Welcome to today's FDA/CDRH Webinar

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

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U.S. FOOD & DRUG ADMINISTRATION

REGULATORY OVERVIEW FOR DEVELOPERS AND SPONSORS OF NEUROLOGICAL DEVICES:

An Introduction to Premarket Approvals (PMA)

Wednesday, July 26, 2017
1:00PM-2:30PM

Agenda

- Introduction to the Premarket Approvals Process
- How Sponsors and Principle Investigators Move Their Product to Market
- Clinical Testing
- Non-Clinical Testing Overview
- Post-Approval Studies
- Bioresearch Monitoring
- Question & Answer Session

Introduction

Michael Hoffman
Deputy 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

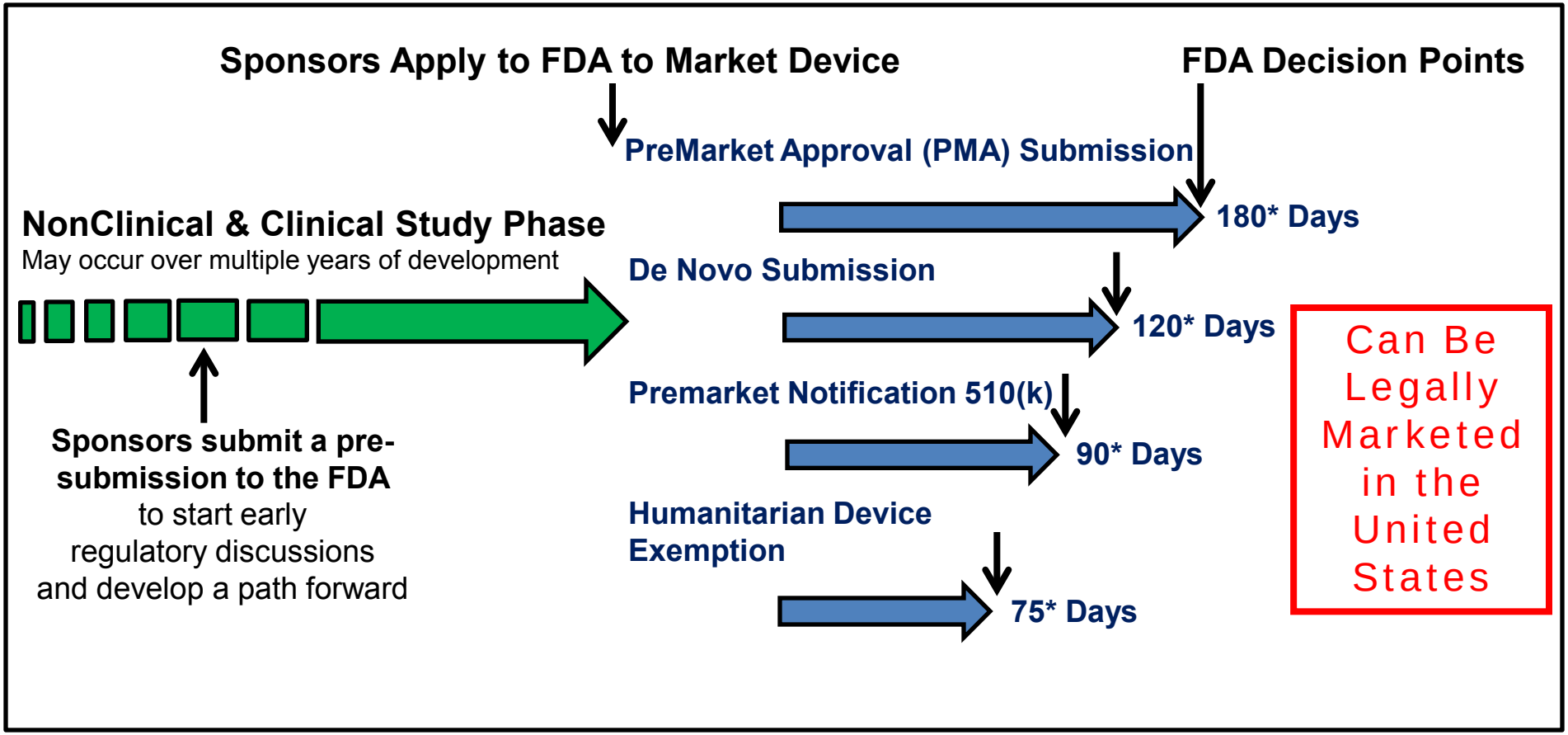
Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) states, in part:

- "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…."

Regulatory Pathways for Medical Devices



*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.

Anderson, Leigh et al. FDA Regulation of Neurological and Physical Medicine Devices: Access to Safe and Effective Neurotechnologies for All Americans. Neuron , Volume 92 , Issue 5 , 943 - 948

Examples of Neurological Products Reviewed in the FDA's Center for Devices and Radiological Health (CDRH)

Neurodiagnostic and Neurosurgical Devices	Neurointerventional Devices	Neurostimulation Devices Neurology	Neurostimulation Devices Psychiatry	Physical Medicine & Rehabilitation Devices
•Cranial Materials & Other Sealants •EEG & Non-EEG Diagnostic Devices •Neurocognitive Diagnostic Devices •Surgical Instruments & Tools for the Neurovasculature •Stereotactic Systems for the Neurovasculature	•Embolization Coils •Flow Diverters •Guidewires & Catheters for the Neurovasculature •Neurothrombectomy Devices •Neurovascular & Cerebral Interventional Devices •Cerebrospinal Fluid Shunts	•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	•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	•Brain Computer Interfaces •Diathermy •Functional Electrical Stimulators •Iontophoresis Devices •Massagers/Vibrators •Orthoses, Exoskeletons •Powered Muscle Stimulators •Rehabilitation Equipment •Wheelchairs, Walkers

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

Clot Retriever for Ischemic Stroke

Ablation Therapy

Cognitive Function following concussion

Prosthetic Arm

Neurostimulation Device For Migraine

Microcatheters for the neurovasculature

Background on Regulatory Requirements

More information is available in the Center for Devices and Radiological Health (CDRH)'s industry education page, CDRHLearn.

https://www.fda.gov/downloads/Training/CDRHLearn/UCM400786.pdf

Premarket Approval Statute and Regulations

- Statute: Section 515 of the Food, Drug, and Cosmetic Act (FD&C Act) [21 USC 360e]
  - Establishes the general requirement for PMAs
  - https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e.htm
- Regulations: 21 CFR 814
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1
  - Includes the regulations for Humanitarian Device Exemption (HDE, not covered as part of this webinar)

How are Premarket Approvals Different?

- Safety and effectiveness standard
  - Not “substantial equivalence”
- Post-market requirements
  - Annual reporting
  - Manufacturing changes
- Review process
  - Filing review
  - Manufacturing review

Premarket Approvals: Modular vs. Traditional

- Traditional: Complete PMA application is submitted to the FDA at once
- Modular: Contents of a PMA application are broken down into components and submitted over time
- Modular review may or may not suit your needs well; make sure you understand the implications and timelines, and ask questions

Guidance – "Premarket Approval Application Modular Review": https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089767.pdf

Premarket Approval Review Process

In depth overview of the PMA Review Process is available in CDRH's Device Advice section at:
https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/ucm047991.htm

Important timeframes:

- Refuse to Accept (RTA) review (within 15 days of receipt)
- Filing review (within 30 days of receipt)
- Substantive review (first 90 days after receipt)

Premarket Approval Review Process (Post-Substantive Interaction)

Substantive review ends with “substantive interaction” decision point (SI). By day 90, the FDA will:

- Request additional information (by letter) if needed to help determine the reasonable assurance of safety and effectiveness of the device. When this is done, review clock stops.

OR

- Determine there are minor questions that can be addressed interactively. When this is done, review clock does not stop.

Premarket Approval Review Process (Post-Substantive Interaction)

After substantive interaction:

- All remaining questions will be resolved interactively
- Be prepared for multiple interactions about labeling
- If a panel meeting is scheduled, it will likely occur after the substantive interaction decision point

Advisory Committee Input

- 21 CFR 814.44(a) - “FDA will begin substantive review of a PMA after the PMA is accepted for filing under 814.42. FDA may refer the PMA to a panel on its own initiative, and will do so upon request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel.”

- Applicants may request that the FDA refer their PMA to an appropriate panel for a formal review and recommendation if a major deficiency letter is received.

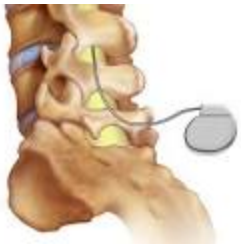
- The panel’s input is a recommendation; the FDA makes the final decision on the PMA.

Premarket Approval Supplements

- Several types:
  - "Panel-track Supplement"
  - "180-Day"
  - "Real-time Review" (has its own guidance document)
  - "30-Day Notice" (has its own guidance document)
  - "Special Supplement: Changes Being Effected"

Guidance – "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process": https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf

How Sponsors and Principle Investigators Move Their Product to Market



Safety

Reasonable assurance that a device is safe: Based on valid scientific evidence, the probable benefits of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness

Reasonable assurance that a device is effective: Based on valid scientific evidence, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Reasonable Assurance and Valid Scientific Evidence

- The FDA relies on **valid scientific evidence** to determine whether there is reasonable assurance that the device is safe and effective.

- Valid scientific evidence can come from:
  - well-controlled investigations,
  - studies and objective trials without matched controls,
  - well-documented case histories conducted by qualified experts, and
  - reports of significant human experience with a marketed device.

Well-Controlled Clinical Investigation

The **plan or protocol** for the study, and the report of the results should include the following:

- A clear statement of the objectives of the study
- A method of selection of the subjects that includes the following:
  - Adequate assurance that subjects are suitable for the study
  - Minimization of any possible bias
  - Comparability between test groups and any control groups

Well-Controlled Clinical Investigation, cont.

Should also include:

- Explanation of the methods of observation and recording of results utilized
- Comparison of results of treatment or diagnosis with a control to permit quantitative evaluation
- Summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods utilized

Pre-Submission 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

NON-CLINICAL TESTING
OVERVIEW

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Non-Clinical Testing

- Also known as “pre-clinical testing”
- Encompasses all testing conducted outside of a human subject
  - Performance/bench testing
    - Includes standards testing
  - Animal testing

Common Non-Clinical Tests

- Testing conducted among many device types
  - Electrical safety
  - Battery reliability (if applicable)
  - Electromagnetic compatibility (including MR compatibility)
  - Biocompatibility
  - Sterility and shelf life
  - Software
  - Engineering
  - GLP-compliant animal studies
- FDA Guidance Documents (https://www.fda.gov/Regulatoryinformation/Guidances/)
- FDA Recognized Consensus Standards Database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm)

Other Performance Testing

- **Device specific tests**
  - May or may not have specific guidance documents and/or standards
  - Always check the databases at fda.gov
- **General examples**
  - Functional testing (demonstrate the device will function as intended)
  - Mechanical testing
  - Fatigue testing
  - Coating integrity, if applicable
  - Others as needed

Considerations for Non-Clinical Testing

- Test devices should be identical to final, finished device intended for human use
  - Same manufacturing processes (materials, equipment, environment, etc.)
  - Post-sterilization processing
    - To demonstrate that sterilization does not alter performance
- If the test device is not identical, justifications for not testing should be provided

Considerations for Non-Clinical Testing, cont.

- Full test reports should be included
  (may not apply when testing is completed in accordance with standards)
  - Summary reports do not always provide sufficient detail
- Testing in compliance with FDA-recognized consensus standards should be listed on Form FDA 3514
- Testing to alternate standard is not advised if there is a corresponding FDA-recognized standard

Post-Approval Studies (PAS)

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Post Approval Studies

- May be required as condition of approval of premarket application under 21 CFR 814.82(a)(2) to assure continued safety and effectiveness of an approved device.
  - May be clinical or pre-clinical studies
  - May be result of long-term safety and effectiveness of device that cannot be addressed by premarket data

- Post approval study protocols may be developed and agreed upon by FDA and applicant during premarket approval review or after premarket approval to be reviewed under a premarket approval supplement.

- The decision of whether a post approval study is needed and the general framework of the study will always be concurred during the premarket approval review process and/or communicated in the approval decision.

Post Approval Study Protocol

- Background (e.g., regulatory history, device description, indications for use)
- Purpose of study
- Study objectives and hypotheses
- Study design
- Study population (inclusion/exclusion criteria, definition and source of comparator group)
- Sample size calculation (statistically justified and based on study hypothesis)
- Primary and secondary endpoints
- Length of follow-up, follow-up schedule, baseline and follow-up assessments

Post Approval Study Protocol Cont.

- Description of data collection procedures
- Statistical analysis
- Data collection forms, informed consent forms, IRB approval forms
- Reporting requirements for interim and final reports
- Study milestones/timelines

Interim & Final Reports

- Interim report: Submitted every 6 months for the first 2 years of the post approval study and annually thereafter, from the date of the premarket approval letter.
  - Should be an update of the study progress with respect to the study design elements described in the protocol and summary of safety and/or effectiveness data and an interpretation of study results to date.

- Final report: Submitted no later than 3 months after study completion (i.e., all subjects have completed follow-up).

Failure to Complete Post Approval Study

- May result in withdrawal of approved PMA

- If study cannot be completed, please communicate with the FDA as soon as possible in interim reports or through a PMA supplement.

Guidances for Post Approval Studies

- Guidance for Industry and FDA Staff "*Procedures for Handling Post-Approval Studies Imposed by PMA Order*"
  - Issued on August 1, 2007
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071013.pdf

- Post-Approval Studies Public Database
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm
  - General status information on each PAS ordered since January 1, 2005

- FDA Post-Approval Studies Website
  - https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovaStudies/default.htm

Bioresearch Monitoring

CDR Isatu Bah, MS, BSN, RN
Division of Bioresearch Monitoring
Office of Compliance
Center for Devices and Radiological Health

Bioresearch Monitoring Program Description

- A comprehensive, FDA-wide program
- On-site inspections and data audits
- Designed to monitor all aspects of the conduct and reporting of FDA-regulated research

Bioresearch Monitoring Program Objectives

- To protect the rights, safety, and welfare of human research subjects
- To determine the accuracy, reliability, and integrity of clinical trials data submitted to the FDA
- To assess compliance with the FDA's regulations governing the conduct of clinical trials including those for informed consent and ethical review

Bioresearch Monitoring Regulations: FDA-Wide

- **21 CFR Part 50:** Protection of Human Subjects
- **21 CFR Part 54:** Financial Disclosure
- **21 CFR Part 56:** Institutional Review Boards
- **21 CFR Part 58:** Good Laboratory Practice for Non-Clinical Laboratory Studies
- **21 CFR Part 11:** Electronic Records/Signatures

Medical Device Regulations

- **21 CFR 807:** Registration/Listing
- **21 CFR 807 Subpart E -** Premarket Notification (510k)
- **21 CFR 809:** In Vitro Diagnostic Products (IVD)
- **21 CFR 812:** Investigational Device Exemptions (IDE)
- **21 CFR 814:** Premarket Approval (PMA) and Humanitarian Device Exemption (HDE)

Pre-Inspection

- Select sites
  - Consider number of subjects, protocol deviations, adverse events, inspection history, etc.
- Issue assignments
- Pre-announce*
  - usually three to five days in advance
  - allows the study site to ensure that the site staff and all required records are available

** unless "For Cause"*

- Memo
- Date:
- To: District Office
- From: BIMO
- Subject: PMA #
- ……
  ……
  ……
  ……
  ……..

Inspection Conduct

- Issue “Notice of Inspection”
- Interview site personnel
- Review records
- Audit data
- Issue 483, if deviations from the regulations
- Discuss verbal observations, if any

Documents Reviewed During PMA Inspections

- Standard operating procedures (monitoring logs, investigator agreement, clinical site procedures, and correspondence between the Sponsor, IRB, CIs, FDA, etc.)
- Progress Reports (adverse events, protocol deviations...)
- Subject Records (medical record, Case Report Forms, ...)
- Data Line Listings (Stratified by site then site)
- Study Protocols & Revisions
- Informed Consent Versions
- Hospital and laboratory records
- Radiological files
- Device accountability records, device Use, disposition, and shipping/return records
- Financial Disclosure Form - Form FDA 3454

http://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/ucm255614.htm

If FDA-483 Issues…

- Be responsive
- Present any corrective actions taken to the FDA investigator
- Respond in writing
  - Assess root cause and extent of the problem
  - Include corrective and preventive actions
  - Include projected timelines for implementation
  - Include supporting documentation

Consider re-evaluating corrective/preventive actions in 6 months

Post-Inspection

- Review Establishment Inspection Report (EIR)
- Review any 483 response(s)
- Classify inspection
- Issue correspondence and review memos

Considerations:

  - Impact on human subject protection
  - Impact on data integrity
  - Adequacy of response
  - Inspectional history

Compliance Classifications

- No Action Indicated (NAI)
  - No or minor objectionable conditions or practices
- Voluntary Action Indicated (VAI)
  - Objectionable conditions/practices
  - Isolated, low-risk, can be corrected easily
- Official Action Indicated (OAI)
  - Significant or egregious violations of regulations
  - Sanctions recommended

Opportunities for Collaboration

- Pre-submissions meetings (Q-sub)**
- Modular PMAs
- 510(k)/De Novo meetings
- IDE meetings
- Pre-PMA meetings**

Contact Information

Phone: (301) 796-5490

E-mail:BIMO-CDRH@fda.hhs.gov

PMA Manufacturing Information

Vesa Vuniqui
Consumer Safety Officer
Division of Manufacturing and Quality
Office of Compliance
Center for Devices and Radiological Health

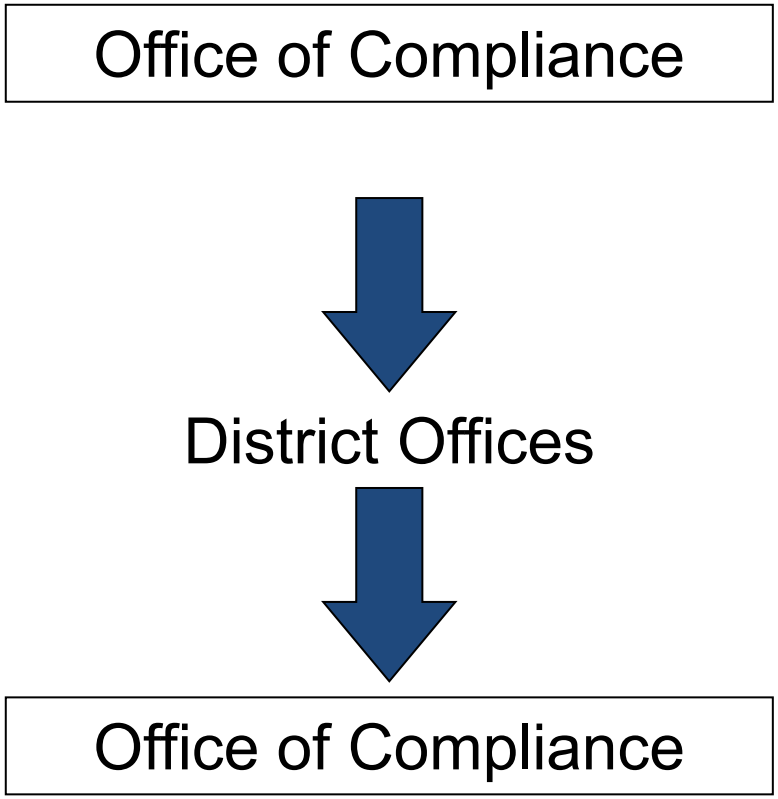
Manufacturing Related Submissions

- Original/modular PMAs
- Pre-approval inspections
- Site change supplements
- 30-day notices

ORIGINAL/MODULAR PMA

Major Steps for PMA

- Review of manufacturing information
- Inspection requests generated and sent to Office of Regulatory Affairs
- Inspections scheduled and completed through Office of Regulatory Affairs
- Establishment Inspection Report written
- Establishment Inspection reviewed in CDRH



Original PMAs

- Manufacturing information reviewed by CDRH Office of Compliance
- Should include information outlined in the guidance, "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff" dated February 3, 2003
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf
- Consistent with quality system regulation requirements (21 CFR 820) and is divided into sections:
  - Design Controls
  - Manufacturing Controls
- Ensures that the premarket submissions comply with the content requirements (21 CFR 814.20(b)(4))

Manufacturing Section Information

Please be sure to include:

- Cover letter
- Overview of what the manufacturing section contains and how it is organized
- Device description
- Overview of the manufacturing facility(ies)
- Copy of your quality manual
- List of standards used in the manufacturing process

Manufacturing Section Information, cont.

- Two principle component sections
  - Design control information
  - Information on other key procedures
    - Mostly manufacturing but also includes procedures such as complaint handling, corrective and preventive action
- FDA guidance asks mostly for procedures
- In addition to procedures, you can submit a narrative summary of the procedures
- Identify location of attached procedures
- Submit separate volumes for different manufacturing sites or vendors

Office of Compliance Review Process

- Office of Compliance will review the manufacturing section of the submission according to the guidance document.

- Office of Compliance will communicate their assessment to the applicant if there are deficiencies identified in the Quality System information included in the submission.
  - Deficiencies may be communicated in a formal deficiency letter or via e-mail through an interactive review process.

PMA Pre-Approval Inspections

- Conducted at sites manufacturing finished devices, critical components, or performing sterilization
- Will be scheduled on or after the date you indicate that the site will be ready for inspection
  - Sites that are not ready for inspection may result in delayed approval of the PMA (approvable pending good manufacturing practices)
- Based on any past inspection history
- Domestic or foreign as appropriate

SITE CHANGE SUPPLEMENTS

When to Submit a Site Change Supplement

- Site was not approved as part of the original PMA or a PMA supplement
- Site(s) was (were) approved as part of the original PMA or a PMA supplement, but for the performance of different manufacturing activities
- Note: Draft guidance previously issued for comment on October 21, 2015

Site Change Supplement Content

- Similar to Original PMA manufacturing information
- Does not require Design Control information (820.30) since the design would not change
- Should clearly indicate when validations will be complete and facility ready for inspection

Pre-approval Inspections

- Subject to pre-approval inspection
- Follows the same time goals as in an original PMA
- CDRH Office of Compliance will communicate their assessment to the applicant if there are deficiencies identified in the Quality System information included in the submission

30-DAY NOTICE

What Changes Qualify for a 30-Day Notice

- Manufacturing process change that could affect the safety or effectiveness of the device
  - Changes to the manufacturing procedure
  - Changes to the method of manufacture
- Guidance document: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

Changes Typically Appropriate for 30-Day Notice

- Manual process to an automated process
- Changes to a cleaning process which is performed in manufacturing device
- Change in machining lubricants
- Sterilization cycle or sterility dose auditing
- Addition of manufacturing space to current facility or the addition of manufacturing line at same facility

Changes Not Appropriate for 30-Day Notice

- New manufacturing site
- Changes to device design
  - Device specifications
  - Device material changes
- Minor changes that are “annual reportable” because they do not affect safety or effectiveness

30-Day Notice Review Clock

- Acceptance of 30-day notice
- Conversion to 135-day supplement
  - May be converted with or without deficiencies
  - Common for deficiencies to be conveyed
- Approval of 135-day supplement
- Not approvable 135-day supplement

30-Day Notice Information

- Description of change
- Summary of the data or information supporting the change
- Statement that the change was made under requirements of §520(f) of FDCA and 21 CFR Part 820
- Reason for change, including description of any adverse event or field failures being addressed

Closing Remarks

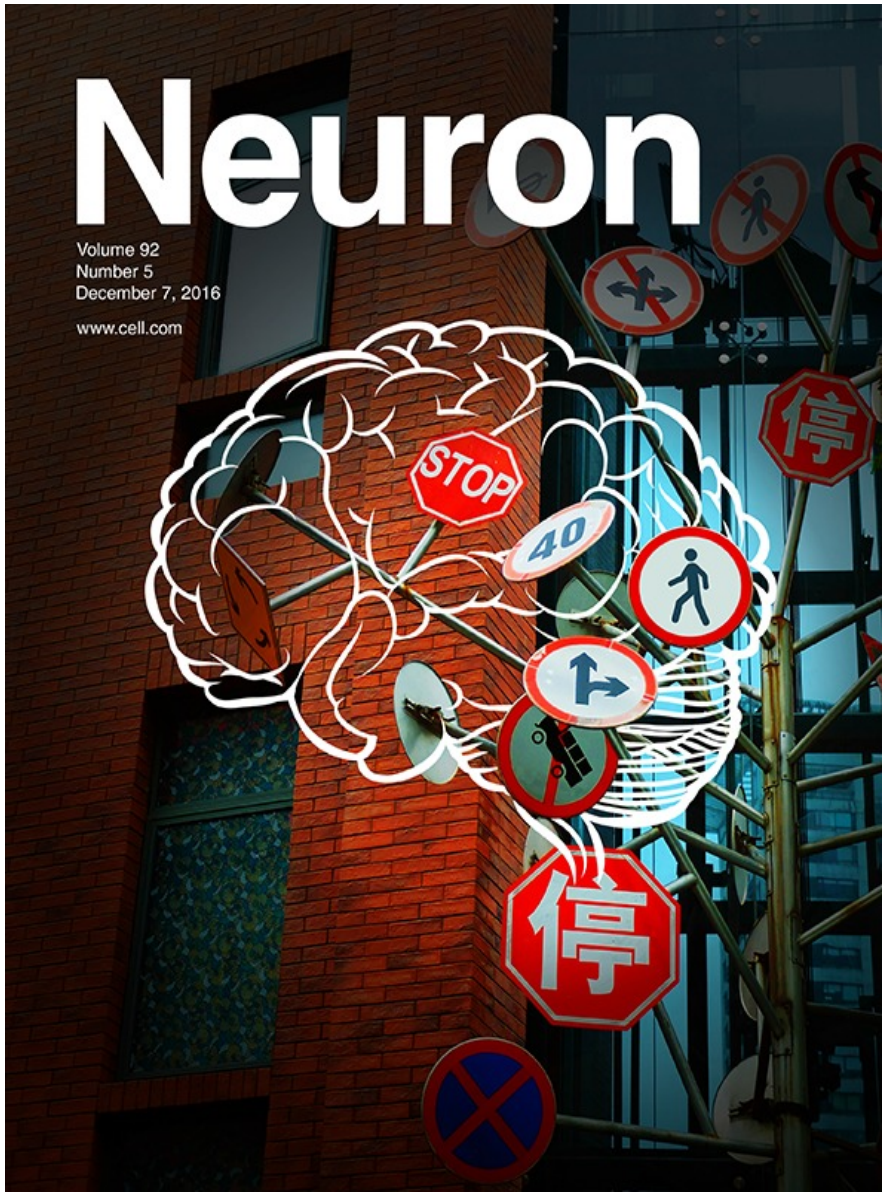
Pre-Submissions

WHAT: an opportunity to obtain FDA feedback prior to IDE or marketing submission

Guidance Document

"Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"

(Issued February 18, 2014)



NeuroView

FDA Regulation of Neurological and Physical Medicine Devices: Access to Safe and Effective Neurotechnologies for All Americans

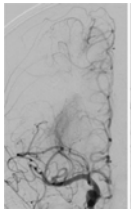
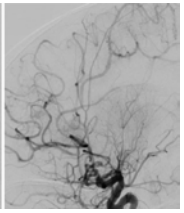
Neuron. 2016 Dec 7;92(5):943-948. doi: 10.1016/j.**neuron**.2016.10.036.

NEW FDA website for Neurological Devices:
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/NeurologicalDevices/default.htm

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: How to Study and Market Your Device

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.