The FDA PMA Process for *In Vitro* Diagnostic Devices

FDA/Center for Devices and Radiological Health/Office of *In Vitro* Diagnostic Device Evaluation and Safety

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What is the PMA Review Process?

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Overview of PMA Submission Review Process

Premarket-Traditional PMA

A. Scientific Review – assay performance: analytical and clinical studies, product stability, device hardware / software, etc.

B. Manufacturing Review – Quality System Regulation 21 CFR Part 820 GMP compliance for manufacturing the device

PMA Changes – Pre and Post Approval

- Changes to PMA device since submission date, but before approval date, should be submitted as an amendment to the PMA
- Changes after approval require supplements
- Amendments will be reviewed and become part of the approved PMA device (MFG amendments have a 30 day review clock)

Postmarket

PMA Maintenance - 21 CFR Parts 814 and 820

Refer to Guidance #2:

- Periodic Reports (Annual Reports, post-approval study reports)
- Special PMA Supplements – Changes Being Effected (CBE)
- 30-Day Notices => 135-Day Supplements
- 180-Day Supplements
- Panel-Track Supplements
- Real-Time Supplements
- Manufacturing Site Change Supplements

Premarket – General Review

- OIVD receives PMA from DMC and assigns a Lead Reviewer and a GMP Reviewer – 180 day clock starts with date received
- Lead Reviewer responsible for PMA Team lead, scientific review and final decision for PMA
- GMP Reviewer is a member of the PMA Team and responsible for Design Controls and Manufacturing Section review (Traditional or Modular)

Premarket – Manufacturing Review

PMA Review Time Clock = 180 calendar days

- Manufacturing section review – 30 days
- Manufacturing amendment submission review – 30 days
- Pre-approval Inspections: inspection order to DO from FOB
  To schedule/complete – 6 weeks domestic, 8 weeks foreign
  To write report (EIR) - 4 weeks domestic, 4 weeks foreign
  To review EIR – 30 days

Total Time = 135-180 days maximum (DGMP)

PMA Pre-approval Inspections

- Inspect Design Control site and Manufacturing site(s)
- PAI can be waived by OIVD if: (rare for Original PMAs)
  - Firm has had an NAI or VAI inspection within 2 years at each site listed in the PMA application
  - Inspections for similar processes as device under review
  - Validations completed (protocols and reports submitted)
- PAI inspections focus on device processes and firm's Quality System

Premarket – Manufacturing Review

- Review against Guidance #1 and 21 CFR 820

- Write appropriate letter to sponsor:

  Approvable – no letter issued, manufacturing and design control site inspections requested or waived, sponsor notified, FDA clock continues

  Deficiencies – DGMP letter for QS Regulation deficiencies, FDA clock stops => sponsor's clock begins (360 days max)

  Withdrawal – Acknowledgement letter to sponsor's withdrawal request pre or post-approval, or by default, FDA clock ends

Postmarket - PMA Supplements

Review Time Clocks

- Annual Reports – 90 days
- Special PMA Supplements (CBE) – 30 days
- 30-Day Notices – 30 days
- 135-Day Supplements – 105 days or 135 days
- 180-Day PMA Supplements – 180 days
- Panel-Track Supplements – 180 days
- Real-Time PMA Supplements – varies, 90 days
- Manufacturing Site Change Supplements – 180 days

Postmarket - PMA Supplements

Annual Reports – 90 day review

- Submit for annual reportable changes each anniversary date per Guidance #3
- Do not submit for simple changes to device or manufacturing process documentation (QS function)
- **Report Acknowledgement (RACK) letter** issued if reported changes meet annual reportable criteria
- **Deficiency letter** issued for reported changes that require another supplement type

Postmarket - PMA Supplements

Special PMA Supplements (CBE) – 30 day review

- Submit for changes that affect safety of device, or affect the safety in the use of the device
- Generally used for labeling changes
- Changes to quality control or a manufacturing process could apply
- **Approval letter** issued if reported changes fit the scope of CBEs
- **Deficiency letter** issued for reported changes that require another supplement type

Postmarket - PMA Supplements

30-Day Notices – 30 day review

- Submit for changes that affect safety and effectiveness of device per Guidance #4
- Generally used for changes to QC method, manufacturing method or process, suppliers, or production capacity
- **Acceptance letter** issued if reported changes fit criteria
- **Rejection letter** issued if reported changes require another supplement type
- **Conversion letter** issued for reported changes that do not contain adequate information/data, or require detailed review

Postmarket - PMA Supplements

30-Day Notices – 30 day review

Conversion to 135-Day Supplement: 3 types

Minor Deficiencies - Used when additional information/data is needed to complete the 30-day notice submission. This conversion does not stop the review clock (**105 days remain**)

Significant Deficiencies - This conversion sets the review clock on hold, and the clock resumes on the amendment filing date (**105 days remain**)

Supplement Does Not Meet Content - This conversion stops the review clock. The review clock restarts on the amendment filing date (**135 days remain**)

Postmarket - PMA Supplements

135-Day Supplements – 105/135 day review

- For changes that affect safety and effectiveness of device that are converted from a 30-Day Notice
- Generally used for reported changes that do not contain adequate information (deficiencies), or require a more detailed review of the information/data submitted
- **Approval Order** issued if amendment information resolves deficiencies
- **Not Approvable letter** issued if amendment information does not resolve the deficiencies within the 135 day time period

Postmarket - PMA Supplements

180-Day Supplements - 180 day review

- Submit for significant changes to the device:

  Design, Performance, Indication for Use, Principle of Operation, Control Mechanism, Product Specifications, Testing Specifications or Acceptance Criteria, Labeling, Device Software

- Clinical data needed to demonstrate safety and effectiveness of the modified device, original clinical data supports the modified device

- **Approval letter** issued if information in supplement supports the traditional PMA device approval for the modified device

Postmarket - PMA Supplements

Panel-Track Supplements - 180 day review

- Submit for significant changes to the design or performance of the device, a new indication for use, or removal of a contraindication of the device
- Original clinical data no longer applicable for support of the modified device
- Substantial clinical testing is necessary to provide assurance of safety and effectiveness of the modified device
- FDA Panel meeting and/or homework assignments may be necessary
- **Approval letter** issued if information in supplement supports the traditional PMA device approval for the modified device

Postmarket - PMA Supplements

Real-Time PMA Supplements- 180 day (90 day goal)

- Submit for minor changes to the device per Guidance #5
- Contact CDRH/OIVD to determine if Real-Time is appropriate
- Review process is interactive – could include face-to-face
- Identify all modifications planned for the device and labeling
- Include testing and results
- Risk assessment including risk mitigation for modified device

Postmarket - PMA Supplements

Real-Time PMA Supplements- 180 day (90 day goal)

- **Approval letter** issued based on changes that are supported by the results of testing
- **Approvable letter** issued based on additional information/data or studies required to support the changes
- **Not Approvable letter** issued based on lack of support for the changes based on the results of testing.

Postmarket - PMA Supplements

MFG Site Change Supplements - 180 day review

- Same review cycle and clock as the Traditional or Modular PMA Manufacturing Section review
- Submit for changes that use a different facility or establishment to manufacture, process, or package a device
- May qualify for 30-Day Notice if within same FEI

Postmarket - PMA Supplements

MFG Site Change Supplements - 180 day review

Items to submit:

- Description of nature and purpose of site change
- Manufacturing functions to be performed at the new or re-designed facility
- Diagram of new manufacturing site(s)
- Description of proposed manufacturing process flow for each MFG process/component

Postmarket - PMA Supplements

MFG Site Change Supplements - 180 day review

Items to submit:

- Procedures for control of suppliers (820.50)
- Procedures for environmental and contamination control (820.70)
- Description of equipment and processes involved in site change (820.70)

Postmarket - PMA Supplements

MFG Site Change Supplements – 180 day review

Items to submit:

- Procedures for Inspection, Measuring, and Test Equipment (820.72)
- List of processes to be fully verified (820.75)
- Validation Master Plan (facilities, processes, QS software) (820.75)
- Process validation protocols and reports (reports optional if PAI) (820.75)

Postmarket - PMA Supplements

MFG Site Change Supplements – 180 day review

Items to submit:

- Procedures for Receiving Acceptance Activities (820.80 (b))
- Procedures for Final Acceptance Activities (820.80 (d))

Postmarket - PMA Supplements

MFG Site Change Supplements – 180 day review

Write appropriate letter to sponsor:

- **Approvable** – no letter issued, manufacturing site inspections requested, sponsor notified, FDA clock continues
- **Deficiencies** – DGMP letter for QS Regulation deficiencies, FDA clock stops (HOLD) => sponsor's clock
- **Withdrawal** – Acknowledgement letter to sponsor's withdrawal request, FDA clock ends
- **Approval** – letter issued by OIVD if deficiencies are resolved, and inspections show site(s) are in compliance with 21 CFR 820

PMA Submission Review Process

SUMMARY – How to successfully obtain a rapid PMA Approval

- Submit **adequate** and **relevant** scientific and manufacturing information with the PMA device application and any amendments
- Perform risk assessment on the impact of any changes to the device (premarket and postmarket)
- Properly and adequately validate changes to the device
- Submit the appropriate amendment or supplement type for changes – check with CDRH/OIVD is unsure
- Provide timely responses to reviewer requests

PMA Specific Guidances

Guidance #1 - Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff – issued Feb 3, 2003

Guidance #2 – Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process – issued Dec 11, 2008

Guidance #3 - Annual Reports for Approved Premarket Approval Applications (PMA); Draft Guidance for Industry and FDA Staff – issued Oct 26, 2006

Guidance #4 – 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes - issued Apr 13, 2011

Guidance #5 – Real-Time Premarket Approval Application (PMA) Supplements – issued Apr 28, 2006

QUESTIONS?

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