Premarket Approval Application (PMA) Program: Postapproval Requirements

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Approved PMA

Postapproval Requirements

Learning Objectives

- Define PMA
- Understand regulatory controls
- Understand regulatory responsibilities for an approved PMA:
  - Post-approval studies (PAS) and reports
  - Amendments
  - Supplements
  - 30-Day Notices
  - Postapproval periodic reporting (annual reports)

PMA

(21 CFR 814)

- **Marketing application** for a Class III medical device (21 CFR 814.3(e))
- **Class III, highest risk devices**
- **Support or sustain** human life, substantial importance in **preventing impairment** of human health, potential for **unreasonable risk** of illness or injury
- **Unable to solely rely on *general* and *special controls*** to reasonably assure safety and effectiveness

What are “Regulatory Controls”

- Apply to a particular device type
- Describe appropriate level of regulatory burden or oversight to ensure safety and effectiveness
- Generally broad, but may be specific

Regulatory Controls

- Increased risk of device → increased regulatory controls

Class	Risk	Controls
I	low	general
II	moderate	general and special
III	high	general and PMA

- Regulatory Controls webpage

Postapproval Controls for Approved PMA Devices

PMA Postapproval Controls

- Postapproval studies (PAS) and reports
- Amendments
- Supplements
- 30-Day Notices
- Postapproval periodic reporting (annual reports)

Post-Approval Studies (PAS)

- May be required *at time of approval*, as a condition of approval
- FDA and Applicant agree on general purpose and outline
- Distinct from postmarket surveillance/522 studies, which may be required any time *after* PMA approval
- Resources:
    - Regulation: 21 CFR 814.82
    - Webpage: Post-Approval Studies and the PAS FAQs
    - Guidance: "Procedures for Handling Post-Approval Studies Imposed by PMA Order"
    - Database: Post-Approval Studies (PAS)

Post-Approval Study Reports

- Study information:
  - Purpose, goals, objectives and endpoints, and patient population being studied
- Summary of study progress:
  - IRB approvals
  - Number of clinical sites
  - Enrollment status
- Summary of safety and/or effectiveness data and an interpretation of study results

Amendments

- Time-sensitive updates that do *not* affect safety and effectiveness
- Examples:
  - Change in ownership
  - Change in contact information (e.g., company name, official correspondent, address)
  - Voluntary market withdrawal (cease marketing)
- Resources:
  - Regulation: 21 CFR 814.37
  - Webpage: PMA Supplements and Amendments

Supplements

- Changes affecting safety or effectiveness
- Required *prior* to implementing the change(s)
- Examples:
  - New indication for use
  - Changes in design, packaging, or labeling
  - Changes in manufacturing site
- Resources:
  - Regulation: 21 CFR 814.39
  - Webpage: PMA Supplements and Amendments

Supplements

- Types of PMA Supplements
  - Panel-Track supplement
  - 180-Day supplement
  - Real-Time supplement
  - Special PMA supplement - Changes Being Effected
  - Manufacturing site change supplement
- Resources:
  - Guidance: "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"

Supplements – *Panel Track*

- Significant change requiring **new substantial clinical data**
- Examples:
  - New indication for use
  - Design
  - Performance
  - Change or removal of contraindication
- Resources:
  - Act: 21 U.S.C. 379i(4)(B)

Supplements – *Panel Track*

- Case Example:
  - Prosthetic heart valve
  - **New indication for use**: aortic valve to be used in mitral position
  - **No change in design**
  - New environment can impact performance → **new clinical data needed**
  - Appropriate for Panel Track supplement

Supplements – *180-Day*

- Significant change requiring **new preclinical test data**
- Original clinical data are still applicable
- May include limited, confirmatory clinical data
- Examples:
  - Design, Software, Labeling, Trade name change
- Resources:
  - Act: 21 U.S.C. 379i(4)(C)

Supplements – *180-Day*

- Case Example:
  - Ventricular assist device (VAD)
  - **New design** for the lead
  - **No change to indication for use** or patient population
  - Mechanical testing, only
  - **No new clinical data** needed
  - 180-Day supplement appropriate

Supplements – *Real-Time*

- **Minor changes** supported by pre-clinical or animal testing, with **no new clinical data**
- Involve review within a **single scientific discipline**, rather than multidisciplinary review
- Meeting, or similar forum, to jointly review and determine status of supplement
- Prior to submitting, must obtain concurrence from FDA review team
- Refer to “Real-Time” guidance (see next slide) for procedure to submit Real-Time supplement; email may be used instead of fax

Supplements – *Real-Time*

- Examples:
  - Design
  - Software
  - Labeling
  - Sterilization and packaging methods
- Resources:
  - Act: 21 U.S.C. 379i(4)(D)
  - Guidance: "Real-Time Premarket Approval Application (PMA) Supplements"

Supplements – *Real-Time*

- Case Example:
  - Alternate sterilization method
  - **Previously reviewed and approved** for this device type
  - Validation testing, only
  - **Single discipline** of sterilization
  - Real-Time supplement appropriate

Supplements – *Special Changes Being Effected*

- Must **enhance safety**
- May include **labeling** and/or **manufacturing** changes
- **No design changes**
- Narrow exception to the general rule of prior FDA *approval* of changes to a PMA

Supplements – *Special Changes Being Effected*

- Examples:
  - Improved **labeling** (e.g., add/strengthen a contraindication, warning, precaution)
  - Additional **manufacturing** quality assurance step; may not impact effectiveness
- Resources:
  - 21 CFR 814.39(d)(1) and (d)(2)

Supplements – *Special Changes Being Effected*

- Case Example:
  - **Improved labeling** instructions
  - **No impact on effectiveness**
  - Special – Changes Being Effective supplement appropriate

Supplements – *Manufacturing Site Change*

- Use of a different site or moving the manufacturing site → 180-day "site change supplement"
- Supplement must demonstrate compliance with QS regulation (21 CFR 820)
- Preapproval inspection may be necessary
- Resources:
  - Guidance: "Manufacturing Site Change Supplements: Content and Submission"

Supplements

Supplement	Clinical Data	Preclinical Data	Single Review Discipline/Area	FDA Review
Panel-Track	✓	x	✓	320
180-Day	x	✓	x	180
Real-Time	x	✓	✓	90
Special	x	x	x	Change may be implemented prior to FDA approval order
Mfg Site Change	x	x	✓	180

✓applicable
x not applicable

30-Day Notice

- Written notification of change in manufacturing procedure or method, affecting safety and effectiveness
- May distribute 30 days after notification, unless:
  - FDA notifies applicant of conversion to 135-Day supplement
  - FDA describes further information/action required

30-Day Notice

- Examples:
  - Manual to automated process
  - Alternate supplier
  - Modified sterilization process parameters
- Resources:
  - Guidance: "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes"

Postapproval Periodic Reports

- Also known as PMA “annual report”
- Due **annually** from date of approval

  (e.g., if PMA is approved Feb. 1, 2019, then report is due by Feb. 1, 2020, 2021, etc.)
- Requirement will cease only upon PMA withdrawal
- MDUFA* fee; **invoice is mailed** to applicant

  (no Form FDA 3601 is needed)

* MDUFA = Medical Device User Fee Amendments

Postapproval Periodic Reports

- Includes:
  - Changes submitted as supplements, plus other changes, not previously submitted
  - Summary and bibliography of published and unpublished reports
  - Number devices shipped or sold; number implanted (as applicable)
- Resources:
  - Regulation: 21 CFR 814.82(a)(7) and 21 CFR 814.84
  - Webpage: Postapproval (Annual) Reports section of PMA Postapproval Requirements
  - Guidance: "Annual Reports for Approved Premarket Approval Applications (PMA)"

Summary

- Class III medical device are subject to PMA controls after approval
- PMA controls feature these types of postapproval submissions:
  - Post-approval studies (PAS) and reports
  - Amendments
  - Supplements
  - 30-Day Notices
  - Postapproval periodic reporting (annual reports)
- Each submission type addresses different aspects of postapproval activity related to the device

Resources

Slide Number	Cited Resource	URL
4	21 CFR 814	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=814
4	21 CFR 814.3(e)	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.3
6	Regulatory Controls (webpage)	https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls
9	21 CFR 814.82	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.82
9	Post-Approval Studies (webpage)	https://www.fda.gov/medical-devices/postmarket-requirements-devices/post-approval-studies
9	PAS FAQs (webpage)	https://www.fda.gov/medical-devices/post-approval-studies/post-approval-studies-pas-frequently-asked-questions-faq
9	"*Procedures for Handling Post-Approval Studies Imposed by PMA Order*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order
9	Post-Approval Studies (database)	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm
11	21 CFR 814.37	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.37
11, 12	PMA Supplements and Amendments (webpage)	https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments

Resources (continued)

Slide Number	Cited Resource	URL
12	21 CFR 814.39	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.39
13	"*Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process
14	21 U.S.C. 379i(4)(B)	https://uscode.house.gov/view.xhtml?req=(title:21%20section:379i%20edition:prelim)%20OR%20(granuleid:USC-prelim-title21-section379i)&f=treesort&edition=prelim&num=0&jumpTo=true
16	21 U.S.C. 379i(4)(C)	https://uscode.house.gov/view.xhtml?req=(title:21%20section:379i%20edition:prelim)%20OR%20(granuleid:USC-prelim-title21-section379i)&f=treesort&edition=prelim&num=0&jumpTo=true
19	21 U.S.C. 379i(4)(D)	https://uscode.house.gov/view.xhtml?req=(title:21%20section:379i%20edition:prelim)%20OR%20(granuleid:USC-prelim-title21-section379i)&f=treesort&edition=prelim&num=0&jumpTo=true
19	"*Real-Time Premarket Approval Application (PMA) Supplements*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-time-premarket-approval-application-pma-supplements
22	21 CFR 814.39(d)(1) and (d)(2)	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.39
24	21 CFR 820	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=820

Resources (continued)

Slide Number	Cited Resource	URL
24	"*Manufacturing Site Change Supplements: Content and Submission*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-site-change-supplements-content-and-submission?utm_campaign=Final%20Guidance%20on%20Manufacturing%20Site%20Change%20Supplements
27	"*30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/30-day-notices-135-day-premarket-approval-pma-supplements-and-75-day-humanitarian-device-exemption
29	21 CFR 814.82(a)(7)	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.82
29	21 CFR 814.84	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.84
29	Postapproval (Annual) Reports (section of PMA Postapproval Requirements webpage)	https://www.fda.gov/medical-devices/premarket-approval-pma/pma-postapproval-requirements#postapproval
29	PMA Postapproval Requirements (webpage)	https://www.fda.gov/medical-devices/premarket-approval-pma/pma-postapproval-requirements
29	"*Annual Reports for Approved Premarket Approval Applications (PMA)*" (guidance)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/annual-reports-approved-premarket-approval-applications-pma

Your Call to Action

- Review all relevant cited references:
  - Regulations (**Code of Federal Regulations**)
  - FDA guidance documents
  - **Device Advice** webpages
  - **CDRH Learn**
- Contact the Division of Industry and Consumer Education

DICE Contact

- **Phone:** **(800) 638-2041**
  - Monday – Friday:
  - 9:00 am – 12:30 pm; 1:00 pm - 4:30 pm

- **Email:** **dice@fda.hhs.gov**
  - respond within 2 business days

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