Building Quality Clinical Data into Premarket Approval Applications (PMAs)

FDA Small Business
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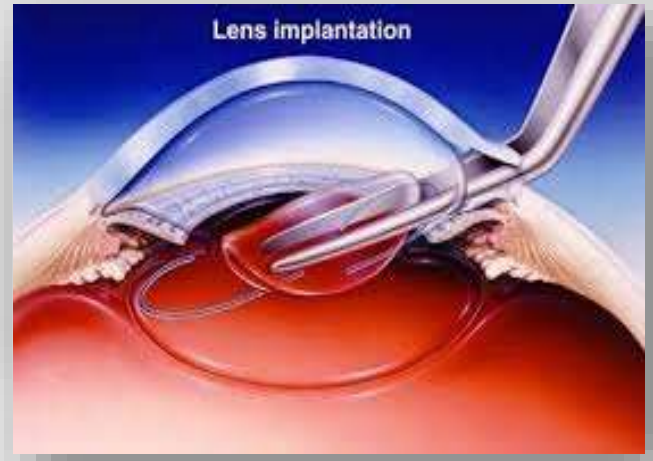
PMA Devices



Learning Objectives

- Define PMA
- Describe contents of PMA
- Discuss quality data
  - Data Lifecycle
  - Elements of quality data
- Identify some best practices for conduct of a quality study
  - Roles and Responsibilities of Sponsors and Investigators

Poll

Are you involved in the development or marketing of a PMA device?

1. Yes
2. No
3. Not now, but will be

Class III Medical Devices

- **Highest risk category**
- **Support or sustain** human life, substantial importance in **preventing impairment** of human health, potential for **unreasonable risk** of illness or injury
- **Insufficient evidence** to solely rely on **general and special controls** to assure safety and effectiveness
- Subject to **PMA regulatory requirements**
  - Most stringent marketing application

Contents of a PMA

Contents of PMA

- Name and address of applicant
- Table of content
- Description of device and functional components or ingredients
- Reference to performance standards
- Environmental assessment
- Manufacturing

21 CFR 814.20

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

Contents of PMA

- **Non-clinical studies**: test reports, summaries and conclusions
- **Clinical studies:** methods, results and conclusions
- Bibliography
- Sample of device – if practical
- Proposed labeling
- Financial certification or disclosure
- Information concerning uses in pediatric patients

21 CFR 814.20

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

PMA vs 510(k)

	Premarket Approval Application (PMA)	Premarket Notification (510(k))
Device Class	Class III	Class I or Class II
Foundation of Application	Stand-Alone	Substantial Equivalence (SE) to Predicate Device
Clinical Evidence	Almost 100% have Clinical Evidence	Approximately 15% have Clinical Evidence
MDUFA FDA Review Performance Goal (calendar days)	180 days – no panel 320 days– if panel	90 days
Final Decision	Approval	Clearance

FDA Review of PMA

FDA Review of PMA

- **Scientific, Regulatory and Quality System Review**
  - Evaluate reasonable assurance of **safety and effectiveness**;
    - For an indication for use, defined:
      - With respect for patient population,
      - With respect to the conditions of use prescribed

Safety 21 CFR 860.7 (d)(1)
Effectiveness 21 CFR 860.7 (e)(1)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=860.7

Indication for Use

"Bronchoscopic treatment of **adult patients** with **hyperinflation** associated with **severe emphysema** in **regions of the lung that have little to no collateral ventilation**"

- **Patient Population**
  - **adult patients with hyperinflation – severe emphysema**
- **Conditions of Use**
  - **regions of the lung that have little to no collateral ventilation**

FDA Review

- **Valid scientific evidence**
  - **Well/partially-controlled,** clinical investigations or other objective information
  - Not opinions, random reports or un-interpretable data

- **Considerations**
  - Device safety, performance and reliability
  - Conditions of device use
  - **Benefits vs. risks** for indicated **patient population**

21 CFR Part 860.7(C)(2)
www.accessdata.fda.gov/scripts/cdrh/c)fdocs/cfCFR/CFRSearch.cfm?FR=860.7

Guidance: 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

Partner with Patients

- **Patient Perspective in Regulatory Decisions**
  - Consideration of patient preference information
  - Patients' view of benefits and risks
  - Patient perspective studies and data

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications

Leverage Data

Balancing

- Premarket and Postmarket Data Collection

Utilize

- Real World Evidence

Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval

Use of Real World Evidence

- **Real World Evidence (RWE)**
  - Derived from collection and analysis of **real world data** (RWD)
    - Collected from clinical experience routine course and treatment
  - May **augment** understanding of **benefit/risk profile**
  - Need to consider overall relevance and reliability of data

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

Acceptance of Clinical Data Rule

Acceptance of Clinical Data Rule

Ensure:

- **Credibility** and **accuracy** of clinical data
- **Protection of human subjects**
- **Consistent** approach to acceptance of clinical data collected inside and outside United States

Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked

Implementation Date

- Clinical Data Rule applies to clinical investigations that began on or after **February 21, 2019**
  - Enrollment date of first subject
    - Signing Informed Consent

Human Subject Protection; Acceptance of Data From Clinical Investigations for Medical Devices

https://www.federalregister.gov/documents/2018/02/21/2018-03244/human-subject-protection-acceptance-of-data-from-clinical-investigations-for-medical-devices

Good Clinical Practice (GCP)

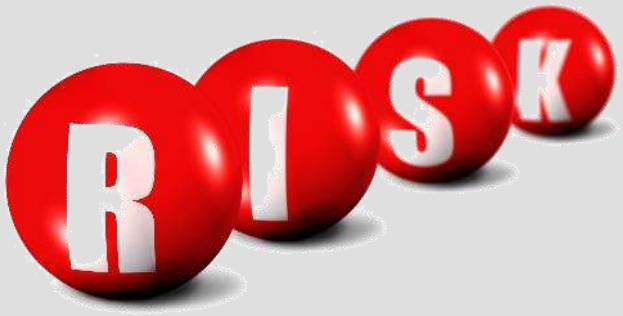
"… a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are ***credible*** and ***accurate*** and that ***the rights, safety, and well-being of subjects are protected***."

21 CFR 812.28(1)

https://www.ecfr.gov/cgi-bin/text-idx?SID=33b64f8bee5222ca30c6500fee3170a2&mc=true&node=pt21.8.812&rgn=div5#se21.8.812_128

Types of Device Clinical Investigations

- Significant Risk (SR)
- Non Significant Risk (NSR)
- Exempt



Risk Determination based on risk of device used in the investigation

21 CFR 812

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812

21 CFR 812.28 (new GCP)

Requirement	SR	NSR	Exempt
	✓		Upon Request

21 CFR 812.28 (new GCP)

Requirement	SR	NSR	Exempt
Name of investigators and names/addresses of research facilities and sites where records are kept	✓	✓	Upon Request
Investigator's qualifications	✓		
Description of research facilities	✓		
Detailed summary of the protocol and results of the investigation and if requested, case records or other institutional records	✓	✓	Upon Request
Information about device iteration used in clinical study compared to submission	✓	✓	Upon Request

21 CFR 812.28 (new GCP)

Requirement	SR	NSR	Exempt
Discussion regarding data constituting valid scientific evidence	✓		
Name and address of Institutional Review Board/Independent Ethics Committee (IRB/IEC) and statement that it meets definition	✓	✓	Upon Request
Summary of IRB/IEC decision	✓	✓	Upon Request
Description of how Informed Consent (IC) was obtained	✓	✓	Upon Request

21 CFR 812.28 (new GCP)

Requirement	SR	NSR	Exempt
Description of incentives provided to subjects	✓	Upon Request	Upon Request
Description of monitoring and protocol execution verification	✓	✓	Upon Request
Description of investigator GCP training	✓		
Statement of certification of investigator's compliance with GCP	✓		
Rationale for NSR or Exempt		Upon Request	Upon Request

Statement of Conformance
Investigations Conducted in US

- Provide a statement:
  - Each investigation was conducted in compliance with 21 CFR Parts 50, 56 and 812

or

  - If not conducted in compliance a brief statement of the reason for noncompliance

Statement of Conformance
Investigations Conducted in Outside US

- Provide a statement:
  - Each investigation was conducted in accordance with GCP

    or

  - If the investigation was not conducted in accordance with GCP:
    - A waiver request

      or

    - Explanation for not conducting the investigations in accordance with GCP and a description of steps taken to ensure that the data and results are **credible and accurate** and that the **rights, safety, and well-being of subjects** have been adequately **protected**

Acceptance Criteria for PMA

- Requirement to include statement of Compliance for Clinical Investigations

Section 12 Statement/ Certifications/Declaration of Conformity			YES	N/A	No
		f. Statements of Compliance for Clinical Investigations Select "N/A" if the application does not contain any clinical data from investigations (as defined in 21 CFR 812.3(h)) to demonstrate reasonable assurance of safety and effectiveness. For multicenter clinical investigations involving both United States (US) and outside the United States (OUS) sites, part (i) should be addressed for the US sites and part (ii) should be addressed for the OUS sites. 21 CFR 812.28 applies to all OUS clinical investigations that enroll the first subject on or after February 21, 2019.	☐	☐	

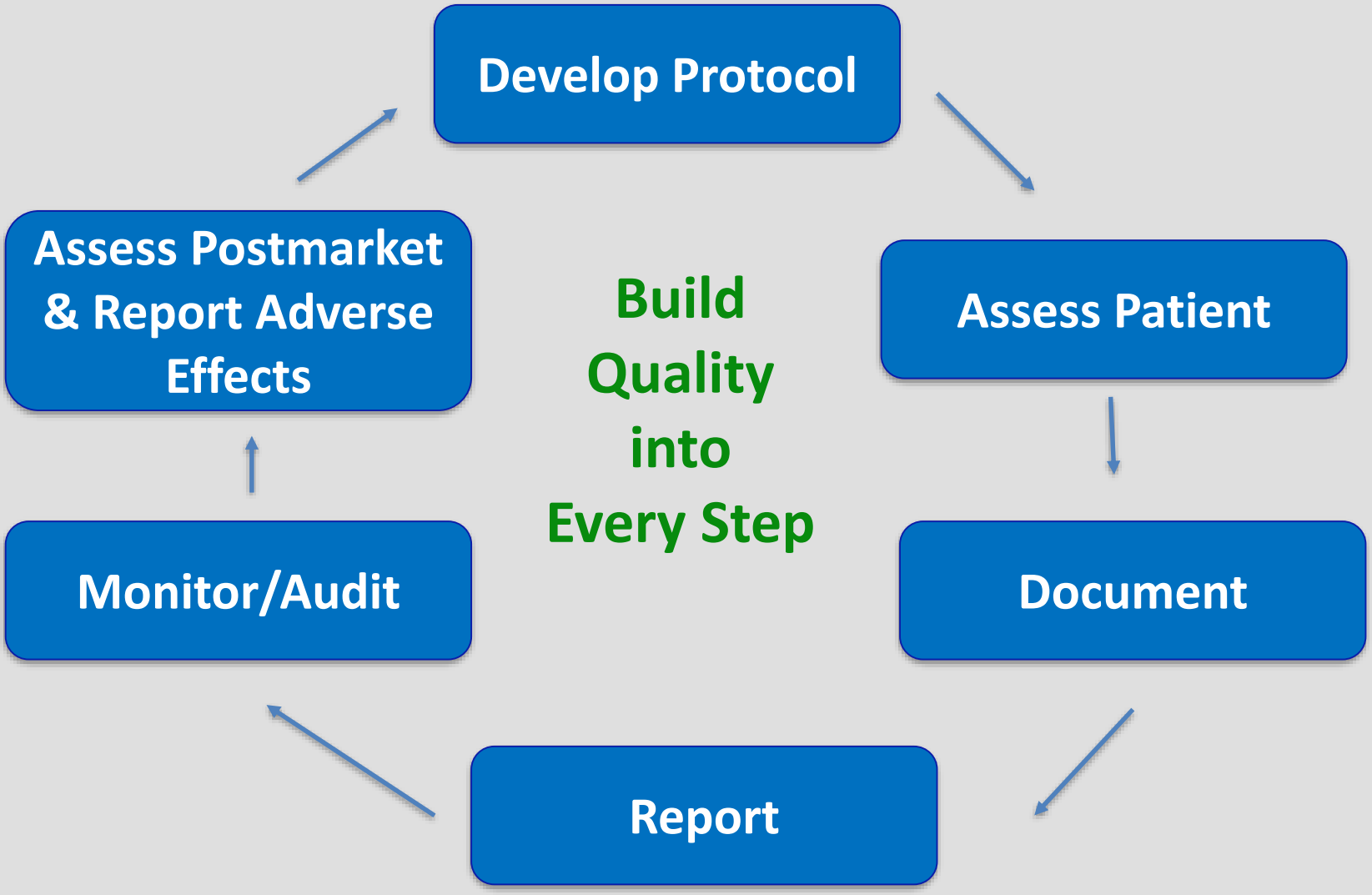
Acceptance and Filing Reviews for Premarket Approval Applications (PMAs): Guidance for Industry and Food and Drug Administrations Staff

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-and-filing-reviews-premarket-approval-applications-pmas

Strategies for Conduct of a Quality Study

- Data Lifecycle
- Elements of Quality Data
- Roles and Responsibilities of Sponsors & Investigators

Data Lifecycle



What are Elements of Quality Data?

- **A**ttributable
- **L**egible
- **C**ontemporaneous
- **O**riginal
- **A**ccurate

Building Quality into Clinical Data: Sponsor

Sponsor Strategies

- Select Qualified Investigators
  - Knowledge, training & expertise

- Select Adequate Study Sites
  - Adequate staff
  - Proper patient population
  - Adequate resources

21 CFR 812.43(a)

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.43)

Sponsor Strategies

- Collaborate obtain feedback on protocol requirements

- Communicate with study team, IRB, and Regulatory Agencies

Sponsor Strategies

- Train investigators and study staff
  - Before, when essential staff are replaced, and as needed

- Monitor study
  - In accordance with monitoring plan
  - Early and frequently enough

21 CFR 812 40 and 812.46

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.40

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.46

Building Quality into Clinical Data: Clinical Investigator

Clinical Investigator Strategies

- Follow signed investigator agreement, investigational plan and protocol
- Obtain IRB/IEC approval
- Obtain Informed Consent
- Control investigational devices

21 CFR 812.100

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812&showFR=1&subpartNode=21:8.0.1.1.9.5

Clinical Investigator Strategies

- Document case histories
- Document Adverse Device Effects
- Document and report unanticipated adverse device effects (UADE)
  - within 10 working days after first learning of the effect.

21 CFR 812.140(a) and 21 CFR 812.150(a)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812&showFR=1&subpartNode=21:8.0.1.1.9.7

Corrective and Preventive Action Plan

1. Assess **root cause**
2. Evaluate **extent of the problem**
3. Implement **corrective** actions
4. **Evaluate** actions
5. Institute **preventive** actions
6. **Monitor** actions

Summary

- PMA is the marketing application for the **highest risk** medical devices that FDA regulates
- Include **valid scientific evidence** to support reasonable assurance of safety and effectiveness of device for intended use
- Incorporate the **elements of quality** throughout the data lifecycle

References

- **Guidance on PMA Interactive Procedures for Day 100-Meetings and Subsequent Deficiencies**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-pma-interactive-procedures-day-100-meetings-and-subsequent-deficiencies-use-cdrh-and

- **Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions**

  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM606051.pdf?utm_campaign=2019-04-25%20FDA%20Finalizes%20Guidance%20for%20Non-Clinical%20Bench%20Performance%20Testing&utm_medium=email&utm_source=Eloqua

- **The Least Burdensome Provisions: Concept and Principles**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles

References

- **User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications

- **FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-approval-applications-pmas-effect-fda-review-clock-and-goals

- **Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process**
  https://www.fda.gov/media/81431/download

Questions

Your Call To Action

- Incorporate the elements of **quality** throughout the **entire data lifecycle**
- Submit **a well organized** PMA with **valid scientific evidence** to support the intended use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