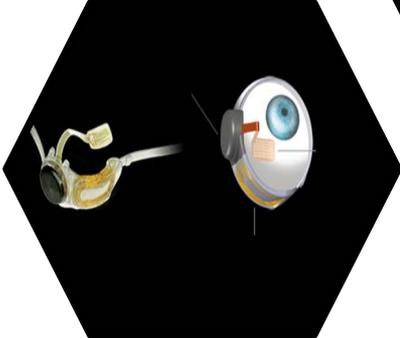
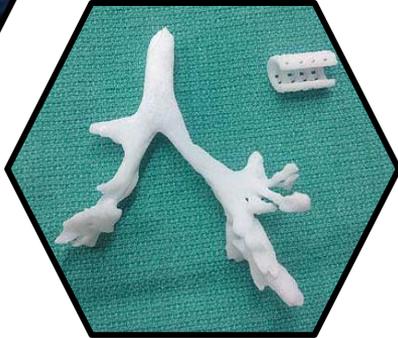
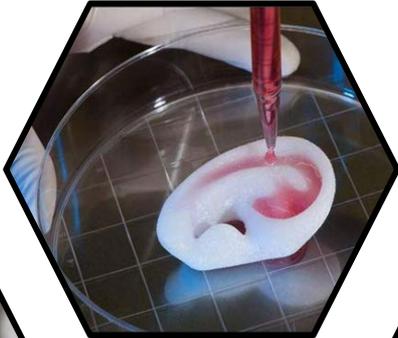
SIGNIFICANT RISK, NON-SIGNIFICANT RISK, AND BASIC PHYSIOLOGICAL RESEARCH

When is an IDE Not Required?

- Exempt studies per 21 CFR 812.2(c), such as:
 - Studies of approved devices used in accordance with their labeling
 - Certain diagnostic device studies
- Basic physiological research: Not for the purpose of evaluating safety/effectiveness of the device
- “Practice of medicine” – care of specific patient with an approved device.
- Non-significant risk studies

Closing Remarks

It's About the Patients



Other Available Resources and Programs

www.fda.gov/MedicalDevices

- CDRH Learn
- Device Advice
- CDRHNew



Resources

Nonclinical & Animal Studies

Biocompatibility Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (June 16, 2016)

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>

21 CFR PART 58 GLP FOR NONCLINICAL LABORATORY STUDIES:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58>

Recognized Consensus Standards:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/Search.cfm>

FDA Guidance Documents:

<http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

Resources

Early Feasibility Studies

- Early Feasibility Study Guidance
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf2>
- EFS CDRH Learn Modules
http://www.accessdata.fda.gov/cdrh_docs/presentations/EFS/story.html
- Pre-Submission Guidance
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>
- IDE Submission Information
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm#regele>
- Design Controls Guidance
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm>
- Electronic Submissions Guidance
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf>

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; Sub-heading:
Device-Specific Topics