

## Premarket Approval Application (PMA) Program: Postapproval Requirements

### Slide 1

Hello, I am Diane Nell, and I work in the Division of Industry and Consumer Education, within the Center for Devices and Radiological Health. Welcome to CDRH Learn, the Center's resource for multimedia industry education. The title of this presentation is "Premarket Approval Application (PMA) Program: Post-approval Requirements."

### Slide 2

Once your PMA is approved, your regulatory requirements are NOT completed: there are post-approval requirements. This module will highlight the regulatory requirements that apply after you receive your PMA Approval Order.

### Slide 3

By the end of this module, you will be able to describe how the FDA defines a PMA. You will be able to describe the various types of regulatory controls that apply to PMA devices. And, you will be able to describe the regulatory responsibilities for the applicant of an approved PMA. Such responsibilities include complying with any mandated post-approval studies and reports, the submission of appropriate amendments and supplements, the provision of 30-Day Notices of manufacturing changes, and post-approval periodic reporting.

### Slide 4

A PMA is a marketing application for a Class III medical device and is regulated under 21 Code of Federal Regulations, or CFR, 814. The Class III devices are the highest risk devices. They are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. These are devices for which the general and special controls, alone, are insufficient to provide reasonable assurances of the safety and effectiveness of the device.

### Slide 5

Regulatory controls are requirements that apply to a particular device type. Regulatory controls provide consistent requirements to predictably foster safe and effective medical devices, and they describe the appropriate level of regulatory burden or FDA oversight of a given device area. Regulatory controls are usually broad, but some may be specific to a particular product area.

### Slide 6

Just to review, each device is assigned to one of 3 classes, based on the level of regulatory control necessary to establish and maintain safety and effectiveness. As devices increase in risk from Class I to Class III, the regulatory controls increase, with Class III being the most stringent. There are three categories of regulatory controls: General Controls, Special Controls, and PMA. You may refer to the "Regulatory Controls" webpage for details on these various controls. Note that PMA devices are subject to both the General Controls as well as the PMA controls, with this presentation focusing on the PMA controls that exist after a PMA has been approved.

### Slide 7

Now, let's turn our attention to the post-approval regulatory controls that the FDA utilizes to ensure the continued safety and effectiveness of devices that have received approval of their Premarket Approval Application.

#### Slide 8

So, as introduced, the post-approval controls that exist for PMA devices include post-approval studies and reports, amendments and supplements, 30-Day Notices of manufacturing changes, and post-approval periodic reporting. I will now discuss each one, in turn.

#### Slide 9

The FDA has the authority to require applicants, as a condition of approval, to perform a post-approval study or studies at the time of approval of a PMA to ensure the continued safety and effectiveness of the approved device. Such a study may be required, for instance, to provide additional long-term performance data. The specific requirements for the conduct and the reporting of the post-approval study are stipulated in the Approval Order. The general purpose and outline of the study will be agreed upon by the FDA and the applicant prior to approval and will be stipulated as a condition of approval. Post-approval studies are distinct from post-market surveillance studies, also known as 522 studies, which may be required any time after PMA approval.

On the bottom of this slide, and on many other slides throughout this presentation, you will find a listing of applicable resources that provide some additional information. Such resources may include FDA webpages, guidance documents, and/or references to specific sections of the Federal Food, Drug and Cosmetic Act and the medical device regulations. In addition to appearing on the individual slides themselves, these resources have been compiled and tabulated for your reference at the end of this presentation.

#### Slide 10

If a post-approval study has been stipulated as a condition of approval, the applicant must submit Post-Approval Study Reports at the intervals specified in the Approval Order. Those reports must provide an overview of the study, a summary of the study progress, and a summary of the safety and/or effectiveness data, as well as an interpretation of the study results, obtained at the time of the report.

#### Slide 11

After approval of a PMA, time-sensitive updates of information that do not affect the safety and effectiveness of the device are required to be reported to the FDA in the form of a post-approval amendment to the PMA. These are changes for which it is not appropriate to delay notifying the FDA until the next annual report. Changes that require a post-approval amendment include a change in ownership, a change in applicant contact information, and notice that the applicant will no longer be marketing the device.

#### Slide 12

Submission of a PMA supplement is required for a change that affects the safety and effectiveness of a PMA approved device; such supplements must be submitted prior to implementing the change. Such changes may include a new indication for use, changes in the design, packaging, or labeling, changes in the manufacturing site, or other changes.

#### Slide 13

The specific types of PMA supplements are defined under the Federal Food, Drug and Cosmetic Act. The type of PMA supplement that should be submitted depends upon the type of change to be made. The supplement types listed here are discussed in the guidance document cited below. I will now summarize each one, in turn, in the order they are discussed in the guidance.

#### Slide 14

A Panel-Track supplement is required for significant changes to the device, for which new, substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness. Such changes may include, for instance, a new indication for use, a significant change in the design or performance of the device, or a change or removal of a contraindication.

#### Slide 15

For example, the FDA approved a PMA for a prosthetic heart valve for use in the aortic position. The PMA applicant modified the indication for use to include use in the mitral position. No changes were made to the device itself. In the mitral position, the valve is subjected to different physiological conditions, such as valve closing pressures and flow rates. These conditions can affect the performance of the valve by affecting the hemodynamics, which can, in turn, affect the complication rates for thrombosis, thromboembolism, and hemolysis. Therefore, new clinical data were needed to provide reasonable assurances that the heart valve remained safe and effective when implanted in the new location. Therefore, the FDA determined that the submission of a panel-track supplement was appropriate for this change.

#### Slide 16

A 180-Day supplement is required for significant changes to the device for which new, substantial preclinical test data are necessary to provide a reasonable assurance of safety and effectiveness. In general, for a change to be submitted as a 180-day supplement, the clinical data provided to support approval of the original device should still be applicable in supporting approval of the modified device. However, additional limited, confirmatory clinical data may be necessary to provide a bridge between the clinical data set for the original device and the expected clinical performance of the modified device. Confirmatory clinical data typically involve a limited number of patients, shorter study duration, and/or a subset of endpoints as compared to the clinical data for the original PMA. Such changes may include, for instance, a significant change in design, software, labeling, and even in the trade name of the device.

#### Slide 17

For example, the FDA approved a ventricular assist device intended as temporary mechanical circulatory support for patients awaiting a cardiac transplant. The PMA applicant changed the design of the percutaneous ventricular lead in order to improve the interaction between the lead and the patient by making the lead more flexible and smaller in diameter. This design change was intended to reduce the physical damage to the lead at the site where it leaves the patient. No change was made to the indication for use or the patient population. To demonstrate that the modified device remained safe and effective, only mechanical tests, such as pull, bend, and twist testing were needed. Since the FDA determined that this change could be evaluated with mechanical tests and that no new clinical data were needed, the submission of a 180-day supplement was appropriate for this change.

#### Slide 18

A Real-Time supplement is appropriate for minor changes to the device, for which neither new, substantial preclinical test data nor clinical data are necessary to provide a reasonable assurance of safety and effectiveness. As such, Real-Time supplements are not appropriate for changes to the indications for use. Real-Time supplements generally consist of changes involving the review within a single scientific discipline, rather than a multidisciplinary review. Furthermore, a meeting or similar forum between the FDA and the applicant may be appropriate to jointly review and determine the status of the supplement. Prior to submitting a Real-Time supplement an applicant must obtain

concurrence from the appropriate review team that the change is appropriate for a Real-Time supplement.

You may refer to the Real-Time guidance document, identified on the next slide, for a description of the procedure to submit a Real-Time supplement. Note that email communication may be used in lieu of the fax communication referenced in the guidance.

#### Slide 19

Appropriate changes may include, for instance, a minor change in design, software, labeling, or sterilization and/or packaging methods.

#### Slide 20

For example, a PMA applicant employed an alternative sterilization method for its cardiac ablation catheter. The sterilization method was one that was previously reviewed and approved by the FDA for this type of device. Validation testing alone was sufficient to ensure that the alternative method adequately sterilized the device. In addition, the supporting test data for this change were within the single scientific discipline of sterilization. Therefore, the FDA determined that a Real-Time supplement was appropriate for this change.

#### Slide 21

The regulations provide that certain labeling and manufacturing changes that enhance the safety of the device, or the safety in the use of the device, may be submitted as a supplement marked “Special PMA Supplement – Changes Being Effectuated.” Note that design changes are not considered appropriate for a Special PMA supplement.

For these types of changes, the applicant may place the change into effect prior to receipt of a written FDA order approving the supplement, provided that certain conditions exist – you may refer to the PMA “modifications” guidance, cited previously, for a listing of those conditions. However, any such change should be considered temporary while the FDA reviews the supplement, including the basis for how the change enhances the safety of the device or the safety in the use of the device.

#### Slide 22

Changes that are appropriate for this type of supplement include labeling instructions that enhance the safe use of the device and/or the addition of an inspection step to improve quality in the manufacturing of the device.

#### Slide 23

For example, a PMA applicant made a labeling change to its urethral stent to improve the instructions for device removal after urothelial coverage. Because this modification enhanced safety with no impact on effectiveness, a Special PMA supplement was appropriate.

#### Slide 24

The FDA considers the use of a different facility or establishment to manufacture, process, or package a finished device to require a 180-day PMA supplement, referred to as a “manufacturing site change supplement.” The information submitted to the FDA in the supplement must demonstrate compliance with the Quality System regulation. A preapproval inspection may be necessary to evaluate the firm’s implementation of the Quality System regulation requirements.

#### Slide 25

A high-level overview of the major characteristics of the various types of PMA supplements is provided here, including whether clinical data or preclinical data are required to support the change, whether the change constitutes a single review discipline, and the FDA review goal for the supplement.

#### Slide 26

A PMA applicant may submit written notification to the FDA of a modification to the manufacturing procedure or method of manufacture affecting the safety and effectiveness of the device rather than submitting such change as a PMA supplement. Such a notification is referred to as a "30-Day Notice." The applicant may distribute the device 30 days after the date on which the FDA receives the notice, unless the FDA finds such information in the notice is not adequate, notifies the applicant that the notice has been converted to a 135-Day supplement, and describes further information or action that is required for acceptance of the modification.

#### Slide 27

Appropriate changes may include, for instance, a change from a manual to an automated process, the change to or addition of an alternate supplier, or the modification of sterilization process parameters. For additional information about the types of changes that qualify for a 30-Day Notice and for information on when the FDA may convert a 30-Day Notice to a 135-Day supplement, you may refer to the guidance document cited here. This guidance also provides further examples of the types of changes that the FDA has considered to be appropriate for the submission of a 30-Day Notice.

#### Slide 28

Continued approval of the PMA is contingent upon the submission of post-approval periodic reports, commonly known as "PMA annual reports." This requirement will cease only upon withdrawal of the PMA. There is a MDUFA fee for the periodic reports, and the FDA mails the invoice, annually, to the PMA applicant. Since the invoice is mailed, the PMA applicant does not need to complete the online Form FDA 3601, nor does the applicant need to submit or make payment for the report before submitting it to the FDA.

#### Slide 29

The report should cover the device approved under the original PMA as well as any devices approved under supplements to the original PMA. The report should identify all changes that were submitted to the FDA, during the reporting period, either as PMA supplements and/or 30-Day Notices, as well as other changes not previously submitted to the Agency.

In addition, the reports should provide a summary and bibliography of published reports and/or unpublished reports that are reasonably known to the Applicant, regarding any clinical or nonclinical investigations of the device or related devices. And, the report should identify the number of devices shipped or sold, as well as the number of devices implanted, as applicable.

#### Slide 30

This presentation provided a high-level overview of the post-approval regulatory controls that the FDA utilizes to ensure the continued safety and effectiveness of devices that have received approval of their Premarket Approval Application.

These controls include provisions for requiring post-approval studies and their reports, amendments and supplements, 30-Day Notices of manufacturing changes, and post-approval periodic reporting.

Slides 31-33

Various resources were highlighted throughout this presentation, and the following slides provide the URL addresses for each of those resources.

Slide 34

Let's conclude this module with your call to action.

First, to understand your regulatory responsibilities, we encourage you to review the references cited throughout this presentation. Information regarding PMA post-approval regulatory requirements is provided in much greater detail on the FDA website, including information in the medical device regulations, information in the various FDA guidance documents, and information posted on the FDA's Device Advice webpages. Additionally, you may wish to view other educational modules in CDRH Learn. Those resources were highlighted throughout this presentation, and the previous slides provide the URL addresses for each of those resources.

Second, if you cannot find the information you need from those resources, you may always contact us at the Division of Industry and Consumer Education. You may call us at the phone number listed on the following slide for a live discussion, or if you prefer, you may email us at the address provided.

Slide 35

We'll respond to your email within two business days. More information about the Division and the educational programs we offer may be found at: [www.fda.gov/DICE](http://www.fda.gov/DICE). Thank you for watching this program.

\*\*\*\*\*