Draft Guidance for Industry and FDA Staff

Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process

DRAFT GUIDANCE

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For questions regarding this document contact the PMA Staff in CDRH (Thinh Nguyen, CDR Samie Allen, Lisa Fisher, Patricia Beverly, Marsha Melvin, and Laura Byrd) at 240-276-4040. For questions regarding the 30-Day Notice program or regarding manufacturing site changes, please contact Christy Foreman in the Office of Compliance at 240-276-0120.

For questions regarding the application of this guidance to devices regulated by the Center for Biologics Evaluation and Research (CBER), please contact Leonard Wilson at 301-827-9433 (or 0373) or by email at leonard.wilson@fda.hhs.gov.

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Preface

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Draft Guidance for Industry and FDA Staff

Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance is intended for manufacturers of class III devices that are subject to Premarket Approval (PMA) requirements of section 515 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e). This guidance provides the criteria for the industry and Food and Drug Administration (FDA) staff to use in determining the type of PMA applications (original, panel track supplements, 180-day supplements, real-time supplements, Special PMA Supplements-Changes Being Effected, 30-day notices, or periodic reports) that you should submit to FDA when you modify the design or labeling of your PMA device, its manufacturing process or the location of manufacturing, processing or packaging. The guidance also provides examples of various types of device modifications, describes the types of testing that were performed to support the safety and effectiveness for each device modification, as well as the type of PMA application that was submitted. It does not address how to test a specific device to determine the effects of modifications.

This guidance is not intended to replace existing, device-specific guidance or other guidance documents related to the PMA program.[1]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

[1] All CDRH guidance documents are available at http://www.fda.gov/cdrh/guidance.html using the online search feature there.

requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to providing regulatory submissions for modifications to medical devices (including *in vitro* diagnostics regulated by the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER)) and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

II. Background

The "PMA regulation" (21 CFR Part 814) sets forth general criteria for determining when you must submit a PMA supplement or a 30-Day Notice for a device modification or manufacturing change (21 CFR 814.39). Subpart B "Premarket Approval Application" of the PMA regulation in Part 814 describes PMA amendments and supplements. Subpart E -"Post Approval Requirements" describes requirements for continuing evaluation (post-approval studies), periodic reporting, and other requirements related to the reasonable assurance of continued safety and effectiveness of an approved PMA device. The act defines different types of PMA supplements that are used to request approval of a change to a device that has an approved PMA (see section 737(4) of the act (21 U.S.C. 379i(4)) for definitions of 180-day supplements, real-time supplements, panel-track supplements). These definitions form the basis for the recommendations provided in this draft guidance document.

This draft guidance is the result of an extensive effort by a working group consisting of regulatory and scientific experts from CDRH and CBER. This draft guidance replaces the draft entitled, **Modifications To Devices Subject to Premarket Approval – The PMA Supplement Decision Making Process**, issued for comment August 6, 1998[2]. Comments by the industry on the earlier draft and comments we received at subsequent meetings on this issue have been considered by FDA during the development of this draft. FDA understands that there is a general desire among PMA holders for a detailed flow chart or easy to use paradigm that will identify the appropriate type of supplement to submit. However, FDA does not believe the complexity and uniqueness of class III devices makes it possible to establish that type of guidance. The agency believes that the principles and examples discussed in the various sections of this draft guidance below will prove useful to industry and staff in

[2] The 1998 guidance, **Modifications To Devices Subject to Premarket Approval – The PMA Supplement Decision Making Process** was withdrawn on January 5, 2005 (70 FR 824) because of amendments made to the act after 1998 that affected our recommendations (i.e., the amendments made by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107-250), which added specific definitions for 180-day supplement, real-time supplement, and panel-track supplement (section 737(4) of the act)).

establishing a clear and consistent way to approach this particular decision-making process. We look forward to specific comments on the draft that FDA can consider to improve its utility to stakeholders.

III. Scope of Guidance

This guidance document has been developed to describe the decision-making steps we recommend you follow to determine the type of regulatory submission, if any, that may be required when you modify your lawfully marketed PMA device. This guidance also applies if you modify your PMA device in response to a recall or field corrective action to assure the continued safety and effectiveness of the device.

IV. Determining What Type of Supplement You Should Submit

In accordance with 21 CFR 814.39, you must submit a PMA supplement for review and approval by FDA before making a change that affects the safety or effectiveness of your device that has an approved PMA, unless certain exceptions apply.[3] A generic list of changes that require a PMA supplement (because such changes affect the safety or effectiveness of the device) is provided below (see 21 CFR 814.39(a)). The list illustrates the kind of modifications that require a PMA supplement, but it is not an exhaustive list.

Examples of modifications that require a PMA supplement (21 CFR 814.39(a)) include:

- new indications for use of the device
- labeling changes
- the use of a different facility or establishment to manufacture, process, or package the device
- changes in sterilization procedures
- changes in packaging
- changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.
- extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. If FDA has approved your protocol, the change must be reported in a post-approval periodic report (21 CFR 814.39(b)).

[3] In accordance with 21 CFR 814.39(b), you may change your approved device without submitting a PMA supplement, if the change does not affect the device's safety or effectiveness and you report the change to FDA in your periodic report.

Under 21 CFR 814.39(f), you may submit, instead of a PMA supplement, a 30-Day Notice for changes to manufacturing procedures or methods of manufacture that affect the safety and effectiveness of your device. We recommend that you carefully assess whether a PMA supplement (21 CFR 814.39(a)) or a 30-Day Notice (21 CFR 814.39(f)) is appropriate for any modification you plan to undertake. The Quality System (QS) regulation (21 CFR Part 820) requires that you have in place a system to document and assess design changes (21 CFR 820.30). Part of the assessment for all changes should include a risk analysis verification, and validation of the changes to the design or manufacturing process and subsequent assessment of the need for regulatory submission. (More information regarding 30-Day Notices is provided in Section F of this guidance.)

Figure 1 at the end of this guidance illustrates the initial steps we recommend you follow in selecting the appropriate regulatory path for a modification to your PMA device.

V. Types of Applications

A primary indicator of what type of PMA application is needed is the nature of the testing, if any, that is needed to demonstrate the safety and effectiveness of the modified device. Each of the following sections describes one of the various types of PMA applications that may be submitted to FDA (original PMA, a Panel-Track Supplement, a 180-Day Supplement, a Real-Time Supplement, a Special PMA Supplement – Changes Being Effected, and a 30-day Notice). For each type of PMA application discussed in each section, we discuss the types of changes we would consider to be appropriate for the type of application, the types of test data we believe are needed to support the safety and effectiveness of such changes, and criteria we may use when determining whether that type of application should be submitted. We also provide, in each section, examples of various types of modifications submitted to the Office of Device Evaluation (ODE), the Office of In-Vitro Diagnostic Devices (OIVD), and CBER to illustrate what we believe are appropriate submissions for the type of PMA application discussed in that section. For each example, we provide the specific changes that were made to the approved device, the impact that changes had on the intended patients or on the use of the device, and the test data that FDA believes are needed to demonstrate that the modified device remains safe and effective.

A. When to Submit an Original PMA for a Modification

In general, a new original PMA application (rather than a PMA supplement) is appropriate when the modifications you make to your approved PMA device result in a new device. We would consider a new device to be one where a modification results in a device design so different from the original that the pre-clinical[4] ("analytical" for in vitro diagnostics

[4] For purposes of this guidance only, the term "pre-clinical testing" refers to non-clinical testing that is used to characterize a device (e.g., animal, bench, biocompatibility, electrical safety, software, reproducibility, reliability, accuracy, limit of detection, analytical testing).

(IVDs)) and clinical data [5] you submitted on your original device are no longer applicable in demonstrating reasonable assurance of the safety and effectiveness of the modified device.

In deciding whether to submit a supplement to your original PMA or to submit a new original PMA[6] for a modification to your approved device, we recommend you first ascertain whether, and to what extent, you can rely on the pre-clinical testing and clinical studies submitted in your original PMA to support the safety and effectiveness of your modified device. If you need to conduct new pre-clinical testing and new clinical studies to demonstrate reasonable assurance of safety and effectiveness of the modified device, you should assume that this is a new device that will require a submission of an original PMA.

The examples below illustrate when FDA has considered a new original PMA to be appropriate for a device modification based on the types of changes made and the testing that was necessary to demonstrate a reasonable assurance of safety and effectiveness. Each example describes a device reviewed in ODE, unless indicated as reviewed in OIVD or CBER.

A1. (New PMA) Redesigned Device for a New Indication for Use

FDA originally approved a PMA for the TransMyocardial Revascularization (TMR) holmium laser for surgical treatment of stable patients with angina that is refractory to medical treatment and not amenable to direct coronary revascularization. In this procedure, the chest is opened by surgical incision. Once the heart is exposed, the surgeon places the end of a fiber light guide onto the surface of the epicardium and the laser is activated making a hole through the ventricular wall, penetrating entirely through the wall into the ventricular cavity. This is repeated at several locations in the region to be treated.

The PMA holder redesigned its laser system by incorporating it into a fiber optic guide to make it suitable for percutaneous use. The PMA holder also modified the indication for use to include percutaneous myocardial revascularization (PMR), a non-surgical procedure. In PMR, the surgeon percutaneously places a catheter containing a fiber optic light guide into the left ventricle and uses the laser to make several gouges in the endocardium (inside) ventricular wall.

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[5] For purposes of this guidance only, the term "clinical data" refers to data derived from a study using a patient population with a defined clinical condition to determine the safety and effectiveness of the device including clinical performance characteristics (e.g., clinical specificity, clinical sensitivity).

[6] A new original PMA application may be either a traditional or modular PMA. The criteria and process for the modular review program are discussed in **Premarket Approval Application Modular Review Program,** (http://www.fda.gov/cdrh/mdufma/guidance/835.html).

The TMR device creates a hole that penetrates the inside ventricular wall and the PMR device creates a gouge that scoops out tissue, but does not penetrate through the ventricular wall (i.e., the injury to the myocardial tissue is different). In order to assess the impact of this change, new pre-clinical tests were necessary to demonstrate that the performance of the device, such as maneuverability, and reliable deployment and retraction, were adequate for percutaneous use. New clinical studies were also necessary because of the possibility of differences in the clinical outcome that could result from the differences in the indication for use of the devices (TMR vs. PMR), as well as to assess the difference in risk between an open surgical procedure and a percutaneous procedure.

Because new pre-clinical and clinical studies were necessary to demonstrate a reasonable assurance of safety and effectiveness for the modification, FDA determined that the changes resulted in a new device and as such, a submission of a new original PMA was appropriate for this modification.

A2. (New PMA) Redesigned Device with New Clinical Effects

FDA approved a PMA for an implantable cardiac pacemaker system consisting of a pulse generator and a lead. The system is indicated for patients who have bradyarrhythmias or other cardiac conduction abnormalities. The PMA holder redesigned the lead by adding a steroid eluting piece to the distal lead tip to reduce the inflammatory process (where the lead comes in contact with the endocardial tissue) and the impedance between the lead and the tissue. As a result, the amount of energy (the stimulation threshold) needed to achieve heart pacing was reduced, and the battery life was improved. The indication for use for the modified device remained the same as the original device.

The modified lead design raised questions related to device performance such as longer battery life and lower stimulation threshold, as well as questions of clinical safety and effectiveness. To adequately assess these changes, it was necessary for the PMA holder to conduct new pre-clinical tests to characterize the electrical performance and biocompatibility of the redesigned lead, as well as animal studies to demonstrate the *in vivo* effect of the steroid on pacing stimulation thresholds. New clinical studies were also needed to demonstrate that the steroid-eluting lead remained as safe and effective as the approved non-steroid lead. Because new pre-clinical and clinical studies were needed to demonstrate a reasonable assurance of safety and effectiveness of the modified design, FDA determined that this change resulted in a new device and as such, a submission of a new original PMA was appropriate for this modification.

A3. (New PMA) Different Analyte and a New Indication/Patient Population (OIVD)

FDA approved a PMA for an in vitro diagnostic immunoassay for the detection of total prostate-specific antigen (total PSA) in serum to aid in detection of prostate cancer in conjunction with the digital rectal exam (DRE). Free prostate-specific antigen (free

PSA) is a component of the total PSA. The PMA holder modified the device to detect free PSA in serum, which was considered a new analyte, and added a new indication, to distinguish prostate cancer from benign prostate disease. The PMA holder also intended that the device be used in a new patient population with defined total PSA levels and specific DRE characteristics. Consequently, the original pre-clinical and clinical data set were no longer adequate to support a finding of safety and effectiveness of the modified device. The analytical performance characteristics, (e.g., precision, reproducibility, and sensitivity) of the two assays differ. In addition, the clinical performance characteristics, (e.g., clinical sensitivity and specificity) also differ.

To demonstrate reasonable assurance of the safety and effectiveness of the modified device in the new patient population, new analytical (i.e., pre-clinical testing) and clinical data were necessary. Therefore, FDA determined that an original PMA application was appropriate for this modification.

A4. (New PMA) Significant Modification of Technology (OIVD)

FDA approved a PMA for the in vitro detection of bladder cancer in urine that used microwell enzyme immunoassay (EIA) technology (i.e., the reagents and analyte react in solution). The PMA holder modified the technology to a membrane–bound EIA (i.e., the reagents are bound to a membrane and the urine specimen is applied to the membrane). Because of the differences in the two technologies, the analytical performance characteristics (e.g., precision, reproducibility, and sensitivity) and the clinical performance characteristics (e.g., clinical sensitivity and specificity) of the two assays differ. Therefore, to demonstrate a reasonable assurance of safety and effectiveness for this new technology, it was necessary to conduct both new analytical and new clinical studies. Therefore, FDA determined that the submission of a new original PMA was appropriate for this modification.

B. When to Submit a Panel-Track PMA Supplement[7]

The FDA regulation in § 814.39(c) refers to any type of PMA supplement. However, specific types of PMA supplements are defined under the act. The term "Panel-Track Supplement" is defined in section 737(4)(B) of the act (21 U.S.C. 379i(4)(B)), (added by MDUFMA, as amended by the Medical Devices Technical Corrections Act (MDTCA) (Pub. L. 108-214 (2004))), as:

> "a supplement to an approved premarket application or premarket report under section 515 that requests a significant change in design or performance of the device, or a new

[7] 21 CFR 814.44 describes when a Panel Meeting may be held and the criteria for taking supplements to an FDA Advisory Panel for review are discussed in **Guidance on Amended Procedures for Advisory Panel Meeting**, (http://www.fda.gov/cdrh/modact/amendpan.html).

indication for use of the device, and for which substantial clinical[8] data are necessary to provide a reasonable assurance of safety and effectiveness."

We have considered Panel-Track Supplements to be most appropriate for changes in the indication for use. Significant design changes generally modify the pre-clinical and clinical performance of a device to such an extent that the PMA holder needs to conduct new pre-clinical tests and clinical studies to demonstrate that there is reasonable assurance of safety and effectiveness of the modified device. In such a case, as discussed in section A, a new original PMA is appropriate because the manufacturer needs to conduct both new pre-clinical tests and clinical studies to support the change.

A change in the indication for use may incorporate a change to the intended patient population, disease state or to other clinical aspects of the device use, such as duration of use, anatomical site, or surgical procedure. Changes in these clinical aspects would generally require significant labeling changes for which new clinical data are generally needed. A change to the indication for use may also include a change to a contraindication, such as the removal of a contraindication. FDA considers Panel-Track Supplements to be appropriate in these situations.

A Panel-Track Supplement, therefore, should be submitted for a change in indication for use of the device because:

- new clinical data are necessary to provide reasonable assurance of safety and effectiveness for the change in indication for use, and
- indication changes generally either do not require or require very limited new pre-clinical test data (i.e., all or most of the pre-clinical data previously submitted and reviewed in the original PMA are still applicable for the change in indication).

The following examples illustrate when FDA has considered a Panel-Track Supplement to be appropriate for a device modification, based on the types of changes made and the testing that was necessary to demonstrate a reasonable assurance of safety and effectiveness.

B1. Change in the Indication for Use– Different Patient Population

FDA approved a PMA for a ventricular assist device (VAD) indicated for the temporary, mechanical circulatory support of nonreversible left ventricular failure in patients awaiting cardiac transplant (as a temporary bridge to transplantation). The PMA holder modified the indication for use to include patients not eligible for cardiac

[8] FDA considers the term "substantial clinical data" in the definition of "Panel-Track Supplement" to refer to a new clinical data set that is intended to provide valid scientific evidence necessary to support the safety and effectiveness of the modified device (i.e., the clinical data provided in support of the original device approval is no longer applicable in supporting the approval of the modified device).

transplantation (i.e., "destination therapy"). No modifications were made to the device itself. In destination therapy, the VAD is permanently implanted.

There are significant differences in the clinical conditions of these two patient populations. For example, destination therapy patients are precluded from a transplant because they do not meet the age requirement or they have one or more co-morbid conditions (e.g., diabetes). The PMA holder conducted clinical studies for the proposed change to the indication for use to demonstrate safety and effectiveness in this new patient population.

In addition, destination therapy patients will use the device for a much longer period (years) compared to patients who use it as a temporary bridge to transplantation where the device may be used only for a few weeks or months, and rarely longer than 1 year. New clinical data were needed to demonstrate reasonable assurance of safety and effectiveness for longer term implantation. Although the device itself was not modified, the new conditions of use raise a new pre-clinical concern regarding device reliability. Therefore, the reliability test that was conducted for the original PMA had to be repeated to support the safety and effectiveness for use in the new patient population. The test conditions were modified to reflect the new clinical use conditions.

FDA determined that a Panel Track supplement was appropriate for this modification because new clinical data were needed to support the safety and effectiveness of the device and, although some additional preclinical tests were needed to address the new conditions of use, the full battery of pre-clinical testing was not needed because the device itself was not modified.

B2. Change in the Indication for Use - Different Patient Population

FDA approved a PMA for a urethral stent indicated to relieve urinary obstruction secondary to recurrent bulbar urethral strictures. The PMA applicant requested FDA's approval to market the identical device for the treatment of urinary obstruction secondary to benign prostate hyperplasia (BPH). In the original indication for urethral strictures, the device is inserted into the bulbar urethra in order to improve urine flow and prevent recurrence of strictures. In the new indication for BPH, the urethral stent compresses the enlarged prostatic tissue widening the urinary tract within the prostatic urethra in order to relieve urinary symptoms. The use of the permanent stent in this new urethral location (i.e., the prostate) introduces different safety concerns as compared to the original indication because the new target patient population has different risks related to age, overall health and anatomical location where the device is to be used. Strictures typically occur in younger healthy men, whereas patients with BPH are generally men greater than 60 years of age and who may have more health problems. The different anatomical location also presents new risks (e.g., adverse tissue response due to the presence of the stent in hyperplastic tissue, ejaculatory impairment and associated reduced fertility).

Because of the clinical differences related to age, overall health, and anatomical location where the device is to be used between the new and original patient populations, new clinical data were needed to support the safety and effectiveness of the new indication for use. No new preclinical data were needed because the device was not modified and the conditions of use (e.g., implant duration) were similar. Therefore, FDA determined that a Panel-Track Supplement was appropriate for this modification.

B3. Change in Indication for Use- Different Patient Population

FDA approved a PMA for a high frequency oscillatory ventilator (HFOV) indicated for ventilatory support and treatment of respiratory failure and barotrauma in low birth weight neonates. The PMA holder modified the indication to include ventilatory support and treatment in adult patients with (adult) respiratory distress syndrome. The device itself was not modified. The patients in the original PMA consisted of infants with respiratory failure associated with lung immaturity, or other causes of respiratory failure in newborns. The new indication was for adults with adult respiratory distress syndrome, which is a condition associated with trauma and sepsis. Although both groups suffered from respiratory failure, the underlying lung pathology, the cause of the lung pathology, and the potential clinical outcomes for the two populations are different. Because of these clinical differences between these two patient populations, new clinical data were needed to evaluate the safety and effectiveness of the device in the new population. Since the device and the conditions of use remained the same, no new pre-clinical testing was necessary. Therefore, FDA determined that a Panel-Track Supplement was appropriate for this modification.

B4. Change in Indication for Use – Different Patient Population (OIVD)

FDA approved a PMA for glucose monitoring system for detecting trends and tracking patterns in glucose levels in adults (age 18 and older) with diabetes. The PMA holder modified the indication for use to add pediatric patients (age 7 to 17 years). The differences between adults and children, in body surface area, daily activities, physiology, and underlying disease may affect clinical outcomes in the two patient populations. For this reason, it was necessary to conduct new clinical studies to demonstrate that the device provided reasonable assurance of safety and effectiveness for the new pediatric patient population. Since the device and the conditions of use remained the same, no new pre-clinical testing was necessary. Therefore, FDA determined that the submission of a new Panel-Track Supplement was appropriate for this modification.

B5. Change in Indication for Use– Different Surgical Procedure

FDA approved a PMA for an excimer laser system for photorefractive keratectomy (PRK) for the reduction or elimination of myopia (nearsightedness). The PMA holder modified the indication to add laser assisted in-situ keratomileusis (LASIK), a different procedure, for the reduction or elimination of myopia using the identical laser system. PRK uses laser ablation on the surface of the cornea to reshape it, whereas LASIK

involves cutting a flap in the cornea and using laser ablation underneath the flap. The new indication involves a more invasive procedure with different risks associated with the creation, replacement, and maintenance of the flap. There were also new risks and clinical effectiveness concerns associated with intrastomal ablation rather than the surface ablation technique used in the new indication. These concerns include a different healing response, longer recovery times, different ablation profiles and deeper ablation into the cornea, potentially leaving it thinner, which may affect the physical integrity of the eye. The new indication for use differs from the original indication. Therefore, new clinical studies were needed to demonstrate reasonable assurance of safety and effectiveness for the new indication for use. No pre-clinical testing was necessary, since the device was not modified and the conditions of use remained the same. Therefore, FDA determined that the submission of a Panel-Track Supplement was appropriate for this modification.

B6. Change in Indication for Use–Different Conditions of Use

FDA approved a PMA for a soft silcone hydrogel extended wear (1 to 7 days) contact lens indicated for the correction of myopia or hyperopia. The PMA holder modified the indication to include extended wear up to 30 days. The device remained unchanged and the intended patient population remained the same, however, the conditions of use changed. The extended time of wear raised new safety concerns including increased risk of ocular adverse events, such as corneal microbial keratitis, and corneal infiltrated lesions. In order to evaluate the risks associated with extended wear from 7 days to up to 30 days, substantial clinical data were necessary to demonstrate a reasonable assurance of safety and effectiveness. No new pre-clinical testing was needed because the testing previously performed adequately addressed the new conditions of use. Therefore, FDA determined that the submission of a Panel-Track Supplement was appropriate for this modification.

B7. Change in Indication for Use- Different Specimen (Sample) Type (CBER)

FDA approved a PMA for an HIV diagnostic (whole blood specimens). The PMA holder modified the indication to oral fluid specimens (i.e., a new sample type). The characteristics of oral fluid specimens are different from that of whole blood specimens. Therefore clinical studies are necessary to determine the safety and effectiveness of the device. However, while the specimen matrix changed, the actual analyte did not (HIV antibodies). In this case, limited analytical studies were sufficient to examine specimen matrix effects. FDA determined that a Panel Track supplement was appropriate for this modification because only new clinical data and limited additional analytical data were needed to support the safety and effectiveness of the device.

B8. Change in Indication for Use - Different Physiological Location

FDA approved a PMA for a prosthetic heart valve for use in the aortic position. The PMA holder modified the indication to include 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 than in the aortic position. These conditions can affect the performance of the valve by affecting the hemodynamics (e.g., forward flow pressure drop (gradient) and regurgitation). These conditions can also affect the complication rates for thrombosis, thromboembolism, and hemolysis. The physiological and potential performance differences between the two positions may significantly impact clinical outcome. Therefore, new clinical studies were needed to ensure that the heart valve remained safe and effective when implanted in the new location. Additional pre-clinical tests were not needed because the test data provided in the original PMA to support the valve for use in the aortic position were sufficient to support the valve for use in the mitral position. Therefore, FDA determined that the submission of a Panel Track Supplement was appropriate for this change.

C. When to Submit a 180-Day Supplement

According to section 737(4)(C) of the act (21 U.S.C. 379i(4)(C)), "180-Day Supplement" is defined as:

"a supplement to an approved premarket application or premarket report under section 515 that is not a Panel-Track Supplement and requests a significant change in components, materials, design, specification, software, color additives, and labeling."

Submission of a 180-Day Supplement is required for certain types of significant changes to the approved device that affects safety and effectiveness of the device. In general, in order for a change to be submitted as a 180-Day Supplement, the clinical data provided in support of the original device approval should still be applicable in supporting the approval of the modified device. In most cases, for such modifications, only new pre-clinical testing is needed to demonstrate reasonable assurance of safety and effectiveness of the modified device. In some instances, 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. Although additional clinical data may be necessary, the data collected are usually from a limited number of patients. In these situations, FDA believes that a 180-Day Supplement, rather than a Panel-Track Supplement, is appropriate because of the limited nature of the supplementary clinical data. Therefore, applicants should submit a 180-Day Supplement for the following types of changes (the list is illustrative but not exhaustive):

- the principle of operation
- the control mechanism
- the device design or performance
- the labeling
- new testing requirements or acceptance criteria.

Below are examples illustrating when FDA has considered a 180-Day Supplement to be appropriate for a device modification, based on the types of changes made and the testing that was necessary to demonstrate a reasonable assurance of safety and effectiveness.

C1. (180-Day Supplement) Design Change – Pre-clinical Data Sufficient

FDA approved a ventricular assist device (VAD) intended as temporary mechanical circulatory support for patients awaiting a cardiac transplant. The 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 exits the patient. No change was made to the indication for use and the patient population. To demonstrate that the modified device remained safe and effective, only mechanical tests, such as pull/bend/twist testing were needed. Since FDA determined that this change could be evaluated with mechanical tests and no new clinical data were needed, the submission of a 180-Day Supplement was appropriate for this change.

C2. (180-Day Supplement) New Device Feature – Pre-clinical Data Sufficient

FDA approved a PMA for an excimer laser system indicated for wavefront-guided LASIK to reduce or eliminate myopia and astigmatism. The PMA holder added an iris identification and registration system to the device to control for torsional movement of the eye. No changes were made to the indication for use, the intended patient population, the ablation characteristics of the excimer laser, or the intended clinical outcome. For this change, FDA determined that pre-clinical testing such as engineering tests, visual optics evaluation, and software validation along with the revised labeling were adequate to demonstrate reasonable assurance of the safety and effectiveness of the modification. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate.

C3. (180-Day Supplement) Modified Chemical Formulation – Pre-clinical Data Sufficient

FDA approved a PMA for a hydrophilic contact lens. The PMA holder modified the chemical formulation of the lens by adding an ultraviolet (UV) light blocking material and also modified the manufacturing process. For this change, FDA determined that pre-clinical studies to assess the modified manufacturing processes, biocompatibility, shelf-life, UV light transmission, and materials characterization, including an assessment of leachability were sufficient to demonstrate a reasonable assurance of the safety and effectiveness of this modification. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C4. (180-Day Supplement) Hardware and Software Modifications – Pre-clinical Data Sufficient

FDA approved a PMA for a transurethral microwave system that is indicated to relieve symptoms associated with benign prostatic hyperplasia (BPH). The PMA holder

modified several critical components of the system, including the computer motherboard, computer operating system, and software for the user interface screens. To demonstrate that the modified device met the specifications of the original device (and thus remained safe and effective), comparative bench testing was needed, including software, electromagnetic compatibility (EMC), electrical safety, shock, vibration, and functional testing. The treatment parameters and algorithm remained unchanged such that clinical data were not needed to evaluate the performance of the modified device. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C5. (180-Day Supplement) New Analyzer – Assay Unchanged (OIVD) – Pre-clinical Data Sufficient Sufficient

FDA approved a PMA for a total prostate-specific antigen (total PSA) immunoassay using an automated analyzer. The PMA holder developed a new automated analyzer to perform the total PSA assay. The indications for use and the technology of the total PSA assay remained unchanged, and no new clinical studies were warranted. The PMA holder conducted new analytical performance testing at internal and external sites to demonstrate that the new analyzer does not alter the performance of the assay. Therefore, FDA determined that a submission of a 180-Day Supplement was appropriate for this change.

C6. (180-Day Supplement) Design and Software Modification – Pre-clinical Data Sufficient

FDA approved a PMA for a bone growth stimulator for use as an adjunct to primary lumbar spinal fusion surgery. The PMA holder changed the type of battery used and modified the LCD display, which required modifications to the housing, the printed circuit board, and the software. Because these changes impacted the electrical characteristics of the device, it was necessary to conduct pre-clinical testing including EMC, electrical safety, shock and vibration, battery life, software and functionality to verify that the modified device operated within the original device's specifications. Clinical data were not necessary to support the safety and effectiveness of the modified device. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C7. (180-Day Supplement) Modified physical characteristics – Pre-clinical Data Sufficient

FDA approved a PMA for an endovascular stent graft system for the treatment of infra-renal abdominal aortic or aorto-iliac vessels. The PMA holder modified the physical characteristics of the material used in the manufacture of the stent graft. The modified material had the same chemical composition as the original material; however, the weaving process was different. The new graft was woven into a denser weave configuration which was intended to enhance the robustness of the graft material. Bench testing, including dimension verification, joint strength, burst strength, tensile strength, fatigue, and water permeability was needed to demonstrate that the new

weaving process did not adversely affect the physical performance properties of the device. Animal testing was also needed to compare the vessel healing and patency of the new material with the material used in the original device. Pre-clinical testing, including animal testing, was adequate to demonstrate a reasonable assurance of the safety and effectiveness of the device. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C8. (180-Day Supplement) New Device Feature – Pre-clinical Data Sufficient

FDA approved a PMA for a cardiac radiofrequency (RF) ablation system. The PMA holder modified the system by adding a feature that allows the physician to visualize catheter navigation during the procedure. The modification did not change the delivery of RF energy to the tissue, and therefore, the clinical performance of the device was not impacted by this modification. Consequently, clinical data were not necessary to support this change. However, verification and validation testing were needed to assess the performance of the modified device. This assessment consisted of bench testing including functionality, EMC, lesion qualification, compatibility testing (between the generator, which has the new feature, and the approved catheters) and animal testing. Bench testing and animal testing were adequate to demonstrate a reasonable assurance of safety and effectiveness of the modified device. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C9. (180-Day Supplement) Design Change - Pre-clinical Data and Limited Confirmatory Clinical Studies Sufficient

FDA approved a PMA for a pneumatic ventricular assist device (VAD) intended as temporary mechanical circulatory support for patients with heart failure awaiting a cardiac transplant. The PMA holder modified the system from a pneumatically driven system to an electrically driven one, by replacing the original controller with a new device controller. The PMA holder was asked to conduct bench testing to demonstrate the similarities and differences between the performance characteristics (e.g., flow pattern, pressures, alarm functions) of the new controller and the original controller. A limited clinical study was also needed to confirm that the modification did not raise new safety and effectiveness questions. The new bench testing and the limited confirmatory clinical study of the modified device, along with the original clinical data set, were sufficient to demonstrate reasonable assurance of safety and effectiveness of the modified device. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for this change.

C10. (180-Day Supplement) New Specimen (Sample) Type (CBER) – Pre-Clinical Data and Limited Confirmatory Clinical Studies Sufficient

FDA approved a PMA for an HIV diagnostic intended for fingerstick, whole blood specimens. The PMA holder modified the device for use with venipuncture, whole blood specimens. Specimen characteristics of venipuncture blood and fingerstick blood are not significantly different. The PMA holder conducted analytical (e.g., reproducibility) and limited clinical studies (e.g., clinical sensitivity and specificity) to

confirm adequate performance of the modification to demonstrate reasonable assurance of safety and effectiveness for the modification. The clinical data necessary to support this modification was limited. Therefore, FDA determined that the submission of a 180-Day Supplement was appropriate for the change.

D. When to Submit a Real-Time Supplement

According to section 737(4)(D) of the act (21 U.S.C. 379i(4)(D)) (added by MDUFMA, as amended by MDTCA), a "Real-Time Supplement" is defined as:

> "a supplement to an approved premarket application or premarket report under section 515 that requests a minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement."

In general, we believe a Real-Time Supplement is most appropriate for a minor change that can be expected within a specific class of devices (e.g., pacemakers, orthopedic implants, intra-ocular lenses). This may include changes to:

- device design (other than those described in the examples in **C. When to Submit a 180-Day Supplement**)
- instructions for use, warnings, or precautions or other labeling that does not affect the indications or contraindications
- sterilization and packaging methods
- software

In addition, a Real-Time Supplement is most appropriate when these circumstances also exist:

- there is an accepted test method, FDA-recognized standard or guidance document to address the safety or effectiveness of the change;
- the change is adequately supported by bench or animal testing, with no new clinical data needed;
- an inspection of the manufacturing facility is not required;

- the review of the application would involve a single scientific discipline. That is, it would not be subject to an multidisciplinary review;[9] and

- FDA believes that the review may be achieved in a real-time setting.

The process for the real-time review program is further discussed in the guidance, **Premarket Approval Application Real-Time Review**."[10]

The following examples illustrate when FDA has considered a real-time PMA supplement to be appropriate, based on the types of changes made, the testing that was necessary to demonstrate a reasonable assurance of safety and effectiveness, and other applicable criteria. Please note that FDA is not aware of a situation in which a Real-Time Supplement would be appropriate for changes that affect an indication for use; therefore, there are no discussions of indications changes in the examples below.

D1. (Real-Time Supplement) Minor Modification to Correct Battery Failures

The PMA holder made minor modifications to the circuitry associated with the battery supervisor chip in the portable driver used with its ventricular assist device (VAD). The modification is intended to correct a battery failure problem. The bench testing was conducted using a test method that was previously accepted by FDA and was sufficient to support the change to the device. In addition, the supporting test data for this change could be adequately reviewed by a single reviewer with electrical engineering expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D2. (Real-Time Supplement) Alternative Sterilization Method

The PMA holder employed an alternative sterilization method for its cardiac ablation catheter. The sterilization method used was a method that was previously reviewed and approved by FDA for this type of device. Validation testing alone was sufficient to ensure the alternative method adequately sterilized the ablation catheter. In addition, the supporting test data for this change could be adequately reviewed by a single reviewer with sterilization expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D3. (Real-Time Supplement) Storage Temperature Change

The PMA holder increased the upper limit for the storage temperature from 25°C to 30°C for its bone graft (i.e., recombinant human bone morphogenetic protein). This is a minor change to the storage condition and device labeling. Stability data at the new higher temperature was sufficient to support the change and was conducted using an

[9] Examples of reviews from various scientific disciplines are clinical, electrical engineering, mechanical engineering, chemical engineering, material engineering, microbiology, biocompatibility/toxicology, microbiology/sterilization.

[10] http://www.fda.gov/cdrh/ode/guidance/673.html.

accepted test method. In addition, the supporting data for this change can be reviewed by a single reviewer with materials engineering expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D4. (Real-Time Supplement) Extended Shelf Life

The PMA holder modified the labeling of its injectable gel for facial wrinkles and folds to extend the shelf life from 24 months to 36 months. Accelerated and long term testing was performed to evaluate the physical, chemical, and biological stability of the device during storage. This is a minor change to the labeling and the stability studies are well understood and have a well defined protocol. In addition, the supporting data for this change can be reviewed by a single reviewer with microbiology expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D5. (Real-Time Supplement) Component Offered as Stand Alone System

The PMA holder proposed to modify an excimer laser system by offering the wavefront system and the surgery planning software included in the original system as a stand-alone system to allow the surgeon to prepare for surgical cases in advance. There were no actual changes to the wavefront system or the surgery planning software and both were included in the original PMA. Verification and validation of data transfer from the stand-alone system to the excimer laser system was sufficient to support this minor change. In addition, the supporting data for this change can be reviewed by a single reviewer with electrical engineering expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D6. (Real-Time Supplement) Alternate Wet Shipping Solution

The PMA holder proposed to use an alternate wet shipping solution for its permeable extended wear contact lenses. This solution was one that was previously approved by the FDA for other contact lenses. The concerns with this type of change include biocompatibility of the new solution, compatibility with the contact lens, adequate preservative efficacy (i.e., ability to maintain low bioburden) and adequate labeling (identification of solution and preservative). The supporting data for this change can be reviewed by a single reviewer with microbiology expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

D7. (Real-Time Supplement) Modified Bonding Method

The PMA holder modified the method of bonding the retention balloon to the catheter in its transurethral microwave system to enhance balloon reliability. This is a minor change, adequately supported by bench testing using the test method previously described in the original approved PMA. In addition, the supporting data for this change can be reviewed by a single reviewer with mechanical engineering expertise. Therefore, FDA determined that a Real-Time Supplement was appropriate for this change.

E. Special PMA Supplement – Changes Being Effected

21 CFR 814.39(d)(1) and (d)(2) 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 Effected." The Special PMA Supplement is a narrow exception to the general rule that prior FDA approval of changes to a PMA, including the labeling for a device, is a condition of lawful distribution and, therefore, may only be utilized where (1) the manufacturer has newly acquired safety-related information; (2) the information in question was not previously considered by the FDA; and (3) valid scientific evidence exists for the modification. Prior to approving a PMA, the FDA undertakes a detailed review of the proposed labeling, allowing only those safety-related warnings with a scientific basis. Allowing a manufacturer to add a safety-related warning using a Special PMA Supplement based on information that was known to the FDA during the rigorous PMA review process would undermine that important process. For the same reason, a manufacturer cannot add a safety-related warning to avoid potential liability under state tort law if there is not a scientific basis for the new warning. Instead, a manufacturer may utilize the limited Special PMA Supplement only when it possesses new information that provides a legitimate foundation for modifying the FDA-approved labeling. For these types of changes, the applicant may place the change in effect prior to receipt of a written FDA order approving the supplement, provided that:

i. the PMA supplement and its mailing cover are plainly marked "Special PMA Supplement – Changes Being Effected;"

ii. the PMA supplement provides a full explanation of the basis for the changes;

iii. the applicant has received acknowledgement from FDA of receipt of the supplement; and

iv. the PMA supplement specifically identifies the date that such changes are being effected.

FDA has authority to approve or reject a Special PMA Supplement. Although a manufacturer may place a change into effect prior to the receipt of a written FDA order approving the change, any such change should be considered temporary while FDA reviews the supplement, including the basis for the how the change enhances the safety of the device or the safety in the use of the device. In general, design changes are not considered appropriate for a Special PMA Supplement. For example, if a manufacturer attempted to change the design of an implantable cardiac device so that it can be more securely held in place inside the patient's chest cavity, such a change would be inappropriate for a Special PMA Supplement. Although the regulation allows both labeling and manufacturing changes that enhance the safety of the device or the safety in the use of the device to be submitted as a Special PMA Supplement, FDA believes that labeling changes (as described in 21 CFR 814.39(d)(2)) are most appropriate for a Special

PMA Supplement. Changes to the quality controls or manufacturing process may fall under the scope of this provision. The manufacturing changes that may be reviewed as a Special PMA Supplement are generally those that add a step to the quality control or manufacturing processes to enhance safety. However, many manufacturing modifications enhance safety **but** also impact effectiveness. For example, if a modification in the quality controls or manufacturing process results from a design control failure[11] and the subsequent corrective action impacts device effectiveness, we believe that change is not appropriate for a Special PMA Supplement. For modifications that can impact both safety and effectiveness, a Panel Track, a 180-Day, a Real-Time Supplement or a 30-Day Notice is more likely to be appropriate.

Below we provide examples to illustrate when FDA has considered a Special PMA Supplement to be appropriate, based on the types of labeling and manufacturing changes made.

E1. (Special PMA Supplement) New Warning Added

The PMA holder made a labeling change in the technical manual for its neurological implantable programmer, by adding a warning against using the device in the presence of any flammable anesthetic mixture in conformance with the FDA-recognized standard (i.e., International Electrotechnical Commission (IEC) 60601-1 Medical Electrical Equipment - Part 1: General Requirements for Safety). Because this modification to the warning of the labeling enhanced safety with no impact on effectiveness, a Special PMA Supplement was appropriate.

E2. (Special PMA Supplement) Manufacturing Process Change

The PMA holder made a modification to its manufacturing process for the source wire component of its intravascular brachytherapy system, by adding a secondary wipe station to the manufacturing process. The PMA holder made this change as a result of detecting incidental radioactive contamination during routine cartridge exchanges. This change was made to provide an additional safeguard to ensure effective removal of contaminants from the wire surface prior to transfer in a production cartridge. Because this modification enhanced safety with no impact on effectiveness, a Special PMA Supplement was appropriate.

E3. (Special PMA Supplement) Improved Instructions

The PMA holder 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.

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[11] Design controls, as defined by 21 CFR 820.30, are established and maintained procedures that control the design of the device in order to ensure that specified design requirements are met. Therefore, a failure is any action that does not conform to the design controls and the specified design requirements, and, hence, does not stay within the acceptable level of risk.

E4. (Special PMA Supplement) Additional Inspection Step in the Manufacturing Process

The PMA holder added an additional incoming inspection step (i.e., measuring the outer diameter of the distal end of the stopcock) to the manufacturing process of a duett sealing device (sealing femoral arterial puncture site). The purpose of this step was to ensure that there was a tight fit between the two mating parts: the distal end of the stopcock and the proximal end of the hub sleeve knob. This change enhanced the reliability of the catheter by providing a more reliable fit when the user attached these two components together. Since the change enhanced the safety in the use of the device with no impact on effectiveness, a Special PMA Supplement was appropriate.

E5. (Special PMA Supplement) Additional Inspection Step in the Manufacturing Process

The PMA holder added an additional inspection step to the manufacturing process for its bone growth stimulator as a result of observing an increased frequency of a particular error message. A greater than normal air gap between two inductors on one of the circuit boards was the source of the error. The process was modified to assess the air gap between the conductors, thereby increasing the reliability of the device. Since the change enhanced the safety of the device and did not impact effectiveness, a Special PMA Supplement was appropriate.

F. 30-Day Notice and 135-Day Supplements

Section 515(d) of the act (21 U.S.C. 360e), as amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA)(Pub. L. 105-115), permits a PMA holder to submit written notification to the agency 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. The manufacturer may distribute the device 30 days after the date on which FDA receives the notice, unless FDA finds such information in the 30-Day Notice is not adequate, notifies the holder, and describes further information or action that is required for acceptance of the modification. If the agency notifies the holder that a supplemental application is required, FDA must review the supplement within 135 days after receipt of the supplement (referred to as a "135-Day PMA Supplement")(Id.; see also 21 CFR 814.39(f)). For additional information about the type of changes that qualify for a 30-Day Notice and for information on when FDA may convert a 30-Day Notice to a 135-Day Supplement, refer to the guidance document entitled **30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes.**[12]

Below, we provide examples of the types of changes that FDA has considered to be appropriate for the submission of a 30-Day Notice. In some cases, the notice was converted to a 135-Day Supplement because the supporting information was inadequate. For those cases, we have included an explanation for the conversion.

[12] http://www.fda.gov/cdrh/modact/daypmasp.html

F1. (30-Day Notice) Manual to Automated Process

The PMA holder has a specified manufacturing process for a cardiac resynchronization therapy pacemaker (CRT-P). As part of its manufacturing process, there is a manual process for applying medical adhesive. The PMA holder made a change that included automating the process of applying the medical adhesive to the device header and affixing the header to the device case. Adequate information was submitted to support the 30-Day Notice for the manufacturing change.

F2. (30-Day Notice) Alternate Qualified Supplier

The PMA holder has a qualified supplier for the manufacture of a component used in the calibrator of its Hepatitis B surface antigen assay. A change in manufacturing process included identifying a different qualified supplier for this component. Adequate information was submitted to support the 30-Day Notice for the change in supplier. This included, but was not limited to, specifications for the raw material, supplier evaluation procedures, and a description of the type and extent of control over the raw material/supplier for the old and new material/supplier.

F3. (30-Day Notice) In-Process Quality Control Step Change

The PMA holder has numerous quality control steps for the manufacture of an inflatable penile prosthesis. An in-process quality control monitoring step for endotoxin testing is part of the manufacturing process. The PMA holder made a change that included moving the in-process quality control monitoring step for endotoxin to a different location in the process flow. The PMA holder provided adequate documentation in the 30-Day Notice to support this change in the manufacturing process of the prosthesis.

F4. (135-Day Supplement) Manual to Automated Process Conversion

The PMA applicant submitted a change to the manufacturing process for forming and folding the balloon wings of an Over-the-Wire Percutaneous Transluminal Angioplasty (PTCA) catheter from a manual process to an automated process. This 30-Day Notice was converted to a 135-Day Supplement because the submission did not contain all of the appropriate testing (e.g., balloon fatigue test, rated burst pressure test, and validation data) to support the change.

F5. (135-Day Supplement) Alternate Supplier of Intra-Occular Lense (IOL) Material

The PMA holder of a polymethylmethacrylate (PMMA) Single-Piece IOL submitted a 30-Day Notice to use an additional supplier of the PMMA material. This 30-Day Notice was converted to a 135-Day Supplement because the submission did not contain all the tests necessary to qualify the new supplier, such as optic tilt test and axial displacement test.

F6. (135-Day Supplement) Modified In-Process Test

The PMA holder of a vascular closure device submitted a 30-Day Notice to incorporate an alternate backup deployment test methodology in its manufacturing process. The notice was converted to a 135-Day Supplement because the test methods and acceptance criteria used to support this change were either not clearly explained or not provided in the application.

G. Manufacturing Facility Site Change

After approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change that affects the safety or effectiveness of the device, including a change that uses a different facility or establishment to manufacture, process or package the device.[13] Such a PMA supplement for a move to a different facility or establishment is called a "Site Change Supplement."

Site Change Supplements are 180-Day PMA Supplements (21 CFR 814.40) and are reviewed by CDRH's Office of Compliance (CDRH/OC) or OIVD (for in vitro diagnostic devices). Firms should contact CDRH/OC or OIVD in advance of the submission to discuss what information should be provided. The following information outlines the types of information that should be considered in such a submission:

- a description of the current facility and the new or different facility
- a statement of the purpose for the move
- a list of manufacturing processes affected by the move
- a list of equipment being moved or acquired
- a copy of your process validation master plan, or a description of which processes you will validate, as well as a list of processes being moved that you do not plan to validate but that you will verify by inspection and test
- a copy of the validation procedure(s) or individual validation plan(s)
- when available, a copy of any completed validation reports
- where validation testing has not been completed, a description of the status of such testing and the completion date.

FDA may inspect the new or different facility as part of its review of the Site Change Supplement. In general, the decision about whether the new or different facility should be inspected is based on the following principles:

[13] 21 CFR 814.39(a).

- type of inspection and timing of the last inspection of the current facility and the facility to which manufacturing is being moved
- classification of the last inspection of the current facility and the facility to which manufacturing is being moved
- nature of the devices that were the subject of previous inspections
- the degree to which process validation data has been submitted in the PMA supplement.

Questions on PMA supplements for facility changes should be directed to the following contacts:

Division Contact	Device Type
Office of Compliance Division of Enforcement A Telephone: (240) 276-0115	• General Surgery • Dental • Ear, Nose and Throat • General Hospital • Ophthalmic • OB/GYN • Gastroenterology and Urology
Office of Compliance Division of Enforcement B Telephone: (240) 276-0120	• Cardiovascular • Neurological • Physical Medicine • Orthopedic • Anesthesiology • Radiology
Office of In Vitro Diagnostic Device Evaluation and Safety Telephone: (240) 276-0484	• In Vitro Diagnostics (IVDs)

VI. Periodic Reports

In accordance with 21 CFR 814.82(a)(7), FDA may require as a condition of approval submission to FDA at intervals specified in the approval order of periodic reports containing the information required by 21 CFR 814.84(b). In most cases, after the PMA is approved, the PMA holder is required to submit reports to FDA annually unless a different time frame is specified in the approval order. Persons who wish to comment on the draft guidance on this topic, see **Annual Reports for Approved Premarket Approval Applications (PMA)**, http://www.fda.gov/cdrh/ode/guidance/1585.html.

Attachment I. Types of PMA Supplements

Type	Panel-Track Supplement	180-Day Supplement	Real-Time Supplement	Special PMA Supplement	30-Day Notice	Manufacturing Facility Site Change Supplement
Definition	"...significant change in design or performance of the device, or a new indication for use of the device, and for which substantial clinical data are generally necessary..."	"...significant change in components, materials, design, specification, software, color additive, and labeling."	"... minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement."	Changes in labeling, quality control, or manufacturing processes "that enhance[s] the safety of the device or the safety in the use of the device…"	Changes to "a manufacturing procedure or method of manufacturing and the holder of the approved application submits a written notice …. "	The use of a different facility or establishment to manufacture, process, or package the device.
Statute/ Regulation Provision	Section 737(4)(B) of the act (and as modified by the Medical Devices Technical Corrections Act (MDTCA), Public Law 108-214)	Section 737(4)(C) of the act	Section 737(4)(D) of the act (and as modified by the Medical Devices Technical Corrections Act (MDTCA), Public Law 108-214)	Sections 21 CFR 814.39(d)(1) and 814.39(d)(2)	Section 515(d)(6)(A)(ii) of the act; 21 CFR 814.39(f)	Section 21 CFR 814.39(a)(3)
Description	A change in: o indication for use o design o performance **Substantial clinical data generally necessary to support the change.** [B]	A significant change involving: o principle of operation o control mechanism o design o performance o labeling o new testing or acceptance criteria. **Preclinical and/or confirmatory clinical data to support the change.**	Minor changes[A] (e.g., **for which clinical data or FDA inspections are not needed),** such as changes in: o design o software o labeling (other than contraindications) o sterilization and packaging. **Changes can be reviewed adequately by a reviewer in one scientific discipline**	If effectiveness is not altered, changes in: o labeling to add, strengthen, or delete information o manufacturing process that adds a new specification or test method or provides additional assurance of	Changes in manufacturing that affect safety and effectiveness.	A move to a different manufacturing facility or establishment.

				purity, identity, strength, or reliability of the device		

[A]Assuming there is also an accepted test method, FDA-recognized standard, or guidance, and FDA agrees that a Real-Time Supplement is appropriate.
[B]As discussed in Section B of this document, we have considered Panel-Track Supplements to be most appropriate for changes in the indication for use.
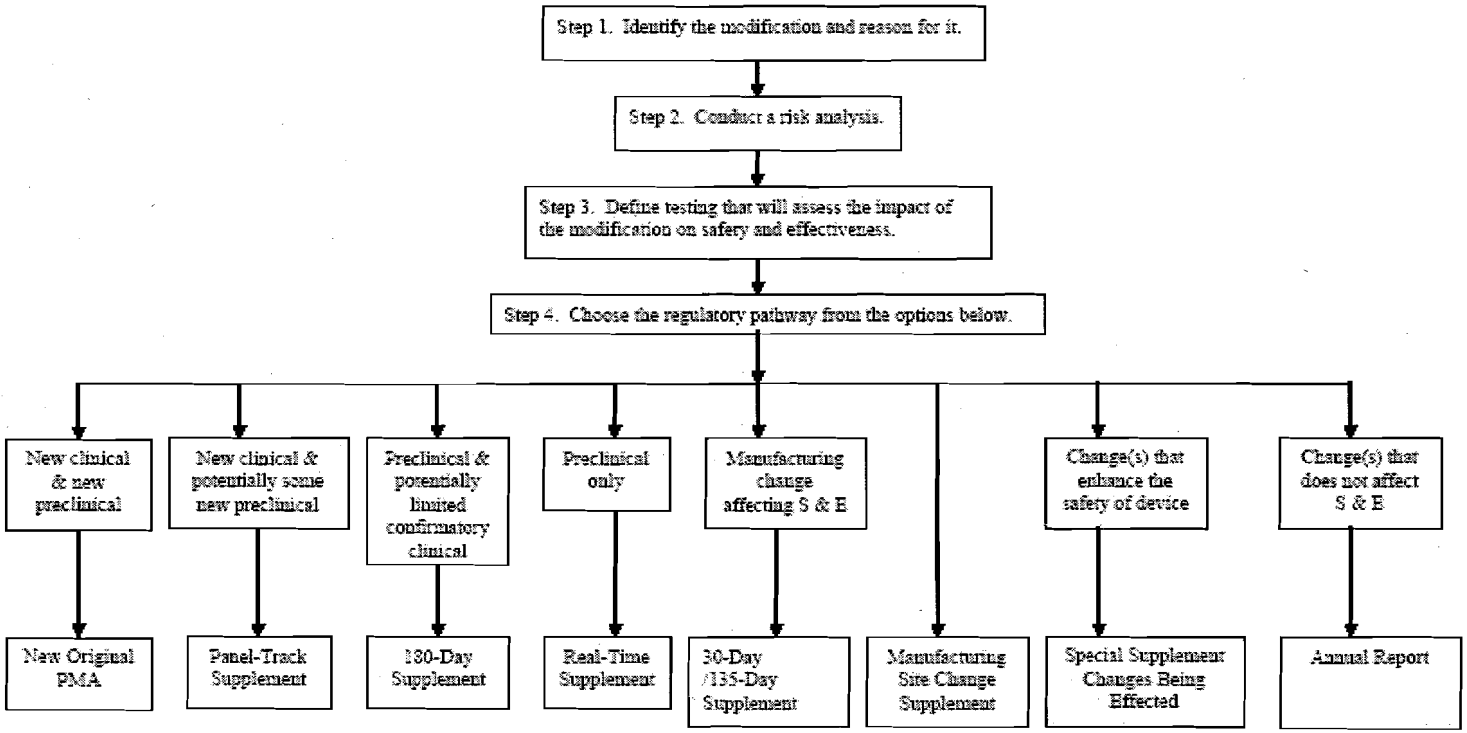
Figure 1. Recommended Steps to Decide the Regulatory Path for a Modified PMA Device