

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.



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

Stacie Gutowski, PhD

Biomedical Engineer

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

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)

Samuel Raben, PhD

Mechanical Engineer

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

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/PostApprovalStudies/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 #
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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

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

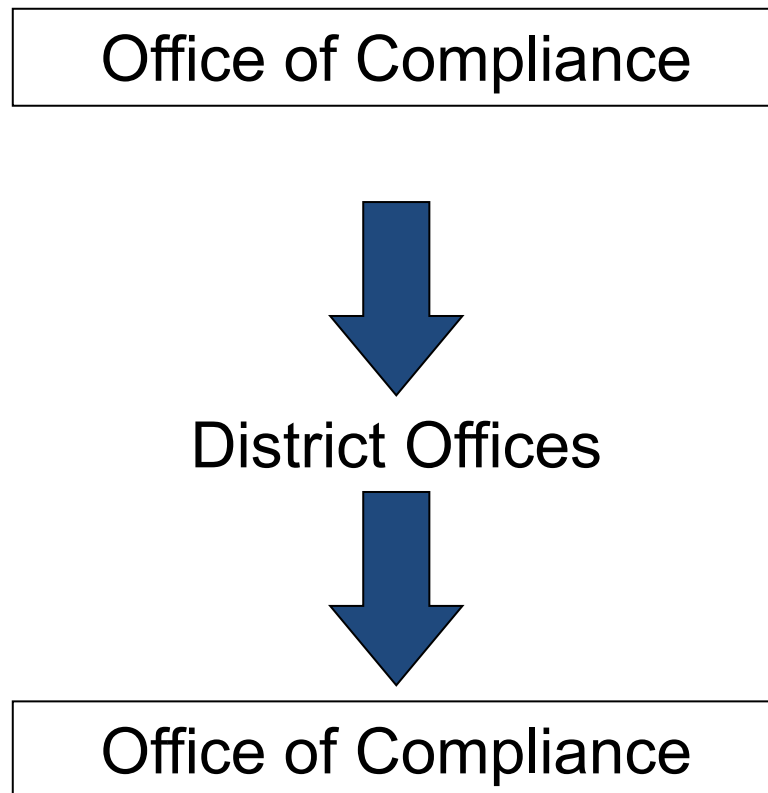
Manufacturing Related Submissions

- 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)

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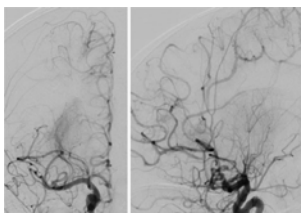


NeuroView FDA Regulation of Neurological and Physical Medicine Devices: Access to Safe and Effective Neurotechnologies for All Americans

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

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