Premarket Approval Application (PMA) Program: Postapproval Requirements

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Office of Communication and Education
Center for Devices and Radiological Health
U.S. Food and Drug Administration
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
Increased risk of device → increased regulatory controls

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>low</td>
<td>general</td>
</tr>
<tr>
<td>II</td>
<td>moderate</td>
<td>general and special</td>
</tr>
<tr>
<td>III</td>
<td>high</td>
<td>general and PMA</td>
</tr>
</tbody>
</table>

• 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:
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 – \textit{Real-Time}

• Examples:
  – Design
  – Software
  – Labeling
  – Sterilization and packaging methods

• Resources:
  • Act: \texttt{21 U.S.C. 379i(4)(D)}
  • Guidance: \texttt{“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

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Clinical Data</th>
<th>Preclinical Data</th>
<th>Single Review Discipline/Area</th>
<th>FDA Review</th>
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<tbody>
<tr>
<td>Panel-Track</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>320</td>
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<tr>
<td>180-Day</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>180</td>
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<tr>
<td>Real-Time</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>90</td>
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<tr>
<td>Special</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Mfg Site Change</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>180</td>
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</table>

✓ applicable

x not applicable

Change may be implemented prior to FDA approval order
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
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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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