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## Device Advice - Premarket Approval (PMA) Printer Friendly Version



**Please note: As of October 1, 2002, FDA charges a fee for review of Premarket Approvals**

### Overview

#### Introduction

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices 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. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. Please note that some Class III preamendment devices may require a Class III 510(k). See "[Historical Background](#)" below for additional information.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. The applicant is often the inventor/developer and ultimately the manufacturer.

FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

The regulation governing premarket approval is located in Title 21 Code of Federal Regulations (CFR) Part 814, Premarket Approval. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed.

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#### Definitions (21 CFR 814.3)

**30-day PMA supplement** - a supplemental application to an approved PMA in accordance with 21 CFR 814.39(e).

**Act** - Federal Food, Drug, and Cosmetic Act (sections 201-902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321-392)).

**Agency** – U.S. Food and Drug Administration

**CFR** - Code of Federal Regulations

**Federal Register (FR)** – Publication of the federal government to establish new regulations or to change existing regulations.

**FDA** – U.S. Food and Drug Administration

**GMP** – Good Manufacturing Practices, also referred to as Quality System under 21 CFR 820

**Humanitarian Device Exemption (HDE)** - a premarket approval application submitted under 21 CFR 814 Subpart H seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the FD&C Act as authorized by section 520(m)(2) of the Act.

**Humanitarian Use Device (HUD)** - a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

**IDE** – an approved or considered approved Investigational Device Exemption under 21 CFR 812 and section 520(g) of the FD&C Act.

**Master file** - a reference source that a person submits to FDA. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a medical device.

**Medical Device Amendment** – an amendment to the Food, Drug, and Cosmetic Act signed into law on May 28, 1976. The amendments gave FDA authority to regulate medical devices.

**Office of Communication, Education and Radiation Programs (OCER)** – The office of FDA/CDRH that reviews PMA labeling.

**Office of Regulatory Affairs (ORA)** – The Office of Regulatory Affairs is responsible for facility inspections of FDA regulated establishments. ORA employees are located in FDA headquarter offices and in more than 150 offices throughout the U.S.

**Office of Surveillance and Biometrics (OSB)** – The office of FDA/CDRH responsible for statistical review of marketing applications and postmarket surveillance.

**Office of Device Evaluation (ODE)** – The office of FDA/CDRH responsible for the review of marketing applications.

**PMA** - any premarket approval application for a class III medical device, including all information submitted with or incorporated by reference. "PMA" includes a new drug application for a device under section 520(l) of the FD&C Act.

**PMA amendment** - information an applicant submits to FDA to modify a pending PMA or a pending PMA supplement.

**PMA supplement** - a supplemental application to an approved PMA for approval of a change or modification in a class III medical device, including all information submitted with or incorporated by reference.

**Person** - any individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or any other legal entity.

**Postamendment device** – a device that is commercially distributed on or after May 28, 1976, the date the Medical Device Amendments of 1976 were signed into law.

**Preamendment device** – a device that was commercially distributed before May 28, 1976, the date of the Medical Device Amendments of 1976 were signed into law.

**QS** – Quality System, 21 CFR 820

**Reasonable probability** - that it is more likely than not that an event will occur.

**Serious, adverse health consequences** - any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible.

**Statement of material fact** - a representation that tends to show that the safety or effectiveness of a device is more probable than it would be in the absence of such a representation. A false affirmation or silence or an omission that would lead a reasonable person to draw a particular conclusion as to the safety or effectiveness of a device also may be a false statement of material fact, even if the statement was not intended by the person making it to be misleading or to have any probative effect.

**Transitional Devices** - Transitional devices are devices that were regulated as drugs prior to the May 28, 1976, the date the Medical Device Amendments were signed into law. Any device that was approved by the New Drug Application process is now governed by the PMA regulations. The original NDA approval number is maintained.

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### When a PMA is Required

PMA requirements apply to Class III devices, the most stringent regulatory category for medical devices. Device product classifications can be found by searching the Product Classification Database, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>. The database search provides the name of the device, classification, and a link to the Code of Federal Regulations (CFR), if any. The CFR provides the device type name, identification of the device, and classification information.

A regulation number for Class III devices marketed prior to the 1976 Medical Device Amendments is provided in the CFR. The CFR for these Class III devices that require a PMA states that the device is Class III and will provide an effective date of the requirement for PMA. If the regulation in the CFR states that "No effective date has been established of the requirement for premarket approval," a Class III 510(k) should be submitted.

Please note that PMA devices often involve new concepts and many are not of a type marketed prior to the Medical Device Amendments. Therefore, they do not have a classification regulation in the CFR. In this case, the product classification database will only cite the device type name and product code.

If it is unclear whether the unclassified device requires a PMA, use the three letter product code to search the PMA database and the Premarket Notification 510(k) database. These databases can be found by clicking on the hypertext links at the top of the product classification database web page. Enter only the three letter product code in the product code box. If there are 510(k)'s cleared by FDA and the new device is substantially equivalent to any of these cleared devices, then the applicant should submit a 510(k).

Furthermore, a new type of device may not be found in the product classification database. If the device is a high risk device (supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury) and has been found to be not substantially equivalent (NSE) to a Class I, II, or III [Class III requiring 510(k)] device, then the device must have an approved PMA before marketing in the U.S. Some devices that are found to be not substantially equivalent to a cleared Class I, II, or III (not requiring PMA) device, may be eligible for the de novo process as a Class I or Class II device. For additional information on the de novo process, see "New section 513(f)(2) - Evaluation of Automatic Class III Designation: Guidance for Industry and CDRH Staff" <http://www.fda.gov/cdrh/modact/classiii.html> or <http://www.fda.gov/cdrh/modact/classiii.pdf>.

### Historical Background

PMA requirements apply to Class III preamendment devices, , transitional devices, and postamendment devices.

#### Preamendment Devices

A preamendments device is one that was in commercial distribution before May 28, 1976, the date the Medical Device Amendments were signed into law. After the Medical Device Amendments became law, the classification of devices was determined by FDA classification panels. Eventually all Class III devices will require a PMA. However, preamendment Class III devices require a PMA only after FDA publishes a regulation calling for PMA submissions. The preamendment devices must have a PMA filed for the device by the effective date published in the regulation in order to continue marketing the device. The CFR will state the date that a PMA is required. Prior to the PMA effective date, the devices must have a cleared Premarket Notification 510(k) prior to marketing. Class III Preamendment devices that require a 510(k) are identified in the CFR as Class III and include the statement "Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. No effective date has been established of the requirement for premarket approval." Examples include intra-aortic balloon and control system (21 CFR 870.3535), ventricular bypass (assist) device (21 CFR 870.3545), cardiovascular permanent pacemaker electrode (21 CFR 870.3680), and topical oxygen chamber for extremities (21 CFR 878.5650).

### Postamendment Devices

A postamendment device is one that was first distributed commercially on or after May 28, 1976. Postamendment devices equivalent to preamendment Class III devices are subject to the same requirements as the preamendment devices.

### Transitional Devices

Transitional devices are devices that were regulated by FDA as new drugs before May 28, 1976. Any Class III device that was approved by a New Drug Application (NDA) is now governed by the PMA regulations. The approval numbers for these devices begin with the letter N. These devices are identified in the CFR as Class III devices and state that an approval under section 515 of the Act (PMA) is required as of May 28, 1976 before this device may be commercially distributed. An example of such device is intraocular lenses (21 CFR 886.3600). Please note that some of the transitional devices have been subsequently downclassified to Class II.

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### **Devices Used in Blood Establishments**

The Center for Biologic, Evaluation, Research (CBER) has expertise in blood, blood products, and cellular therapies as well as the integral association of certain medical devices with these biological products. To utilize this expertise marketing and investigational device submissions (Premarket Notification, Premarket Approval, and Investigational Device Exemption) for medical devices associated with the blood collection and processing procedures as well as those associated with cellular therapies are reviewed by CBER. Although these products are reviewed by CBER, the medical device laws and regulations still apply. The list of medical devices reviewed by CBER are available on the Internet <http://www.fda.gov/cber/dap/devlst.htm>

In addition to CDRH guidance on Premarket Approval, specific medical device guidance for devices reviewed by CBER is available at <http://www.fda.gov/cber/devices.htm> or by contacting:

Center for Biologics Evaluation and Research  
Office of Communication, Training and Manufacturers Assistance (HFM-43)  
1401 Rockville Pike, Room 200N  
Rockville, MD 20852-1448 U.S.A.  
Telephone Number: 301-827-2000 or 800-835-4709  
Fax Number: 301-827-3843

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### **Data Requirements**

A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application. If a PMA application lacks elements listed in the administrative checklist, FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it will delay FDA's review and approval. PMA applications that are incomplete, inaccurate, inconsistent, omit critical information, and poorly organized have

resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.

**Technical Sections:** The technical sections containing data and information should allow FDA to determine whether to approve or disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations.

**Non-clinical Laboratory Studies' Section:** Non-clinical laboratory studies' section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with 21CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies).

**Clinical Investigations' Section:** Clinical investigations' section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.

Like other scientific reports, FDA has observed problems with study designs, study conduct, data analyses, presentations, and conclusions. Investigators should always consult all applicable FDA guidance documents, industry standards, and recommended practices. Numerous device-specific FDA guidance documents that describe data requirements are available. The guidance document database on the Internet can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfGGP/Search.cfm>. Study protocols should include all applicable elements described in the device-specific guidance documents.

## References

Section 515 of the Federal Food, Drug, and Cosmetic Act  
See GPO Site

21 CFR 814

Class III Devices Subject to 515(b) Requirements, Compliance Policy Guide, 300.750 (CPG 7124.18)  
[http://www.fda.gov/ora/compliance\\_ref/cpg/cpgdev/cpg300-750.html](http://www.fda.gov/ora/compliance_ref/cpg/cpgdev/cpg300-750.html)

The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry  
<http://www.fda.gov/cdrh/ode/guidance/1332.html>  
<http://www.fda.gov/cdrh/ode/guidance/1332.pdf>

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## Review Process

### Overview

The review of a premarket approval application (PMA) is a four-step review process consisting of:

- administrative and limited scientific review by FDA staff to determine completeness (filing review);
- in-depth scientific, regulatory, and Quality System review by appropriate FDA personnel;
- review and recommendation by the appropriate advisory committee (panel review); and
- final deliberations, documentation, and notification of the FDA decision.

[Filing a PMA \(21 CFR. 814.42\)](#)

During the administrative and limited scientific review, FDA determines whether a PMA is suitable for filing by reviewing the PMA submission for information required by the FD&C Act, the PMA regulations (21 CFR 814), and Refuse to File policy. FDA has developed a Checklist for Filing Decision for PMAs.

The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to begin an in-depth review. Within 45 days after a PMA is received by FDA, the agency will notify the applicant whether the application has been filed. The letter will include the PMA reference number and the date FDA filed the PMA. Expedited review status, if appropriate, may be communicated at this time. The date of filing is the date that a PMA accepted for filing was received by the agency. The 180-day period for review of a PMA starts on the date of filing.

FDA will refuse to file the application for substantive review if a PMA application does not meet a minimum threshold of acceptability. If the information or data are presented unclearly or incompletely or are not capable of withstanding rigorous scientific review, FDA may consider the PMA incomplete and not file it. If FDA refuses to file a PMA, FDA will notify the applicant of the reasons for the refusal. This notice will identify the deficiencies in the application that prevent filing and will include the PMA reference number. FDA will advise the manufacturer of what information must be provided, or steps to be taken, to make the application fileable.

If FDA refuses to file the PMA, the applicant may:

- The applicant may resubmit the PMA with additional information necessary to comply with the requirements of section §515(c)(1)(A)-(G) of the FD&C Act and 21 CFR 814.20. A resubmitted PMA must include the PMA reference number of the original submission. If the resubmitted PMA is accepted for filing, the date of filing is the date FDA receives the resubmission;
- The applicant may request in writing within 10 working days of the date of receipt of the notice refusing to file the PMA, an informal conference with the Director of the Office of Device Evaluation to review FDA's decision not to file the PMA. FDA will hold the informal conference within 10 working days after receiving the request and will make its decision on filing within 5 working days after the informal conference. If FDA then accepts the PMA for filing, the date of filing will be the date of the decision to accept the PMA for filing. If FDA does not reverse its decision, the applicant may request reconsideration of the decision from the Director of the Center for Devices and Radiological Health. The Director's decision will constitute final administrative action for the purpose of judicial review.

Should the applicant decide to request a meeting concerning a refuse-to-file decision, the applicant must choose either: 1) an informal conference at which the decision not to file the application will be reviewed; or 2) a meeting with the ODE division to discuss the specific deficiencies and the measures necessary to correct these deficiencies. Please be advised that FDA will not typically grant requests for an informal conference **and** a meeting with the reviewing ODE division regarding this decision due to resource limitations. Applicants should either request an informal conference or schedule a meeting with the reviewing ODE division to discuss the preparation of an appropriate response.

FDA may refuse to file a PMA if FDA determines that any of the following applies:

- The application is incomplete because it does not contain all the information required under section 515(c)(1) (A)-(G) of the FD&C Act;
- The PMA does not contain each of the items required under Sec. 814.20 and justification for omission of any item is inadequate;
- The applicant has a pending Premarket Notification 510(k) with respect to the same device, and FDA has not determined whether the device falls within the scope of Sec. 814.1(c).
- The PMA contains a false statement of material fact.
- The PMA is not accompanied by a statement of either certification or disclosure as required by 21 CFR 54 Financial Disclosure by Clinical Investigators.

#### In-depth review (21 CFR 814.44)

FDA will begin substantive review of the PMA after it is accepted for filing (§814.42). During the review process, FDA will notify the PMA applicant via major/minor deficiency letters of any information needed by FDA to complete the review of the application. The applicant may request to meet with FDA within 100 days of the filing of the PMA to discuss the review status of the application. The procedure for "Day-100 Meetings" can be found in the guidance document "Guidance on PMA Interactive

Procedures for Day-100 Meetings and Subsequent Deficiencies - for Use by CDRH and Industry; Final"

<http://www.fda.gov/cdrh/modact/day100mt.html>

<http://www.fda.gov/cdrh/modact/day100mt.pdf>

If the applicant on their own initiative or at FDA's request submits a PMA amendment (§814.37) which contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted, the review period may be extended up to 180 days.

#### Panel Review (21 CFR 814.44)

FDA may refer the PMA to an outside panel of experts (advisory committee). In general, all PMAs for the first-of-a-kind device are taken before the appropriate advisory panel for review and recommendation. However, as soon as FDA believes that (1) the pertinent issues in determining the safety and effectiveness for the type of medical device are understood and (2) FDA has developed the ability to address those issues, future PMAs for devices of that type are not be taken before an advisory panel unless a particular application presents an issue that can best be addressed through panel review.

The PMA, or relevant portions, may be forwarded to each member of the appropriate FDA advisory committee for review. During the review process, FDA may communicate with the applicant [§814.37(b)] or with the advisory committee to respond to questions that may be raised by committee members or to provide additional information to the panel. FDA will maintain a record of all communications with the applicant and with the advisory committee.

If the PMA is referred to an advisory committee, the committee must hold a public meeting to review the PMA in accordance with 21 CFR 14. The advisory committee must submit a final report to FDA that includes the committee's recommendation and the basis for such recommendation on the PMA. The advisory committee report and recommendation may be in the form of a meeting transcript signed by the chairperson of the committee.

The following documents provide guidance for panel review.

Panel Review of Premarket Approval Applications 5/3/91 (P91-2)

<http://www.fda.gov/cdrh/p91-2.html>

Criteria for Panel Review of PMA Supplements 1/30/86 (P86-3)

<http://www.fda.gov/cdrh/p863.html>

FDA takes into consideration the transcript of the meeting, the panel's recommendation(s), and other information in reaching a final decision on the PMA. FDA informs the applicant whether FDA agrees with the panel's recommendation or disagrees and what additional information is needed from the applicant (approvable/not approvable decision). If the application is approvable, the applicant must agree to the "Conditions of Approval."

#### Notification of Approval (§814.44)

Within 180 days of the date of filing of the PMA (§814.40), FDA will complete its review of the PMA and of the advisory committee's report and recommendation and issue one of the following:

- an approval order under §814.44(d),
- an approvable letter under §814.44(e),
- a not approvable letter under §814.44(f), or
- an order denying approval under §814.45.

#### Approval Order

After FDA reviews the committee's final report, the FDA will issue an order to the applicant that the PMA is approved if none of the reasons in §814.45 (Denial of approval for a PMA) for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling. Approval will be based on the condition that the applicant submits to FDA a copy of the final printed labeling before marketing.

FDA will notify the public of the approval. The announcement of the decision and the availability of a summary of the safety and effectiveness data (SSED) on which the decision is based will be published on the Internet at <http://www.fda.gov/cdrh/pmapage.html>. The summary will include information about any adverse effects of the device on health. The announcement also provides the applicant and other interested persons an opportunity for administrative review of the FDA approval under section 515(d)(3) of the FD&C Act. On a quarterly basis, FDA will publish a list of approvals announced during that quarter in the *Federal Register*. When a notice of approval is published, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

#### Approvable Letter

FDA will send the applicant an approvable letter if the application substantially meets the requirements of the FD&C Act, and FDA believes that it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant. The approvable letter will describe the information that FDA requires to be provided by the applicant or the conditions that the applicant is required to meet to obtain approval. FDA may require, for example, as a condition of approval:

- the submission of certain information identified in the approvable letter, such as final draft labeling;
- an FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with the Quality System regulations (21 CFR 820) and, if applicable, verification of records pertinent to the PMA;
- restrictions imposed on the sale, distribution, or use of the device under section 515(d)(1)(B)(ii) or 520(e) of the FD&C Act; or
- postapproval requirements.

The applicant may have to agree to a postapproval study, restrictions on prescription use, or restrictions on the training of individuals who may use the device before approval. The applicant may also be notified of required postmarket surveillance and/or tracking requirements.

In response to an approvable letter, the applicant may:

- amend the PMA as requested;
- consider the approvable letter to be a denial of the PMA (21 CFR 814.45) and request administrative review [section 515(d)(3) of the FD&C Act] by filing a petition for reconsideration (21 CFR 10.33); or
- withdraw the PMA.

#### Not approvable letter

FDA will send the applicant a not approvable letter if FDA believes that the application may not be approved for one or more of the reasons given in §814.45(a) or if FDA is unable to reach an approvable decision due to a lack of significant information in the application. The not approvable letter will describe the deficiencies in the application, including each applicable ground for denial under section 515(d)(2)(A)-(E) of the FD&C Act. When practical, FDA will identify what is necessary to make the PMA approvable. In response to a not approvable letter, the applicant may:

- amend the PMA as requested [such an amendment will be considered a major amendment under §814.37(c)(1)];
- consider the not approvable letter to be a denial of approval of the PMA (§814.45) and request administrative review under section 515(d)(3) of the FD&C Act by filing a petition for reconsideration (21 CFR 10.33); or
- withdraw the PMA.

FDA will consider a PMA to have been withdrawn voluntarily if:



- the applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such a request;
- the applicant fails to respond in writing to an approvable or not approvable letter within 180 days after the date FDA issues such a letter; or
- the applicant submits a written notice to FDA that the PMA has been withdrawn.

#### Service of orders (21 CFR 814.17)

Any FDA orders, such as approval or denial, will generally be faxed and then sent to the PMA applicant or its designated agent by mail. A PMA applicant or its designated agent may arrange to pick up the FDA order at 9200 Corporate Blvd., Rockville, Maryland 20850 by contacting the PMA Staff at 301-594-2186.

#### Standard Conditions of Approval

The "Conditions of Approval" are the standard postapproval conditions imposed by FDA. These are applicable to all original PMAs and PMA supplements. As a condition of approval the sponsor agrees to abide by advertising and final printed labeling requirements and to submit adverse event reports, annual reports, and PMA supplements for certain changes. Additional specific conditions may be required for implanted devices. Applicants should carefully read the conditions of approval enclosed with the FDA approval letter. The "Conditions of Approval" is available on the Internet. <http://www.fda.gov/cdrh/devadvice/pma/conditions.html>

#### PMA Amendments 814.37

An applicant may amend a pending PMA or PMA supplement to revise existing information or to provide additional information.

FDA may request the applicant to amend a PMA or PMA supplement with any information regarding the device that is necessary for FDA or the appropriate advisory committee to complete the review of the PMA or PMA supplement.

A PMA amendment submitted to FDA shall include the PMA or PMA supplement number assigned to the original submission and, if submitted on the applicant's own initiative, the reason for submitting the amendment. FDA may extend the time required for its review of the PMA or PMA supplement:

If the applicant on its own initiative or at FDA's request submits a major PMA amendment (e.g., an amendment that contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted), the review period may be extended up to 180 days.

If an applicant declines to submit a major amendment requested by FDA, the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

#### Resubmitted PMAs 814.37

Applicants may voluntarily withdraw their PMA or PMA supplement. If FDA requests an applicant to submit a PMA amendment, and a written response to FDA's request is not received within 180 days, FDA will consider the pending PMA or PMA supplement to be withdrawn voluntarily by the applicant (abandoned).

An applicant may resubmit a PMA or PMA supplement that was withdrawn, that FDA has refused to accept for filing, or that FDA has denied approval. A resubmitted PMA or PMA supplement must comply with the requirements of §814.20 or §814.39 and must include the PMA number assigned to the original submission as well as the applicant's reason for resubmission.

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## Steps in the PMA Application Process

- ODE filing review
- OSB statistical review for filing
- OC review of manufacturing information for compliance with the Quality System regulation (21 CFR 820).
- PMA filing decision
- Day-100 Meeting
- Quality System Inspection(s) by the FDA field personnel. An FDA manufacturing inspection is conducted for all original PMAs and may be conducted for PMA supplements requesting approval of alternate or additional manufacturing and sterilization facilities.
- Bioresearch Monitoring (BIMO) Audit (audit of clinical study data)
- Substantive review coordination and completion in areas such as:
  - Preparation of FDA Summary of Safety and Effectiveness Data (SSED)
  - Nonclinical Studies  
[Microbiological, Toxicological, Immunological, Biocompatibility, Shelf Life, Analytical (for IVDs), Animal, Engineering (Stress, Wear, Fatigue, etc.)]
  - Clinical Studies
- Panel Meeting Decision and Mailing (if panel meeting is appropriate)
- Panel Date (if appropriate)
- Transcripts Received, Reviewed and Placed in Administrative Record
- QS/GMP Clearance
- Final Response from OC for GMP/BIMO
- Final ODE Decision Memo
- Approval Package

, Approval Order, , SSED, Final Draft Labeling

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## Early Collaboration

Applicants are encouraged to contact FDA to obtain further guidance prior to the submission of a PMA application. This will be especially beneficial to new applicants who have not previously had contact with FDA and for applicants proposing to study new technologies or new uses for existing technologies. Early interaction with FDA should help to increase the applicant's

understanding of FDA requirements, regulations, and guidance documents, and will allow FDA personnel to familiarize themselves with the new technologies. Increased interaction between FDA and applicants should help to speed the regulatory process and minimize delays in the development of useful devices intended for human use.

The applicant may request a "PrePMA determination" meeting with FDA. This meeting held early in device development will provide the applicant with the agency's determination of the type of valid scientific evidence that will be necessary to determine if the device is effective for its intended use. Additional information on early collaborations meetings can be found in "Early Collaboration Meetings under the FDA Modernization Act (FDAMA)" <http://www.fda.gov/cdrh/ode/guidance/310.pdf>

Once the applicant understands the review process through FDA regulations and guidance documents, the applicant is encouraged to contact the review divisions within the Office of Device Evaluation to discuss device-specific requirements. The PMA staff may be contacted for general questions relating to the PMA laws, regulations, policies, and administrative issues on (301) 594-2186.

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## FDA Action On a PMA

### Denial of approval of a PMA (§814.45)

FDA may deny approval of a PMA if the applicant fails to follow the requirements of the PMA regulation or if FDA determines that any of the grounds for denying approval of a PMA specified in section 515(d)(2)(A)-(E) of the FD&C Act applies. In addition, FDA may deny approval of a PMA for any of the following reasons:

- The PMA contains a false statement of material fact.
- The device's proposed labeling does not comply with the requirements in Part 801, Labeling, or Part 809, In Vitro Diagnostic Products for Human Use.
- The applicant does not permit an authorized FDA employee to inspect the facilities and controls in which the device will be manufactured or to have access to and to copy and verify all records pertinent to the application
- An essential nonclinical laboratory study described in the PMA was not conducted in compliance with the good laboratory practice (GLP) regulations in 21 CFR 58 and no reason for the noncompliance is provided, or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.
- Any clinical investigation involving human subjects described in the PMA that is subject to the Institutional Review Board regulations in 21 CFR 56 or to the Informed Consent regulations in 21 CFR 50 and was not conducted in compliance with these regulations such that the rights or safety of human subjects were not adequately protected.

FDA will issue any order denying approval of a PMA in accordance with §814.17. The order will inform the applicant of the deficiencies in the PMA, including each applicable ground for denial under section 515(d)(2) of the FD&C Act and the regulations under Part 814, and, where practical, will identify measures required to place the PMA in approvable form. The order will include a notice of an opportunity to request review under section 515(d)(3) of the FD&C Act.

FDA will use the criteria specified in §860.7 (Determination of Safety and Effectiveness) in deciding whether to approve or deny approval of a PMA. FDA may use information other than that submitted by the applicant in making such determination.

FDA will publish a *Federal Register* notice of an order denying approval of the PMA. The notice will be placed on the Internet (<http://www.fda.gov/cdrh>) and will state that a detailed summary of information concerning the safety and effectiveness of the device, including information about any adverse effects on health, is available on the Internet and has been placed on public display. FDA will publish in the *Federal Register* after each quarter a list of the denials announced in that quarter. When a notice of denial of approval is made publicly available, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

FDA will issue an order denying approval of a PMA after an approvable or not approvable letter has been sent and the applicant has:

- submitted the requested amendment but any ground for denying approval under section 515(d)(2) of the FD&C Act still applies; or
- notified FDA in writing that the requested amendment will not be submitted; or
- petitioned for review under section 515(d)(3) of the FD&C Act by filing a petition in the form of a petition for reconsideration (21 CFR 10.33).

#### Withdrawal of approval of a PMA (21 CFR 814.46)

FDA may issue an order withdrawing approval of a PMA if FDA determines from any information available that:

- any of the grounds under section 515(e)(1)(A)-(G) of the FD&C Act applies;
- any postapproval requirement imposed by the PMA approval order or by regulation has not been met;
- an essential laboratory study described in the PMA was not conducted in compliance with the GLP regulations in 21 CFR 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the GLP regulation do not support the validity of the study; or
- any clinical investigation involving human subjects described in the PMA that is subject to the IRB regulations in 21 CFR 56 or to informed consent regulations in 21 CFR 50, was not conducted in compliance with these regulations, such that the rights or safety of human subjects were not adequately protected.

FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw approval of a PMA. FDA may also use information other than that submitted by the applicant in deciding whether to withdraw approval of a PMA.

Before issuing an order to withdraw approval of a PMA, FDA will issue the holder of the approved application a notice of opportunity for an informal hearing under 21 CFR 16. If the applicant does not request a hearing or, if after the 21 CFR 16 hearing is held, FDA decides to proceed with the withdrawal, FDA will issue an order withdrawing approval of the application. The order (§814.17) will state each ground for withdrawing approval and will include a notice of an opportunity for administrative review under section 515(e)(2) of the FD&C Act.

FDA will publish a *Federal Register* notice of an order withdrawing approval of a PMA. The notice will state that a detailed summary of information concerning the safety and effectiveness of the device, including information about any adverse effects on health, has been placed on public display and that copies are available upon request. When a notice of withdrawal of approval is published, data and information in the PMA file will be available for public disclosure under §814.9.

#### Temporary Suspension of Premarket Approval (§814.47)

If, after providing the sponsor with an opportunity for a regulatory informal hearing regarding the proposed withdrawal of PMA approval, and FDA determines there is a reasonable probability that continued distribution of a PMA-approved device would cause serious adverse health consequences or death, FDA shall by order temporarily suspend the PMA. In cases where there is sufficient grounds, FDA will proceed expeditiously to withdraw the PMA approval.

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#### **References**

Section 515 of the Federal Food, Drug, and Cosmetic Act  
<http://www.fda.gov/opacom/laws/fdcact/fdcact5a.htm>

## 21 CFR 814

### PMA Refuse to File Procedures (P94-1)

<http://www.fda.gov/cdrh/pma941.html>

### PMA Filing Decision (P90-2)

<http://www.fda.gov/cdrh/pma90-2.html>

### Checklist for Filing Decision for PMA

<http://www.fda.gov/cdrh/ode/checklist/pma.html>

### Clinical Utility and Premarket Approval (P91-1)

<http://www.fda.gov/cdrh/p91-1.html>

### Panel Review of Premarket Approval Applications 5/3/91 (P91-2)

<http://www.fda.gov/cdrh/p91-2.html>

### Criteria for Panel Review of PMA Supplements 1/30/86 (P86-3)

<http://www.fda.gov/cdrh/p863.html>

### Panel Review of PMAs for "Me Too" Devices 7/25/86 (P86-6)

<http://www.fda.gov/cdrh/p866.html>

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## **PMA Review Fees**

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### **Overview**

On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 was signed into law. This law authorizes FDA to charge a fee for medical device product reviews. These fees apply to Premarket Approvals (PMAs), Product Development Protocols (PDPs), Biologics Licensing Applications (BLAs for certain medical devices reviewed by FDA's Center for Biologics Evaluation and Research), certain supplements, and Premarket Notification 510(k)s.

The fee must be paid for the above listed applications, unless the applicant is eligible for a waiver or exemption. Small businesses may qualify for a reduced fee. Payment must be received on or before the time the application is submitted. If the applicant has not paid all fees owed, FDA will consider the application incomplete and will not accept it for filing.

### **Fees**

For fiscal year 2008 (October 1, 2007 through September 30, 2008), the fees for PMA applications are:

FY 2008 Device Review User Fees (U.S. Dollars)		
Type of Application	Standard Fee	Small Business Fee (<\$100 million sales)
Premarket Application (PMA, PDP, BLA, PMR)*	\$185,000	\$46,250
<b>NOTE: The fee is waived for the <i>first</i> premarket application from firms with gross receipts or sales &lt;\$30 million.</b>		
Premarket Report (PMR) - premarket approval application for a reprocessed device	\$185,000	\$46,250
Efficacy Supplement (for BLA)	\$185,000	\$46,250
Panel-track Supplement	\$138,750	\$34,688
180-day Supplement	\$27,750	\$6,938
Real-time Supplement	\$12,950	\$3,237
30-Day Notice/135-Day PMA Supplement**	\$2,960	\$1,480
Annual Fee for Periodic Reporting on a Class III Device**	\$6,475	\$1,619

\* PMA=Premarket Approval; PDP=Product Development Protocol; BLA=Biologics License Application; PMR=Premarket Report (for a reprocessed device)

\*\*New for FY08

The applicable fee corresponds with the date of receipt of the submission by FDA. Please note that FDA will consider the application incomplete and will not accept it for filing until the fee is paid in full. That is, the date of receipt is the date that the application has been received AND the fee is paid in full.

Guidance on assessing user fees can be found in "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products" <http://www.fda.gov/cdrh/mdufma/guidance/1201.pdf>

FDA will adjust the fees each year to account for inflation, changes in workloads, and other factors. FDA will announce the new fees for the next fiscal year in a Federal Register notice by August 1 of each year.

**Exemptions and Waivers**

The following types of applications require **no fee**.

- Special PMA Supplements-Changes Being Affected
- Express PMA Supplements
- Humanitarian Device Exemption (HDE)
- BLA for a product licensed for further manufacturing use only.

The following exemptions or waivers apply.

Fee Exemptions and Waivers (No Fee for These)	
Category	Exemption or Waiver
<i>First</i> premarket application (PMA, PDP, BLA, or premarket report) from a small business with gross receipts or sales <\$30 million .	One-time waiver of the fee that would otherwise apply.
	Exempt from any fee. If an applicant obtains an exemption under this provision, and later submits a

Any application for a device intended solely for pediatric use.	supplement for adult use, that supplement is subject to the fee then in effect for an original premarket application.
Any application from a State or Federal Government entity.	Exempt from any fee unless the device is to be distributed commercially.

### When to Pay

Payment must be received at or before the time the application is submitted. If the applicant has not paid all fees owed, FDA will consider the application incomplete and will not accept it for filing.

### How/Where to Send Payment

#### Submit the information and payment in the following order

1. If you believe you qualify as a Small Business and would like to qualify for reduced fees, submit a Small Business Qualification Certification. If you qualify, you will receive a Small Business Decision number. You must provide your Small Business Decision number on the Medical Device User Fee Cover Sheet at the time of submission to be eligible for reduced fees. FDA will not accept reduced fees without a Small Business Decision number and will not refund the difference between the standard fee and the small business fee after the submission has been received.
2. Complete the Medical Device User Fee Cover Sheet and send a completed copy with your payment.
3. Submit your PMA or PMA Supplement and include a copy of the Medical Device User Fee Cover Sheet with your submission.

### Complete the Medical Device User Fee Cover Sheet

You should complete the Medical Device User Fee Cover Sheet (Form FDA-3601) online. The Medical Device User Fee Cover Sheet and instructions are available at <http://www.fda.gov/oc/mdufma/coversheet.html>

You will need to register to create a Medical Device User Fee Cover Sheet. Please note that the User Fee Cover Sheet website was enhanced on March 1, 2005. Even if you have registered in the User Fee Cover Sheet system previously to March 1, 2005, you will need to follow the instructions as a "New User."

You will need one of the following pieces of information to complete the registration process.

Organization #:	123456
Dun and Bradstreet Number (DUNS) #	123456789
Employer Identification Number (EIN) #	123456789

Additionally, you will need to identify a Principal Point of Contact (PPOC) in your organization who will be responsible for validating users for security purposes.

After you have registered and have created a user name and password, you will receive a confirmation email. You may then access the cover sheet creation page. A unique user fee Payment Identification Number will be generated on your cover sheet upon completion. You will need three copies of your completed User Fee Cover Sheet: one copy for your payment, one copy for your PMA application, and one copy for your records.

Frequently Asked Questions addresses common questions regarding the Medical Device User Fee Cover Sheet.

### Submit Your Payment

Send a printed copy of your User Fee Cover Sheet with your payment. Be sure to include the Payment Identification Number (beginning with MD) and the FDA P.O. Box on your check, bank draft, or U.S. Postal Money Order. The review fee may be

submitted by mail, courier, or wire transfer. Send your payment to:

**By Mail:**

Food and Drug Administration  
P.O. Box 956733  
St. Louis, MO 63195-6733

**By Courier:**

If the check is sent by a courier, the courier may deliver the checks to:

US Bank  
Attn: Government Lockbox 956733  
1005 Convention Plaza  
St. Louis, MO 63101  
*(Note: This address is for courier delivery only. Contact the US Bank at (314) 418-4821 if you have any questions concerning courier delivery.)*

**By Wire Transfer:**

If using a wire transfer, you may send your payment using the following information. Please note that you are responsible for paying all wire transfer fees. FDA has found that wire transfer can delay proper crediting of your payment and may delay the start of your review.

Account Name: Food and Drug Administration  
Account Number: 152302010631  
Routing Number: 081000210  
Swift Number: USBKUS44IMT

Also include your user fee Payment Identification Number from your Medical Device User Fee Cover sheet when you send payment by wire transfer.

Note: Contact US Bank at 314-418-4821 if you have a question about how to send payment by wire transfer. Your bank or financial institution may assess a fee for sending a wire transfer.

If needed for accounting purposes, FDA's tax identification number is 53-0196965.

Fees should arrive at the bank at least 1 day before the application arrives at FDA. FDA recommends that you send the payment to the bank 4-5 business days before the application arrives at FDA so there is no delay in starting the review of your application. FDA records as the application receipt date the latter of the following:

1. The date the application was received by FDA; or
2. The date US Bank notifies FDA that payment has been received.

US Bank is required to notify FDA within 1-working day, using the Payment Identification Number.

**Qualification for Small Business Fees**

In FY 2008 (October 1, 2007 through September 30, 2008), firms with annual gross sales and revenues of \$100 million or less, including gross sales and revenues of all affiliates, partners, and parent firms, may qualify for lower rates for PMAs, premarket reports, and supplements. The fee is waived for the *first* premarket application from firms with <\$30 million gross receipts or sales .

An affiliate is defined by §737(8) of the FD&C Act: An affiliate means a business entity that has a relationship with a second business entity if, directly or indirectly,

1. one business entity controls, or has the power to control, the other business entity; or



2. a third party controls, or has power to control, both of the business entities.

To qualify, you must submit the MDUFMA Small Business Qualification Certification (Form FDA 3602). In addition, certified copies of your firm's Federal Income Tax Return for the most recent taxable year, including certified copies of the income tax returns of all affiliates, partners, and parent firms must be provided.

The following guidance and form should be used.

FY2008 MDUFMA Small Business Qualification Worksheet and Certification (Available Soon)

The Certification should be sent to:

MDUFMA Small Business Qualification (HFZ-222)  
Division of Small Manufacturers, International and Consumer Assistance  
1350 Piccard Dr.  
Rockville, MD 20850

FDA will review the Certification within 60 days and send its decision that you are, or are not, a small business eligible for reduced or waived fees. If your firm qualifies as a small business, the decision letter will include a Small Business Decision number. The Small Business Decision number is used on the Medical Device User Fee Cover Sheet (Form FDA 3601) to demonstrate that your firm is entitled to a reduced or waived fee. If you submit a reduced fee to FDA without a Small Business Decision number, the submission will not be accepted for filing.

The small business status expires at the end of each fiscal year (September 30th). A new MDUFMA Small Business Qualification Certification must be submitted each year to qualify as a small business.

Questions concerning Small Business Qualification should be directed to Division of Small Manufacturers, International and Consumer Assistance at 240-276-3150 (800-638-2041) or [dsmica@cdrh.fda.gov](mailto:dsmica@cdrh.fda.gov)

### **Guidance Documents**

[Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products](#)

[Bundling Multiple Devices or Multiple Indications in a Single Submission](#)

[User Fees and Refunds for Premarket Approval Applications](#)

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Additional information and guidance on medical device user fees is available on the [CDRH user fee website](#).

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## **Application Methods**

### **Traditional PMA**

A PMA application involves many volumes of material to be submitted to FDA. The volumes include device description and intended use, nonclinical and clinical studies, case report forms, manufacturing methods, labeling, etc. In the traditional PMA method, the complete PMA application is submitted to FDA at once. This method is generally used if the device has already undergone clinical testing and has been approved in a country with established medical device regulations. FDA has established methods of early collaboration with the sponsor allowing devices to be brought to market as early as possible. These methods

include the Modular PMA, Streamlined PMA, and Product Development Protocol and are discussed below.

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### **Modular PMA**

In a Modular PMA the complete contents of a PMA are broken down into well-delineated components (or module) and each component is submitted to FDA as soon as the applicant has completed the module, compiling a complete PMA over time. The PMA is viewed as a compilation of sections or "modules," such as preclinical, clinical, manufacturing, that together become a complete application. This method is recommended for products that are in early stages of clinical study. This method is not appropriate when the applicant is very close to being ready to submit a PMA or when the device design is in a state of flux or likely to change.

The process begins with a PMA Shell which lays out the plan for submission of the modules. The shell is an outline of modules and identifies information necessary to support the filing and approval of a specific Class III product through a combined IDE-PMA process. The review team will work with applicants to develop a customized shell for each specific product that includes module contents and suggested timelines. It is developed individually with the manufacturer for a specific device.

FDA reviews each module separately as soon as it is received allowing manufacturers to receive timely feedback during the review process. This may allow more rapid closure when the last components are submitted because much of the review work will have already been done.

Additional information on the Modular PMA process can be found in the following documents:

[Premarket Approval Application Modular Review](#)

[Premarket Approval Application Content Shell](#)

[PMA Transformation Team Home Page](#)

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### **Streamlined PMA**

The streamlined PMA is a pilot program in the Division of Clinical Laboratory Devices. A complete PMA is submitted as in a traditional PMA; however, the Streamlined PMA is for a device in which the technology and use are well known to FDA. A Streamlined PMA review may be appropriate for PMAs when there is either:

- an FDA guidance document or other published methods for review which have been evaluated by FDA, or
- an FDA review history dealing with like products (two or more of a kind)

During the protocol and PMA review, the sponsor must be available for an interactive review process. Ideally, prior to beginning studies to determine the safety and effectiveness of the product to be included in this pilot program, the sponsor would submit its protocol for FDA review. Familiarity with the product and protocol as part of this up-front evaluation should streamline the review of the PMA once filed.

Additional information can be found in the following document:

[In Vitro Diagnostic Model for a Pilot for Streamlined PMA Review](#)

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### **Product Development Protocol (§814.19)**

In the product development protocol (PDP) method for gaining marketing approval, the clinical evaluation of a device and the

development of necessary information for marketing approval are merged into one regulatory mechanism. Ideal candidates for the PDP process are those devices in which the technology is well established in industry. The PDP process provides the manufacturer with the advantage of predictability once the agreement has been reached with FDA.

The PDP allows a sponsor to come to early agreement with FDA as to what would be done to demonstrate the safety and effectiveness of a new device. Early interaction in the development cycle of a device allows a sponsor to address the concerns of the FDA before expensive and time consuming resources are expended.

The PDP is essentially a contract that describes the agreed upon details of design and development activities, the outputs of these activities, and acceptance criteria for these outputs. It establishes reporting milestones that convey important information to the FDA as it is generated, where they can be reviewed and responded to in a timely manner. The sponsor would be able to execute their PDP at their own pace, keeping FDA informed of its progress with these milestone reports. A PDP that has been declared completed by FDA is considered to have an approved PMA (§814.19).

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## Humanitarian Device Exemption (§814 Subpart H)

### Overview

An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, an humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is an humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

### Form FDA-3674, ClinicalTrials.gov Data Bank

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) included a provision that all HDE applications are required to be accompanied with certification that all applicable clinical trial information has been submitted to the ClinicalTrials.gov data bank.

Beginning December 26, 2007, HDE applications must include form FDA-3674. If your HDE includes data from a clinical trial, you must determine if your study is applicable for entry into the clinical trial registry data bank at ClinicalTrials.gov. Based on this determination, check box 9.B. or 9.C., and complete the applicable sections of the form. An applicable device clinical trial is a prospective clinical study of health outcomes comparing an intervention with a device against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes). See [Title VIII - Clinical Trial Databases](#). Currently, FDA is reviewing the legislation and developing guidance on which clinical trials meet the definition of "applicable" trials and are required to report to ClinicalTrials.gov. Until FDA issues this guidance, the HDE sponsor is responsible for determining whether its studies meet the definition of an applicable trial and, therefore, are subject to reporting requirements.

Information on how to register your clinical trial(s) in the ClinicalTrials.gov data bank is available on the National Library of

[Medicine \(NLM\) Protocol Registration System \(PRS\) website.](#)

Additional information on HUDs can be found in the following documents.

[Humanitarian Use Program Information](#) (includes a list of approved HDEs)

[Humanitarian Devices Exemptions \(HDE\) Regulation Questions: and Answers](#)

[Humanitarian Devices Exemptions \(HDE\) Checklist for Filing Decision](#)

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## Application Contents

**\*NEW\***

Certification of Compliance with [ClinicalTrials.gov Data Bank, FDA-3674\\*](#)

\*Beginning December 26, 2007, all PMA applications must include a completed copy of form FDA-3674. See [Form FDA-3674, ClinicalTrials.gov Data Bank](#) for additional information.

### Required Elements (§814.20)

There is no preprinted form for a PMA Application. Unless an omission is justified by the applicant [§814.20(d)], a PMA must include all of the following:

1. The name and address of the applicant.
2. A table of contents that specifies the volume and page number for each item referred to in the table.
  - o The PMA must include separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects.
  - o Six copies of the PMA are required, each bound in one or more numbered volumes of reasonable size. To facilitate review by the advisory committee(s), additional copies may be requested by FDA.
  - o Trade secret or confidential commercial or financial information must be included in all copies of the PMA. The applicant must identify in at least one copy any information that they believe to be trade secret or confidential commercial or financial information.
3. A summary section in sufficient detail to provide a general understanding of the data and information in the application. Tip: The summary section should contain brief statements of major points found elsewhere in the PMA and should be approximately 10 to 15 pages in length.

The summary section must contain the following information:

**Indications for use.** Give a general description of the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate and include a description of the patient population for which the device is intended.

**Device description.** Explain how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device. A brief description of the manufacturing process should be included if it will significantly enhance the reader's understanding of the device. The generic name of the device as well as any proprietary name or trade name should be included.

Alternative practices and procedures. Describe any alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended.

Tip: Include a statement such as "other commercially available devices" if similar class III products are available. Do not include any treatment practices or procedures that are considered investigational.

Marketing history. Give a brief description of the foreign and U.S. marketing history, if any, of the device known to the applicant. At a minimum, include a list of all countries in which the device has been marketed and a list of all countries in which the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

Tip: It would be appropriate to include dates of introduction into each country, information about the quantity of product distributed in each country, a brief description of any experience reporting mechanism, a summary of any adverse experiences reported, and information about any withdrawals for any reason related to the safety or effectiveness. Withdrawals because of poor sales or physician disfavor should not be included. A U.S. marketing history may occur if the device is marketed under 510(k) for a different intended use. The description must include the history of the marketing of the device by the applicant and, if known, the history of the marketing of the device by any other person.

Summary of studies. This section must contain a summary of the results of technical data (nonclinical and clinical studies) under §814.20(b)(6) and an abstract of any other data, information, or report described in the PMA under §814.20(b)(8) (ii). The summary must include a description of the objective of each study, a description of the experimental design of the study (or hypothesis tested), a brief discussion of how the data were collected and analyzed, and a brief description of the findings and conclusions, whether positive, negative or inconclusive.

The summary must include a summary of nonclinical laboratory studies submitted in the application and a summary of the clinical investigations involving human subjects. The summary of the clinical investigations should include a discussion of subject selection and exclusion criteria, study population demographics, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, device failures and replacements, tabulations of data from all individual subject reporting forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information from the clinical investigations, as appropriate. Any investigation conducted under an IDE must be identified.

Conclusions drawn from the studies. Discuss how the data and information in the application constitute valid scientific evidence within the meaning of 21 CFR 860.7, Determination of Safety and Effectiveness, and provide reasonable assurance that the device is safe and effective for its intended use. A concluding discussion must present benefit and risk considerations related to the device, including a discussion of any adverse effects of the device on health, and any proposed additional studies or surveillance that the applicant intends to conduct following approval of the PMA.

Tip: The applicant's summary section should objectively link the medical claim(s) for the device to the hypotheses tested and conclusions drawn from the findings of all studies and investigations. Biased presentation of the study data and inclusion of promotional claims are to be avoided. When preparing the summary section, the applicant should be able to detect and correct any accountability discrepancies, incomplete reporting and study design deficiencies which an in-depth scientific review would discover. A properly developed summary section by the applicant can serve as the basis for FDA's Summary of Safety and Effectiveness Data and will facilitate the FDA and panel review process. A full and explicit account of the clinical investigations and supporting data is needed to meet the legal requirements imposed by the FD&C Act. For a more detailed discussion of how to design, document, and present a clinical investigation to demonstrate safety and effectiveness, see "Statistical Guidance for Clinical Trials for Non-diagnostic Medical Devices".

4. A complete description of:

- the device, including pictorial representations;
- each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;
- the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;
- the principles of operation of the device; and
- the methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device in sufficient detail so that a person generally familiar with current good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

Additional guidance on manufacturing information to include in the PMA application can be found in "Quality System Information for Certain Premarket Application Reviews" <http://www.fda.gov/cdrh/comp/guidance/1140.html>

Tip: If complete manufacturing information is not available at the time the PMA is submitted, its temporary omission may be justified as provided in 21 CFR 814.20(d). Refer to Item 31 in the preamble to the PMA regulation for further information.

5. Reference to any performance standard or voluntary standard.

Performance standard refers to those promulgated under Part 514 of the FD&C Act or the Radiation Control for Health and Safety Act of 1968 (RCHSA) in effect or proposed at the time of the PMA submission. At this time the performance standard for electrode lead wires and patient cables under 21 CFR 898 is the only performance standard established for medical devices. Performance standards established under RCHSA can be found in 21 CFR Parts 1000 through 1050. Access to RCHSA performance standards is available on the Internet at <http://www.fda.gov/cdrh/comp/eprc.html>

A voluntary standard refers to one that is specifically applicable to any aspect of the safety or effectiveness of the device and developed in accordance with the FDA policy statement on standards development published in the *Federal Register* of October 23, 1985 (50 FR 43081). FDA recognized many voluntary standards. Guidance on the recognition and use of consensus standards as well as a database of FDA recognized consensus standards can be found on the Internet at <http://www.fda.gov/cdrh/stdsprog.html>.

The applicant must provide adequate information to demonstrate how the device meets, or justify any deviation from, any of the mandatory performance standards noted above and explain any deviation from a voluntary standard.

6. Technical sections containing data and information in sufficient detail to permit FDA to determine whether to approve or deny the application.

These sections and their contents are as follows:

Results of nonclinical laboratory studies – This section should contain the results of the nonclinical laboratory studies with the device including the microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests, as appropriate. Information on nonclinical laboratory studies shall include a statement that each study was conducted in compliance with 21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies. If the study was not conducted in compliance with this regulations, provide a brief statement of the reason for the noncompliance.

Results of clinical investigations involving human subjects – This section should include clinical protocols, number of investigators and subjects per investigator, a discussion of subject selection and exclusion criteria, study population demographics, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject reporting forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information from the clinical investigations, as appropriate. The analysis and discussion should address the impact, if any, on the safety and effectiveness measures. Additional information such as an analysis and discussion of any potential biases related to gender, race/ethnicity, etc. should be included. Any differences in safety and/or effectiveness should be described in the labeling.

Information on clinical studies involving human subjects shall include the following statements with respect to each study:

- o that it either was conducted in compliance with the Institutional Review Board regulations under 21 CFR 56 or was not subject to the regulations under 21 CFR 56.104 or 21 CFR 56.105,
- o that it was conducted in compliance with the Informed Consent regulation under 21 CFR 50, and
- o that it was conducted in compliance with Investigational Device Exemptions regulations under 21 CFR 812 concerning sponsors of clinical investigations and clinical investigators.

If the study was not conducted in compliance with these regulations, include a brief statement of the reason for the noncompliance.

7. For a PMA supported solely by data from one investigator, a justification showing why data and other information from a single investigator is sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.
8. A bibliography of all published reports not already submitted under §814.20(b)(6), whether adverse or supportive, that are known to or should reasonably be known to the applicant and that concern the safety or effectiveness of the device. Applicants should consider providing a copy of all of the key articles, a brief summarization of the salient features of the article, and a brief discussion of how the article relates to the safety and effectiveness evaluation for their device.

An identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device that are known to or should reasonably be known to the applicant from any source, foreign or domestic. This includes information from investigations other than those proposed in the application and from commercial marketing experience.

Copies of such published reports or unpublished information in the possession of, or reasonably obtainable by, the applicant, if an FDA advisory committee or FDA requests.

9. One or more samples of the device and its components, if requested by FDA. If it is impractical to submit a requested sample of the device, the applicant should name the location at which FDA may examine and test one or more devices.
10. Copies of all proposed labeling for the device. Such labeling may include, for example, instructions for installation and any information, literature, or advertising that constitutes labeling under Part 201(m) of the FD&C Act. Note: Any advertising devised by applicant that does not constitute labeling would not be required to be submitted and reviewed prior to approval of the PMA.
11. 21 CFR 814.20(b)(11) states that an environmental assessment in accordance with 21 CFR 25 must be included in the PMA application. Please note that PMAs do not ordinarily require an environmental assessment (EA) or environmental impact statements (EIS) if the device is of the same type and for the same use as a previously approved device [§25.34 (d)]. A statement requesting a categorical exclusion from EA or EIS is no longer required to be submitted in the PMA application. Please contact the PMA Staff at 301-594-2186 if you believe an environmental assessment is necessary for your device. See "Environmental Impact Considerations" for additional guidance.  
[http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127\\_59655](http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127_59655)
12. A financial certification or disclosure statement or both as required by 21 CFR 54. See <http://www.fda.gov/cdrh/devadvice/ide/financial.shtml> for information on financial disclosure.
13. Such other information as FDA may request. If necessary, FDA will obtain the concurrence of the appropriate FDA advisory committee before requesting additional information.

**Other information.** Pertinent information already in FDA files and specifically referred to by an applicant may be incorporated into a PMA by reference. Information in a master file (see "Master Files" [http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7\\_2](http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2)) or other information submitted to FDA by a person other than the applicant will not be considered part of a PMA, unless such reference is authorized in writing by the person who submitted the information or the master file.

**Omissions.** If an applicant believes that certain required information under §814.20(b) is not applicable to the device and omits any such information from their PMA, the applicant must submit a statement that identifies the omitted information and justifies the omission. The statement must be submitted as a separate section in the PMA and identified in the table of contents. If FDA does not accept the justification for the omission, FDA will notify the applicant.

**Tip:** An applicant may request a waiver for the manufacturing information to be submitted later in the application process. Any delayed submission of the manufacturing information may cause a delay in the Quality System inspection process.

**Updates.** An applicant must periodically update its pending application with any new safety and effectiveness information learned about the device from ongoing or completed studies that may affect an evaluation of the safety and effectiveness of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The updated report must be consistent with the data-reporting provisions of the protocol. The applicant must submit three copies of any updated report and must include in the report the PMA number assigned by FDA. These updates are considered to be amendments to the pending PMA. The timeframe for review of a PMA will **not** be extended due to the submission of an update report unless the update is a major amendment [§814.37(c)(1)]. An applicant must submit these reports three months after the filing date, following receipt of an approvable letter, and at any other time as requested by FDA. Note: This periodic updating is limited to studies sponsored by the applicant or to which the applicant has reasonable access.

**Color additive.** A color additive used in or on the device is subject to Part 721 of the FD&C Act and must be listed for such use by FDA. If the color additive has not previously been listed by FDA for such use, an applicant may request FDA to list the color additive by submitting a color additive petition under 21 CFR 71 to the Center for Food Safety and Applied Nutrition (CFSAN). Alternatively, the request may be submitted to CDRH as part of the PMA. If the request is submitted in the PMA, three copies of the color additive petition information must be included, each bound in one or more numbered volumes of reasonable size. A PMA for a device that contains a color additive that is subject to Part 721 of the FD&C Act will not be approved until a color additive is listed by FDA for use in or on the device. See "Color Additives for Medical Devices" [http://www.fda.gov/cdrh/dsma/pmaman/appdxe.html#P7\\_2](http://www.fda.gov/cdrh/dsma/pmaman/appdxe.html#P7_2) for further information.

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### **Premarket Submissions Coversheet**

The completion of this Premarket Submission Coversheet is voluntary and will not affect any Food and Drug Administration (FDA) decision concerning your submission, but will help FDA's Center for Devices and Radiological Health process your submission more efficiently by placing administrative data elements in a consistent format for data entry purposes. The coversheet was developed to reduce the number of administrative deficiencies common in many submissions.

The information provided should apply only to a single accompanying submission; please do not send cover sheets for any previous submissions. When submitting an amendment or supplement, identify the document number and type of submission, and then complete only the information which has changed since your most recent cover sheet relating to the same submission. The coversheet should be used only for submissions that are referenced in the coversheet.

Premarket Submissions Coversheet

<http://www.fda.gov/cdrh/manual/precovsh.html>

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### **Cover Letters**

An applicant's cover letter should accurately identify the type of PMA submission, i.e., an original PMA, PMA supplement, PMA amendment to a pending PMA or PMA supplement, periodic report, etc. and include information needed for FDA tracking purposes. To expedite its processing, the following suggestions and formats have been prepared.

#### General Suggestions

- Use the applicant's letterhead or that of the applicant's authorized representative.
- Address the cover letter as indicated under "Original PMA Cover Letter" below. To minimize misrouting, do not include an FDA staff member's name in the address.
- If submitted by someone other than the applicant (e.g., lawyer or consultant), the identity of the applicant must be included.
- For an original PMA, specify the indication for use for which FDA approval is requested.
- If applicable, include the reference numbers for any premarket notification, investigational device exemption, reclassification petition, or color additive petition submitted by the applicant.
- Indicate whether the submission includes an environmental assessment.
- Date and sign the cover letter and include a copy in the first volume of each copy of the PMA submission.

#### Suggested Formats



The full format of the cover letter for an original PMA appears below. For other types of PMA submissions, only the subject section and opening sentence(s) are provided. In several instances, alternative opening statements are included to address specific situations.

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*Original PMA Cover Letter*

*[Date]*

Document Mail Center (HFZ-401)

Center for Devices and Radiological Health

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

SUBJECT: Original PMA for *[device trade name and model number if applicable]*

To Whom It May Concern:

*[Applicant's name]* is submitting this original premarket approval application for the *[device trade name]*, *[device generic name]* intended for use in *[indication for use]*.

Clinical studies of the above device were initiated on *[date]* and *[were/were not]* conducted under an approved investigational device exemption *[give IDE number if a significant risk device]*. [If applicable, include the FDA reference number for any premarket notification, reclassification petition, or color additive petition submitted for this device].

[Include a paragraph providing the name and address of each facility involved in the manufacture of the device and indicate whether the facility is prepared for an FDA inspection. If not prepared, provide an expected date when the facility will be ready for inspection. If a waiver of the QS information is requested, provide an anticipated date that the information will be provided.]

*If another document is incorporated by reference, e.g., a master file, please include the original letter of authorization as an attachment to this cover letter.*

The existence of this PMA and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed. [Tip: confidentiality claims cannot be made unless the applicant has complied with the applicable requirements.

If there are questions regarding this submission, *[name]* may be contacted at *[give telephone number including area code]*.

Sincerely yours,

[signature]

*[Name and title of applicant's representative]*

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Amendment to Original PMA

SUBJECT: Amendment to [original PMA or PMA supplement reference number] for [device trade name]

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Unsolicited submission of additional information

[Applicant's name] is submitting this amendment to its [premarket approval application] [original PMA reference number] for the [device trade name] to provide [identify the additional information being provided].

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**Suggested Format and Address**

In order to facilitate FDA's handling of PMA applications, the following recommendations are offered:

- Use paper with nominal dimensions of 8 ½" by 11".
- Use at least a 1 ½ " wide left margin to allow for binding into jackets.
- Use 3-hole punched paper to allow for binding into jackets.
- If the submission exceeds 2" in thickness, separate into volumes and identify volume number.
- Clearly and prominently identify submission as original PMA application or, for additional submissions to a PMA application, clearly identify the FDA assigned document number (e.g., P960000) and the type of submission (e.g., amendment, supplement or report) or response (e.g., response to an FDA letter dated \_\_\_\_\_).
- All copies of each submission must be identical.
- Sequentially number the pages, providing a detailed table of contents, and use tabs to identify each section. This will help to facilitate the review of your submission.
- All copies of the first volume of each submission must include a signed and dated cover letter.
- Do not combine PMAs, IDEs, and 510(k)s together. They must be separate submissions.
- Only the PMA applicant on record with FDA may amend, supplement, or submit reports to their PMA, unless the PMA includes the original and not a copy of an appropriate letter of authorization from the applicant permitting another person to submit information on the applicant's behalf. If the information on the applicant's company name or designated submitter information changes, please notify FDA in the form of an amendment to the PMA or PMA Supplement.

The following information should be submitted in separate volumes:

- Manufacturing Information. (five copies)
- Environmental Assessment, if applicable. (three copies)
- Color Additives, if applicable. (six copies)
- Individual Subject Report Forms.

A PMA or PMA supplement, if applicable, is required by §814.20(b)(6)(ii) to include copies of individual subject report forms for each subject who died during a clinical investigation or who did not complete the investigation. Before submitting the PMA, the applicant should consult with the ODE reviewing division to determine the information to be included in these report forms, how many copies are required, and whether these report forms will be required for other subjects enrolled in the study (e.g., subjects experiencing specified adverse effects or complications).

A PMA must be signed by the applicant or an authorized U.S. representative. If the applicant does not reside or have a place of business within the U.S., the PMA must be countersigned by an authorized representative who does. The applicant must also provide the representative's name and address.

Send 6 copies of an original PMA, clearly identified as such, to:

Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, MD 20850

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## **Summary of Safety and Effectiveness Data (§814.44)**

### Overview

The FD&C Act requires that FDA prepare a detailed summary of the safety and effectiveness data on which the approval or denial decision is based.

### Authority

The Summary of Safety and Effectiveness Data (SSED) is a document mandated by 520(h)(1)(A) of the FD&C Act (the act). It is to be publicly available upon issuance of an order approving or denying approval of a premarket approval application (PMA).

### When required

Approval/denial decisions for original PMA applications must include an SSED. An SSED is also prepared for submissions designated by CDRH as panel-track supplements. An abbreviated SSED is required for approval of a PMA based on a licensing agreement. The abbreviated SSED is acceptable because the scientific data on which the PMA relies were previously described in the SSED for the application which is being licensed.

### Purpose

The SSED is an FDA document (originally submitted by the applicant and modified by FDA) which is intended to present a reasoned, objective, and balanced critique of the scientific evidence which served as the basis of the decision to approve or deny the PMA. The SSED documents that there was reasonable assurance of safety and effectiveness for the device as labeled based on the nonclinical and clinical studies described in the PMA. The SSED is a summation of both the positive and negative aspects of the PMA. the scientific evidence. For a PMA to be approved, potential risks versus possible benefits assessment must favor this action. The SSED summarizes these judgments.

### SSED preparation

Initially FDA intended drafting the publicly releasable SSED, which is based on the SSED the applicant is required to submit under 21 CFR 814.20. If FDA must substantially rewrite the applicant's SSED, FDA will often go back to the applicant and request that they make another attempt at writing the publicly releasable SSED. Unfortunately, the applicant SSED too often differs from FDA's objective, i.e., it contains only the positive aspects of the device, it contains marketing language, etc. Consequently, an edit-rewrite exercise often results. Since minor variations in SSED formats are possible, it is best to consult previously released SSEDs (preferably recent ones for similar devices) for guidance. Since the SSED deals with scientific/technical data and will be read by many non-professionals, it is best to keep the format clear by grouping study

objective(s), study methods, results, interpretation(s), and conclusion(s) for each study or substudy. An overall statement/conclusion integrating the individual study outcomes in the light of safety and effectiveness and risk versus benefits and your conclusions can then be written.

#### Level of comprehension

The SSED should be written for the comprehension of a college graduate, but not necessarily a science graduate or professional in the device specific area. Medical and scientific terms should be used whenever needed, but it is preferred that simpler, generally recognized terminology be used (provided it can be used without suffering loss of meaning).

#### Format for Summary of Safety and Effectiveness Data

The following is the format of the summary of safety and effectiveness data prepared by FDA. PMA applicants can facilitate this step of the PMA process by following this format in preparing the summary of safety and effectiveness data required under §814.20(b)(3).

##### I. General Information

Device generic name  
Device trade name  
Applicant's name and address  
PMA number\*  
Date of Panel recommendation\*  
Date of notice of approval to the applicant\*

(\*to be completed by FDA unless known to the applicant)

##### II. Indications for Use

##### III. Device Description

##### IV. Contraindications, Warnings, and Precautions

##### V. Alternative Practices and Procedures

##### VI. Marketing History

##### VII. Potential Adverse Effects of the Device on Health

Tip: Include any information concerning actual or potential adverse effects that the device may have on health (e.g. if an implanted device, discuss the fate of the device in the body)

##### VIII. Summary of Preclinical Studies

Laboratory studies  
Animal studies  
Additional studies

##### IX. Summary of Clinical Studies

Study design  
Patient assessment  
Demographic data  
Data analysis and result  
Device failures and replacements

##### X. Conclusions Drawn from the Studies

Risk/benefit analysis  
Safety  
Effectiveness

- XI. Panel Recommendations (To be completed by FDA)
- XII. CDRH Decision (To be completed by FDA)
- XIII. Approval Specifications (To be completed by FDA)

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### **Statistical Checklist**

The PMA Review Statistical Checklist lists the required elements of the statistical aspects of the PMA submission. This list is used to screen all PMA applications before in-depth review by the Division of Biostatistics. The absence of any of these elements may be sufficient to reject an in-depth statistical review. It is essential, therefore, that the applicant check to determine that the statistical reports in the submission are complete. Additional guidance on statistical evaluation of medical devices can be found in "Statistical Aspects of Submissions to FDA: A Medical Device Perspective."

<http://www.fda.gov/cdrh/osb/guidance/fod537.pdf> (This guidance also includes "Observed Uses and Abuses of Statistical Procedures in Medical Device Submissions.")

PMA Review Statistical Checklist  
<http://www.fda.gov/cdrh/ode/84.pdf>

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### **PMA Review Checklist**

The checklist referenced below is used by PMA reviewers to determine the completeness of a PMA and is a part of the Blue Book Memo, PMA Refuse to File Procedures 5/2/94 (P94-1). PMA applicants may also wish to use the checklist to assure the completeness of the application.

Premarket Approval Application Filing Review  
<http://www.fda.gov/cdrh/ode/guidance/297.html>

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### **References**

[21 CFR 814.20](#)  
[21 CFR 820](#)

Premarket Approval Application Filing Review  
<http://www.fda.gov/cdrh/ode/guidance/297.html>

Quality System Information for Certain Premarket Application Reviews  
<http://www.fda.gov/cdrh/comp/guidance/1140.html>

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices  
<http://www.fda.gov/cdrh/ode/57.html>  
<http://www.fda.gov/cdrh/ode/software.pdf>

Off-The-Shelf Software Use in Medical Devices  
<http://www.fda.gov/cdrh/ode/guidance/585.html>  
<http://www.fda.gov/cdrh/ode/software.pdf>

Statistical Aspects of Submissions to FDA: A Medical Device Perspective (also includes as Appendix the article Observed Uses and Abuses of Statistical Procedures in Medical Device Submissions  
<http://www.fda.gov/cdrh/osb/guidance/fod537.pdf>

PMA Review Statistical Checklist

<http://www.fda.gov/cdrh/ode/84.pdf>

Master Files

[http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7\\_2](http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2)

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## Quality System

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### Design Controls (§ 820.30)

All manufacturers (including specification developers) of Class II and III devices and select Class I devices are required to follow design controls [§820.30] during the development of their device. The design control requirements are basic controls needed to ensure that the device being designed will perform as intended when produced for commercial distribution.

The manufacturer (including specification developer) must establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met [820.30(a)]. Design controls include establishing and maintaining plans that describe the design and development activities and also define responsibility for implementation [820.30(b)]. The plans must identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process [820.30(b)]. The design process also includes:

- Conducting a risk analysis [820.30(g)];
- Identifying design input or requirements for the device [820.30(c)];
- developing the design output or specifications for the device [820.30(d)];
- verifying that the design output meets the design input [820.30(f)];
- holding design reviews at appropriate points during the design process to identify significant problems with the design or the design process [820.30(e)];
- validating that the design meets defined user needs and intended uses [820.30(g)];
- validating any software used in the device [820.30(g)];
- transferring the device design to production specifications [820.30(h)];
- controlling changes to the design during the design process and changes in the design of products on the market [820.30(i)]; and
- documenting design control activities in the design history file [820.30(j)].

*PMA submissions should include a complete description of design controls that the manufacturer implements to comply with the QS regulation. If this information is lacking, FDA cannot complete the premarket review process.*

The manufacturer must have procedures in place and must maintain documentation in the design history file to demonstrate compliance with the design control requirements of §820.30 and completion of the activities identified in the design plan. The design history file must be made available for FDA inspection. FDA will evaluate the adequacy of manufacturers' compliance with design control requirements in pre-approval inspections for Class III devices and also during routine quality systems inspections for all classes of devices subject to design control.

The following documents provide additional guidance on the design control requirements under the Quality System regulation.

Design Control Guidance for Manufacturers  
<http://www.fda.gov/cdrh/comp/designgd.html>

Do It by Design  
<http://www.fda.gov/cdrh/humfac/doi.html>

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### **Manufacturing Controls [§814.20(b)(4) and §820]**

The PMA submission must include a complete description of the methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and where appropriate, installation of the device. The description must include sufficient detail that a person generally familiar with the Quality System/Good Manufacturing Practice requirements can make a knowledgeable judgment about the quality control used in the manufacturing of the device.

Device manufacturers include not only facilities that manufacture or assemble the finished device but also facilities operated or contracted by the PMA applicant to perform a segment of the manufacturing operation such as sterilization or packaging. Contracted facilities may either provide the required manufacturing information applicable to their operation directly to the PMA applicant for inclusion in the PMA submission or submit such information directly to FDA in a Device Master File. The PMA applicant should provide written authorization to reference the Device Master File information in the PMA submission.

While the Office of Device Evaluation (ODE) reviews an original PMA or a PMA supplement requesting approval for an alternate or additional manufacturing facility, the Office of Compliance (OC) will review the Quality System design and manufacturing information in the PMA submission. OC will determine whether the manufacturer has described the processes in sufficient detail and make a preliminary determination of whether the manufacturer meets the QS requirements. If the manufacturer has provided an adequate description of the design and manufacturing process, a preapproval inspection can be initiated.

FDA has prepared a guidance document to assist manufacturers in preparing and maintaining manufacturing information required in PMA and PMA supplements.

The guidance and 21 CFR 820, the Quality System Regulation, is intended to ensure that the manufacturing section in the PMA complies with the content requirements under §814.20(b)(4) and is sufficiently complete and appropriately organized for review.

The following document provides guidance for the preparation of quality system design and manufacturing information to be included in the PMA.

Quality System Information for Certain Premarket Application Reviews  
<http://www.fda.gov/cdrh/comp/guidance/1140.html>  
<http://www.fda.gov/cdrh/comp/guidance/1140.pdf>

Process validation is a key requirement of the Quality System Regulation and will be reviewed during the facility inspection process. The following guidance documents provide guidance on performing process validations.

Guideline on General Principles of Process Validation  
<http://www.fda.gov/cdrh/ode/425.pdf>

Process Validation Guidance for Medical Device Manufacturers, Global Harmonization Task Force  
<http://www.ghtf.org/sg3/inventorysg3/sg3-n99-10.pdf>  
<http://www.ghtf.org/sg3/inventorysg3/sg3-n99-10.doc>

Please note that the GHTF guidance is intended for use by manufacturers worldwide who must comply with other regulatory systems in as well as the U.S.'s system. The guidance provides an option described on page XX that is not available to manufacturers distributing devices in the U.S. That option is to neither validate nor fully verify a low-risk manufacturing process, but to accept the risk. We repeat, neither validating nor fully verifying a low risk process is not an option for manufacturers who distribute devices in the U.S. The Quality System Regulation requires that manufacturing processes be validated if they cannot be fully verified.

Additional guidance on the Quality System regulation can be found on the Internet at

<http://www.fda.gov/cdrh/comp/gmp.html>

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### **Preapproval Inspection**

In making the determination of the firm's ability to design, manufacture or process the device, the Office of Compliance (OC) may issue an inspection assignment to the appropriate FDA district office. The inspection assignment will be issued when OC has determined that the manufacturer has demonstrated in the PMA submission that the design and manufacturing process meets the QS regulation requirements and the facility is ready for inspection.

Inspection will include an assessment of the firm's capability to design and manufacture the device as claimed in the PMA and confirm that the firm's Quality System is in compliance with 21 CFR 820, Quality System Regulation. The inspectional process considers the extent to which the firm has established a formal QS program and has assured that the approved design is properly translated into specifications via process validation. The inspection will follow guidance outlined in Medical Device Premarket Approval Inspections, C.P. 7383.001, and Inspections of Medical Device Manufacturers, C.P. 7382.845. For a copy of C.P. 7383.001, email DSMICA at [dsmica@cdrh.fda.gov](mailto:dsmica@cdrh.fda.gov).

PMA Compliance Program #P91-3 (blue book memo)  
<http://www.fda.gov/cdrh/p91-3.html>

Inspections of Medical Device Manufacturers, C.P. 7382.845  
<http://www.fda.gov/ora/cpdm/default.htm#devices>

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### **Postapproval Inspections**

Postapproval inspections are conducted within eight to twelve months of approval of the PMA submission. The inspection will primarily focus on any changes that may have been made in the device design, manufacturing process, or quality systems. Inspections are conducted in accordance with Inspections of Medical Device Manufacturers, C.P. 7382.845.  
<http://www.fda.gov/ora/cpdm/default.htm#devices>

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## **Labeling**

Copies of all proposed labeling for the device must be included in the PMA submission. The labeling must comply with the requirements in 21 CFR 801 (Labeling) or 21 CFR 809 (In Vitro Diagnostic Products for Human Use). That is, the label must include the common name of the device, quantity of contents, and the name and address of the manufacturer. In addition, labeling may include prescription use restrictions, information for use (including indications, effects, routes, methods, and frequency and duration of administration; and any relevant hazards, contraindications, side effects, and precautions), instructions for installation and operation, and any information, literature, or advertising that constitutes labeling under Part 201 (m) of the FD&C Act.

The indications for use is based on the nonclinical and clinical studies described in the PMA. Indications for use for a device include a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. Any differences related to gender, race/ethnicity, etc. should be included in the labeling.

During the review process, FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final labeling. Approval will be based on the condition that the applicant incorporates the specified labeling changes exactly as directed and submits to FDA a copy of the final printed labeling before marketing.



Additional guidance on labeling can be found in the following guidance documents. The guidance documents are organized in the following categories: PMA Labeling Guidance; General Labeling Guidance; and In Vitro Diagnostic Device Labeling Guidance.

### PMA Labeling Guidance

Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #G96-3)  
<http://www.fda.gov/cdrh/g963.html>

Review of Final Draft Medical Device Labeling (Blue Book Memo #P91-4)  
<http://www.fda.gov/cdrh/p91-4.html>

### General Labeling Guidance

Alternative to Certain Prescription Device Labeling Requirements  
<http://www.fda.gov/cdrh/comp/rxlabeling.html>  
<http://www.fda.gov/cdrh/comp/rxlabeling.pdf>

Device Advice - Labeling Requirements  
<http://www.fda.gov/cdrh/devadvice/33.html>

Device Labeling Guidance #G91-1 (blue book memo)  
<http://www.fda.gov/cdrh/g91-1.html>

Draft Report on Medical Device Labeling: Patients` and Lay Caregivers` Medical Device Information and Labeling Needs - Results of Qualitative Research  
<http://www.fda.gov/cdrh/humfac/humfaclabel.pdf>

Electronic Labeling: Section 206 of the Medical Device User Fee and Modernization Act (MDUFMA) (New section 502(f) of the Federal Food, Drug, and Cosmetic Act) Electronic Labeling for Prescription Devices Intended for Use in Health Care Facilities - #G03-1  
<http://www.fda.gov/cdrh/mdufma/bluebook/g03-1.html>  
<http://www.fda.gov/cdrh/mdufma/bluebook/g03-1.pdf>

Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers  
<http://www.fda.gov/cdrh/ohip/guidance/1128.html>  
<http://www.fda.gov/cdrh/ohip/guidance/1128.pdf>

Human Factors Principles for Medical Device Labeling  
<http://www.fda.gov/cdrh/dsma/227.html>

Labeling - Regulatory Requirements for Medical Devices (FDA 89-4203)  
<http://www.fda.gov/cdrh/dsma/470.pdf>

RX Labeling: Alternative to Certain Prescription Device Labeling Requirements  
<http://www.fda.gov/cdrh/comp/rxlabeling.html>  
<http://www.fda.gov/cdrh/comp/rxlabeling.pdf>

Write it Right  
<http://www.fda.gov/cdrh/dsma/897.pdf>

### In Vitro Diagnostic Device Labeling Guidance

Guidance on Labeling for Laboratory Tests; Draft  
<http://www.fda.gov/cdrh/ode/1352.html>  
<http://www.fda.gov/cdrh/ode/1352.pdf>

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## Clinical Studies

- [Investigational Device Exemption \(§812\)](#)
- [Research conducted outside the United States \(§814.15\)](#)
- [Determination of Safety and Effectiveness \(§860.7\)](#)
- [Data Analysis](#)
- [Bioresearch Monitoring](#)
- [Form FDA-3674, ClinicalTrials.gov Data Bank](#)

### Investigational Device Exemption (§812)

Clinical studies on human subjects that is conducted within the United States and U.S. territories must comply with Good Clinical Practices regulations. These regulations include Investigation Device Exemption (IDE) under 21 CFR 812, Protection of Human Subjects under 21 CFR 50, and Institutional Review Boards under 21 CFR 56. Guidance on these requirements can be found on the CDRH website at <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>

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### Research conducted outside the United States (§814.15)

A study conducted under an investigational device exemption (IDE) outside the United States and submitted in support of a PMA must comply with the IDE regulation (21 CFR 812). A study conducted outside the U.S. which was not conducted under an IDE must comply with one of the following:

- Research begun on or after effective date November 19, 1986: FDA will accept studies which have been conducted outside the U.S. and begun on or after November 19, 1986, if the data constitute valid scientific evidence (§860.7) and the investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research was conducted, whichever offers greater protection to the human subjects. If the standards of the country are used, the applicant must state in detail any differences between those standards and the Declaration of Helsinki and explain why the national standards offer greater protection to the human subjects.
- Research begun before effective date November 19, 1986: FDA will accept studies which have been conducted outside the U.S. and begun before November 19, 1986, if the agency is satisfied that the data constitute valid scientific evidence (§860.7) and that the rights, safety, and welfare of human subjects have not been violated.

A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

- the foreign data are applicable to the U.S. population and medical practice;
- the studies have been performed by clinical investigators of recognized competence; and
- the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

Applicants who seek approval based solely on foreign data are encouraged to meet with FDA officials in a presubmission meeting.

Additional guidance on FDA policy regarding the acceptance of foreign clinical data can be found in the following documents.

Acceptance of Foreign Clinical Studies; Guidance for Industry

<http://www.fda.gov/cder/guidance/fstud.htm>

<http://www.fda.gov/cder/guidance/fstud.pdf>

Declaration of Helsinki

<http://www.fda.gov/oc/health/helsinki89.html>

(World Medical Association's recommendations to every physician in biomedical research involving human subjects)

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## **Determination of Safety and Effectiveness (§860.7)**

### Relevant Factors

In determining the safety and effectiveness of a device for Premarket Approval of class III devices, FDA will consider the following, among other relevant factors:

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

### Valid Scientific Evidence

Although the manufacturer may submit any form of evidence to the FDA in an attempt to substantiate the safety and effectiveness of a device, the FDA relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in §860.7, FDA will determine whether the evidence submitted or otherwise available to the FDA is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.

Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

### Safety

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using laboratory animals, investigations involving human subjects, and nonclinical investigations including in vitro studies.

### Effectiveness

There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in

a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations.

#### Well-Controlled Clinical Investigation

The following principles are recognized by the scientific community as the essentials of a well-controlled clinical investigation. They provide the basis for FDA's determination whether there is reasonable assurance that a device is effective based upon well-controlled investigations and are also useful in assessing the weight to be given to other valid scientific evidence.

The plan or protocol for the study and the report of the results of a well-controlled investigation shall include the following:

1. A clear statement of the objectives of the study;
2. A method of selection of the subjects that:
  - a. Provides adequate assurance that the subjects are suitable for the purposes of the study, provides diagnostic criteria of the condition to be treated or diagnosed, provides confirmatory laboratory tests where appropriate and, in the case of a device to prevent a disease or condition, provides evidence of susceptibility and exposure to the condition against which prophylaxis is desired;
  - b. Assigns the subjects to test groups, if used, in such a way as to minimize any possible bias;
  - c. Assures comparability between test groups and any control groups of pertinent variables such as sex, severity or duration of the disease, and use of therapy other than the test device;
3. An explanation of the methods of observation and recording of results utilized, including the variables measured, quantitation, assessment of any subject's response, and steps taken to minimize any possible bias of subjects and observers;
4. A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be specified and an explanation provided of the methods employed to minimize any possible bias of the observers and analysts of the data. Level and methods of "blinding," if appropriate and used, are to be documented. Generally, four types of comparisons are recognized:
  - a. No treatments.

Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients;

- b. Placebo control.

Where there may be a placebo effect with the use of a device, comparison of the results of use of the device with an ineffective device used under conditions designed to resemble the conditions of use under investigation as far as possible;

- c. Active treatment control.

Where an effective regimen of therapy may be used for comparison, e.g., the condition being treated is such that the use of a placebo or the withholding of treatment would be inappropriate or contrary to the interest of the patient;

- d. Historical control.

In certain circumstances, such as those involving diseases with high and predictable mortality or signs and symptoms of predictable duration or severity, or in the case of prophylaxis where morbidity is predictable, the results of use of the device may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations who received no treatment or who followed an established effective regimen (therapeutic, diagnostic, prophylactic).

5. A summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods utilized.

To insure the reliability of the results of an investigation, a well-controlled investigation shall involve the use of a test device that is standardized in its composition or design and performance.

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## Data Analysis

The PMA application must include a discussion of the conclusions drawn from studies conducted with the medical device [814.20(3)(vi)]. FDA does not prescribe specific statistical analyses for given devices and/or situations. All statistical analyses used in an investigation should be appropriate to the analytical purpose, and thoroughly documented.

The discussion should demonstrate that the data and information in the application constitute valid scientific evidence within the meaning of §860.7 (discussed above) and provide reasonable assurance that the device is safe and effective for its intended use. The indications for use is based on the nonclinical and clinical studies described in the PMA. Indications for use for a device include a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. Any differences related to gender, race, ethnicity, or age, etc. should be discussed in the data analysis and included in the labeling.

The concluding discussion must present benefit and risk considerations related to the device including a discussion of any adverse effects of the device on health and any proposed additional studies or surveillance the applicant intends to conduct following approval of the PMA.

The analysis should include the following:

- Summary of results (graphs are helpful)
- Summary of the study subjects including the number of subjects who have prematurely discontinued participation. (Include patient tree and spreadsheets to provide full accounting of all study subjects including controls and drop-outs, as appropriate)
- Description of events potentially affecting study success (e.g., difficulties enrolling patients; changes in key personnel; discontinuation of participation by subjects and investigators)
- Summary of anticipated and unanticipated adverse effects
- Description of any deviations from the investigational plan by investigators
- Discussion of any missing data and how it impacts the study
- Description of method of statistical analyses used; describe how any assumptions required in the statistical analysis were validated
- Comparison of results to success/failure criteria
- Conclusions drawn from study, relate back to indications for use and how the data supports each indication

Additional guidance can be found in the following documents:

Clinical Utility and Premarket Approval, Blue Book Memo #P91-1  
<http://www.fda.gov/cdrh/p91-1.html>

Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices  
<http://www.fda.gov/cdrh/ode/ot476.html>

Perspectives on Clinical Studies for Medical Device Submissions (Statistical) <http://www.fda.gov/cdrh/ode/78.pdf>

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## Bioresearch Monitoring

Sponsors, IRBs, and investigators, or any person acting on their behalf, are required to permit authorized FDA employees reasonable access at reasonable times to inspect and copy all records relating to clinical and nonclinical investigations. Furthermore, if FDA has reason to suspect that adequate informed consent was not obtained or that reports required to be

submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading, FDA may inspect and copy records that identify subjects.

To assure compliance with the IDE and related regulations, FDA inspects sponsors, clinical investigators, and institutional review boards. Nonclinical laboratories that perform animal studies in which the data are used to support research or marketing permits are included in the inspection program. The inspection program is referred to as bioresearch monitoring (BIMO) and is overseen the CDRHs Office of Compliance, Division of Bioresearch Monitoring.

The objectives of the bioresearch monitoring program are to ensure the quality and integrity of data and information submitted in support of PMA and IDE submissions and to ensure that human subjects taking part in investigations are protected from undue hazard or risk. This is achieved through site audits of clinical data contained in PMAs prior to approval, data audits of IDE submissions, and inspections of Institutional Review Boards and nonclinical laboratories.

Additional guidance on FDA's biological monitoring program can be found in the documents:

§812.145

Bioresearch Monitoring Agreement for PMAs and PDPs

<http://www.fda.gov/cdrh/ode/p98-1.html>

Integrity of Data and Information Submitted to ODE May 29, 1991 (I91-2)

<http://www.fda.gov/cdrh/i91-2.html>

Device Advice: Clinical Trials and Investigational Device Exemption

<http://www.fda.gov/cdrh/devadvice/ide/enforcement.shtml>

Office of Compliance - Bioresearch Monitoring Program

<http://www.fda.gov/cdrh/comp/bimogen.html>

Application Integrity Policy

[http://www.fda.gov/ora/compliance\\_ref/rpm\\_new2/rpm10aip.html](http://www.fda.gov/ora/compliance_ref/rpm_new2/rpm10aip.html)

Office of Regulatory Affairs; Compliance References; Bioresearch Monitoring (BIMO)

[http://www.fda.gov/ora/compliance\\_ref/bimo/default.htm](http://www.fda.gov/ora/compliance_ref/bimo/default.htm)

FDA/Office of Regulatory Affairs

Application Integrity Policy Information

[http://www.fda.gov/ora/compliance\\_ref/aip\\_page.html](http://www.fda.gov/ora/compliance_ref/aip_page.html)

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### **Form FDA-3674, ClinicalTrials.gov Data Bank**

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) included a provision that all PMA applications are required to be accompanied with certification that all applicable clinical trial information has been submitted to the ClinicalTrials.gov data bank.

Beginning December 26, 2007, PMA applications must include form FDA-3674. If your PMA includes data from a clinical trial, you must determine if your study is applicable for entry into the clinical trial registry data bank at ClinicalTrials.gov. Based on this determination, check box 9.B. or 9.C., and complete the applicable sections of the form. An applicable device clinical trial is a prospective clinical study of health outcomes comparing an intervention with a device against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes). See [Title VIII - Clinical Trial Databases](#). Currently, FDA is reviewing the legislation and developing guidance on which clinical trials meet the definition of "applicable" trials and are required to report to ClinicalTrials.gov. Until FDA issues this guidance, the PMA sponsor is responsible for determining whether its studies meet the definition of an applicable trial and, therefore, are subject to reporting requirements.

Information on how to register your clinical trial(s) in the ClinicalTrials.gov data bank is available on the National Library of Medicine (NLM) [Protocol Registration System \(PRS\)](#) website.

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## Postapproval Requirements

### General Requirements (§ 814.82, § 814.80)

FDA may impose postapproval requirements in a PMA approval order, by regulation at the time of approval of the PMA or by regulation subsequent to approval. Postapproval requirements may include as a condition of approval of the device:

- restriction of the sale, distribution or use of the device [section 515(d)(1)(B)(ii) or 520(e) of the FD&C Act];
- continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such a requirement and the number of patients to be evaluated and the reports required to be submitted;
- prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards or precautions important for the device's safe and effective use, including patient information such as information provided to the patient on alternative modes of therapy and on risks and benefits associated with the use of the device;
- inclusion of identification codes on the device or its labeling or, in the case of an implant, on cards given to patients if necessary to protect the public health. *Note: If patient identification cards are required in cases where the devices are sold directly to health practitioners, a PMA applicant's responsibility will be to supply such cards directly to practitioners for distribution to patients and to take reasonable steps to obtain patient identity information from the practitioners.;*
- maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if such information is necessary to protect the public health. *Note: FDA will require that the identity of any patient be disclosed in records maintained under the postapproval reporting requirements only to the extent required for the medical welfare of the individual, to determine the safety or effectiveness of the device, or to verify a record, report or information submitted to the agency;*
- maintenance of records for specified periods of time and organization and indexing of records into identifiable files to enable FDA to determine whether there is reasonable assurance of the continued safety and effectiveness of the device;
- at specified intervals, submission of periodic reports containing the information required by §814.84(b);
- batch testing of the device;
- any other requirements determined by FDA to be necessary to provide reasonable assurance, or continued reasonable assurance, of the safety and effectiveness of the device; and
- device tracking requirements under §821, Medical Device Tracking.

An applicant must grant FDA access to any records and reports required under the provision of §814.82 and permit authorized FDA employees to copy and verify such records and reports and to inspect at a reasonable time and in a reasonable manner all manufacturing facilities to verify that the device is being manufactured, stored, labeled, and shipped under approved conditions.

A device may not be manufactured, sterilized, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions of approval specified in the PMA approval order for the device.

Failure to comply with any postapproval requirement constitutes a reason for withdrawing approval of a PMA.

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### Postapproval (Annual) Reports

Continued approval of the PMA is contingent upon the submission of postapproval reports (annual reports) required under §814.84 at intervals of 1 year from the date of approval of the original PMA. The annual report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

- (1) Identification of changes described in §814.39(a) (PMA supplements) and changes required to be reported to FDA under §814.39(b).
- (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
  - a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
  - b. reports in the scientific literature concerning the device.

If, after reviewing the summary and bibliography, FDA concludes that the agency needs a copy of unpublished or published reports, FDA will notify the applicant that copies (two copies) of such reports must be submitted.

The annual report should summarize information pertaining to the original PMA and any subsequent PMA supplements. In addition, postapproval reports for PMA supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the supplement. Separate reports for individual supplements should not be submitted unless FDA requests them.

When any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report unless specified otherwise in the conditions of approval to the PMA. The annual report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding these events shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use. See **Adverse Reaction and Device Defect Reporting** for additional reporting requirements.

Annual Reports should be identified as "Annual Report" and include the applicable PMA reference number. **Two copies** should be submitted to the Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850.

### Postmarket Surveillance Studies

FDA may order postmarket surveillance studies to be conducted as a condition of PMA approval. The FDA can order postmarket surveillance for any Class II or Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences; or
- which is intended to be implanted in the human body for more than one year; or
- which is intended to be a life sustaining or life supporting device used outside a device user facility.

Manufacturers must submit a plan for approval within 30 days of receiving an order to conduct a postmarket surveillance study from FDA. After receiving the manufacturer's proposed plan, FDA has 60 days to determine if the person designated to conduct the surveillance is qualified and experienced, and if the plan will collect useful data that can reveal unforeseen adverse events or other information necessary to protect the public health.

Additional information can be found in the following documents.



Guidance on Criteria and Approaches for Postmarket Surveillance

<http://www.fda.gov/cdrh/modact/critappr.pdf>

Guidance on Procedures for Review of Postmarket Surveillance Submissions

<http://www.fda.gov/cdrh/modact/postsurv.html>

<http://www.fda.gov/cdrh/modact/postsurv.pdf>

Guidance on Procedures to Determine Application of Postmarket Surveillance Strategies

<http://www.fda.gov/cdrh/modact/postmrk.html>

<http://www.fda.gov/cdrh/modact/postmrk.pdf>

SMDA to FDAMA: Guidance on FDA's Transition Plan for Existing Postmarket Surveillance

<http://www.fda.gov/cdrh/modact/smdatran.html>

<http://www.fda.gov/cdrh/modact/smdatran.pdf>

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### Adverse Reaction and Device Defect Reporting [814.82(a)(9)]

FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit an "Adverse Reaction Report" or "Device Defect Report," as applicable, within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that **could not** cause or contribute to death or serious injury but **are not** correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. The postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

**Three copies** of the written report identified with the PMA reference number and "Adverse Reaction Report" or "Device Defect Report," as applicable, must be submitted **within 10 days** after the applicant receives or has knowledge of information concerning the event. The report should be mailed to:

PMA Document Mail Center (HFZ-401),  
Center for Devices and Radiological Health,  
Food and Drug Administration,  
9200 Corporate Blvd.,  
Rockville, Maryland 20850

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### Medical Device Reporting (MDR)

The Medical Device Reporting (MDR) Regulation (21 CFR 803) requires that all manufacturers report to FDA whenever a device:

- (1) may have caused or contributed to a death or serious injury or
- (2) has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for the PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Adverse Reaction Report" or "Device Defect Report" condition of approval for the PMA, the applicant must submit the report on the MedWatch form as required by the MDR Regulation with the PMA reference number. Additional information on MDR including guidance documents can be found on the Internet at <http://www.fda.gov/cdrh/mdr>

Reports made under the MDR Regulation must be identified as MDR reported events in the periodic (annual) report to the PMA to prevent duplicative entry into FDA information systems.

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### **Premarket Approval Application (PMA) Supplement.**

Before making any change affecting the safety or effectiveness of the device, a PMA supplement for review and approval by FDA must be submitted unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under §814.39(d) or an alternate submission is permitted in accordance with §814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under §814.39 of the final rule for Premarket Approval of Medical Devices.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification. In addition, a PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

Additional guidance on PMA supplements can be found in this section under "[PMA Supplements and Amendments.](#)"

### **References**

21 CFR 814 Subpart E ([§ 814.80](#), [§ 814.82](#), [§ 814.84](#))

[Section 522 of the FD&C Act](#)

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## **PMA Supplements and Amendments**

### **Overview**

Amendments (§ 814.37) or supplements (§814.39) are submitted to FDA for changes or revisions to the original PMA submission. Although a PMA supplement applies to an approved PMA, in many cases there will be amendments to the PMA or to the PMA supplement before it is approved. In addition PMA reports may also have amendments if the applicant is requested to submit additional information on a report. That is,

A PMA supplement is the submission required for a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA; additional information provided to FDA for PMA supplement under review are *amendments* to a

supplement

A PMA amendment includes all additional submissions to a PMA or PMA supplement *before* approval of the PMA or PMA supplement OR all additional correspondence after PMA or PMA supplement approval.

Note: This terminology varies slightly for Investigational Device Exemption (IDE) submissions. An IDE supplement is any additional submission to an IDE *after* approval of the IDE. An IDE amendment is any additional submissions to an IDE before approval of the IDE.

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## When to submit a PMA supplement (§814.39)

### Changes that Require a PMA Supplement

After FDA has approved a PMA, an applicant must submit a PMA supplement for review and approval by FDA before making any change affecting the safety or effectiveness of the device unless FDA has advised that an alternate type of submission is permitted for a particular change. All changes must meet the requirements of the Quality System regulation (Good Manufacturing Practices) under 21 CFR Part 820 including the design control requirement under §820.30. Changes for which an applicant must submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device:

- new indication for use of the device;
- labeling changes;
- the use of a different facility or establishment to manufacture, process, sterilize, or package the device;
- changes in manufacturing facilities, methods, or quality control procedures;
- changes in sterilization procedures;
- changes in packaging;
- changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device; and
- 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 the protocol has been previously approved by FDA, a supplement is not submitted but the change must be reported to FDA in the postapproval periodic reports as described in the §814.39(b).]

Additional guidance on when a PMA Supplement is required can be found in the following document:

When PMA Supplements are Required, #P90-1  
<http://www.fda.gov/cdrh/p90-1.html>

### Changes without a PMA Supplement 814.39(b)

An applicant may make a change in a device after FDA's approval of the PMA without submitting a PMA supplement if (1) the change does not affect the device's safety or effectiveness, and (2) the change is reported to FDA in a postapproval periodic report (annual report) required as a condition of approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device. Trivial changes, such as changes in the color of a label, would not have to be included in the postapproval periodic report.

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## Types of PMA Supplements

The methods of notification and FDA involvement of changes to a PMA approved medical device depend on the type of change made. A summary of the types of notification and FDA involvement is outlined below.

- **PMA supplement (180 days) - §814.39(a)**

- for significant changes that affect the safety and effectiveness of the device
- in-depth review and approval by FDA is required before implementation of the change
- A full PMA review including a review by an outside advisory panel may be required. The criteria for a full PMA review includes changes in the device that may raise different types of safety and effectiveness questions or changes in which there may be no accepted test methods for evaluating the issues of safety or effectiveness. The criteria for taking supplements to the outside advisory panel for review are discussed in Criteria for Panel Review of PMA Supplements <http://www.fda.gov/cdrh/p863.html>

Some 180-day PMA supplements may be reviewed using the **Real-Time Review** process. In this process the supplement is reviewed during a meeting or conference call with the applicant. FDA will fax its decision to the applicant within five working days after the meeting or call. The change must meet certain criteria to be eligible for this type of review. Supplements with detailed clinical data are generally not considered for this program. The criteria and process for the Real Time Review program are outlined in "Real-Time" Review Program for Premarket Approval Application (PMA) Supplements. <http://www.fda.gov/cdrh/ode/realtim2.html>

- **Special PMA Supplement – Changes Being Effected - §814.39(d)**

- for any change that enhances the safety of the device or the safety in the use of the device
- may be placed into effect by the applicant prior to the receipt of a written FDA order approving the PMA supplement.

After FDA approves a PMA, any change described below that enhances the safety of the device or the safety in the use of the device [§814.39(d)(2)] may be placed into effect by the applicant prior to the receipt of a written FDA order approving the PMA supplement, but after the applicant receives specific acknowledgment that the application qualifies for review under §814.39(d)(2) provided that:

- the PMA supplement and its mailing cover are plainly marked "Special PMA Supplement -- Changes Being Effected;"
- the PMA supplement provides a full explanation of the basis for the changes;
- the applicant has received acknowledgment that the application qualifies as a "Special PMA Supplement -- Changes Being Effected" from FDA for the supplement;
- the PMA supplement specifically identifies the date that such changes are being effected; and
- the change is made according to the good manufacturing practices regulation.

The following changes are permitted [§814.39(d)(1)]:

- labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction;
- labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device;
- labeling changes that delete misleading, false, or unsupported indications; and
- changes in quality controls or the manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device.

The applicant is encouraged to contact the PMA Staff to assist in determining if the change meets the requirements of §814.39(b).

- **30-day Notice and 135 PMA Supplement - §814.39(f)**

- Used for modifications to manufacturing procedures or methods of manufacture that affect the safety and effectiveness of the device.
- Changes in a manufacturing/sterilization site or to design or performance specifications do not qualify
- If the change qualifies as a 30day Notice, the change may be made 30 days after FDA receives the 30day notice unless FDA informs the PMA holder that the 30-day Notice is not adequate and describes the additional information or action required. If the 30-day Notice was not adequate, but contained data meeting appropriate content requirements for a PMA supplement, then the 30-day Notice will become a 135-day PMA Supplement.

Additional guidance can be found in "30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH" <http://www.fda.gov/cdrh/modact/daypmasp.html>

<http://www.fda.gov/cdrh/modact/daypmasp.pdf>

Note: 30-day Notice is not the same as a 30-day Supplement. See below for information regarding the 30-day Supplement.

- **Express PMA Supplement for Facilities Change (formerly called Pilot PMA Supplement Program)**
  - For moving the manufacturing site if certain conditions apply.
  - Manufacturing site must have received a Quality System/GMP inspection within the last two years.
  - If requirements are not met, 180-day PMA Supplement must be submitted.
  - Additional information on the Express PMA Supplement process can be found in the guidance document "Draft Guidance: Likelihood of Facilities Inspections When Modifying Devices Subject to Premarket Approval" <http://www.fda.gov/cdrh/comp/likelihood.html>
- **Annual (periodic) Report or 30-day Supplements-§814.39(e)**
  - FDA may allow certain changes to be reported in an annual report or 30-day supplement instead of a PMA supplement submission. (If this method is utilized, FDA will typically request that the information be reported in the annual report and not as a 30-day supplement.)
  - FDA will notify applicants of this alternative through an advisory opinion to the affected industry or in correspondence with the applicant.

FDA will identify a change to a device for which the applicant has an approved PMA and for which a PMA supplement is not required under 814.39(a). FDA will identify such a change in an advisory opinion under §10.85, if the change applies to a generic type of device. Such changes will be identified in written correspondence to each PMA holder who may be affected by FDA's decision.

FDA will require that a change, for which a PMA supplement under §814.39(a) is not required, to be reported to FDA in a periodic (annual) report or a 30-day PMA supplement. In written correspondence, FDA will identify the type of information that is to be included in the report or 30-day PMA supplement.

If FDA requires that the change be reported in a periodic report, the change may be made before it is reported to FDA. If FDA requires that the change be reported in a 30-day PMA supplement, the change may be made 30 days after FDA files the 30-day supplement, unless FDA informs the PMA holder that additional information is required, the supplement is not approvable, or the supplement is denied. The 30-day PMA supplement must follow the instructions in the correspondence or advisory opinion. Any 30-day PMA supplement that does not meet the requirements of the correspondence or advisory opinion will not be filed and, therefore, will not be deemed approved 30 days after receipt.

The applicant is encouraged to contact the PMA staff to assist in determining if the change meets the requirements of §814.39(e).

- **Document to file**
  - for changes that do not affect the safety or effectiveness of the device
  - very limited or no FDA involvement prior to implementation of the change

Minor manufacturing changes and minor quality control changes can be documented to file. Examples of changes that can be documented to file include editorial changes to a Standard Operating Procedure (SOP) to make instructions clearer and combining two SOPs into one.

- **New PMA**
  - Certain changes may require the submission of a complete new PMA. If any of the following changes occur, the applicant should consult the appropriate reviewing branch in the Office of Device Evaluation if:
    - the design change causes a different intended use, mode of operation, and technological basis of operation,
    - there will be a change in the patient population that will be treated with the device, or
    - the design change is so significant that a new generation of the device will be developed.

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## PMA Amendments (§ 814.37)

An applicant may amend a pending PMA or PMA supplement to revise existing information or provide additional information. FDA may request that the applicant amend their PMA or PMA supplement with any necessary information about the device that

FDA considers necessary to complete the review of the PMA or PMA supplement.

If the applicant submits a major PMA amendment on his or her own initiative or at FDA's request, the review period may be extended up to 180 days. A major amendment is one that contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted.

A PMA amendment must include the PMA or PMA supplement number assigned to the original submission and the reason for submitting the amendment.

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### **Withdrawal and Resubmission (§ 814.37)**

Applicants may voluntarily withdraw their PMA or PMA supplement. If FDA requests an applicant to submit a PMA amendment, and a written response to FDA's request is not received within 180 days, FDA will consider the pending PMA supplement to be withdrawn voluntarily by the applicant (abandoned).

An applicant may resubmit a PMA or PMA supplement that was withdrawn, that FDA has refused to accept for filing, or that FDA has disapproved. A resubmitted PMA or PMA supplement must comply with the requirements of §814.20 or §814.39, respectively, and must include the PMA number assigned to the original submission as well as the applicant's reason for resubmission.

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### **Suggested Format For PMA Supplement Cover Letters**

An applicant's cover letter should accurately identify the type of PMA submission and include information needed for FDA tracking purposes. To expedite its processing, the following suggestions and formats have been prepared.

All procedures and actions that apply to a PMA application under §814.20 also apply to PMA supplements, except that the information required in a supplement is limited to that needed to support the change. A summary is required only if there are new indications for use of the device, significant changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device, or when otherwise required by FDA.

**Three copies** of a PMA supplement are required and must include information relevant to the proposed changes in the device. A PMA supplement must include a separate section that identifies each change for which approval is being requested and explains the reason for each change. The applicant must submit additional copies and information if requested by FDA. The timeframes for review of a PMA supplement are the same as those provided for a PMA (§814.40).

PMA supplements and amendments should be mailed to the following address:

Food and Drug Administration  
Center for Devices and Radiological Health  
Document Mail Center (HFZ-401)  
9200 Corporate Blvd.  
Rockville, MD 20850

### General Suggestions

- Use the applicant's letterhead or that of the applicant's authorized representative.
- Address the cover letter as indicated under "PMA Supplement Cover Letter" below. To minimize misrouting, do not include an FDA staff member's name in the address.
- If submitted by someone other than the applicant (e.g., lawyer or consultant), the identity of the applicant must be included.
- In the case of a PMA supplement for a new model or revised indication, specify the indication for use for which FDA

approval is requested.

- If applicable, include the reference numbers for any Premarket Notification, Investigational Device Exemption, reclassification petition, or color additive petition submitted by the applicant.
- Indicate whether the submission includes an environmental assessment. Please note that an environmental assessment is typically not required. See Chapter 3 of the PMA Manual, "Environmental Impact Considerations," for additional guidance.  
[http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127\\_59655](http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127_59655)
- In the case of a PMA supplement, specify the location of the following information required by 21 CFR 814.39(c): identification of each change for which approval is requested and an explanation of the reason for each change.
- In the case of a "Special PMA Supplement - Changes Being Effected" under 21 CFR 814.39(d), identify the submission as such, provide a full explanation of the basis for the changes and identify the date that such changes are being effected.
- In the case of a 30-day PMA supplement under 21 CFR 814.39(e), specify the date of the FDA advisory opinion or correspondence providing for the change(s) to be reported in this manner and identify the submission as specified in the FDA advisory opinion or correspondence. In the cover letter for the 30-day supplement, provide a statement that confirms only changes identified in the advisory opinion or previous FDA correspondence are being requested via the supplement.
- Date and sign the cover letter and include a copy in the first volume of each copy of the PMA submission.

### Suggested Formats

To minimize delays in processing of PMA submissions, it is important that the applicant's cover letter correctly identify the type of submission, i.e., a PMA supplement, an amendment to a pending PMA or PMA supplement, or a required periodic report to an approved original PMA, PMA supplement or report amendment. Although FDA correspondence requesting additional information or approving a PMA submission identifies the form in which a subsequent submission is to be made, the incidence of incorrectly identified submissions has been significant. Delays in FDA processing occur when a document is misidentified and the submission must be reprocessed.

The general full format of the cover letter for a PMA supplement appears below. Only the subject section and opening sentence (s) are provided for the various types of PMA supplement submissions. In several instances, alternative opening statements are included to address specific situations.

### **PMA Supplement Cover Letter**

*[Date]*

Food and Drug Administration  
Center for Devices and Radiological Health  
Document Mail Center (HFZ-401)  
9200 Corporate Blvd.  
Rockville, MD 20850

**SUBJECT:** PMA Supplement to *[original PMA reference number]* for *[new device trade name or present device trade name if not being revised as a result of the modification]*

To Whom It May Concern:

*[Applicant's name]* is submitting this supplement to our approved Premarket Approval application for the *[present device trade name]* to request approval to *[identify the changes or modifications to be made in the device]*.

*[If the supplement involves a new manufacturing or sterilization facility, indicate whether the facility is prepared for an FDA inspection. If not prepared, provide the expected date when the facility will be ready for inspection.]*

*If another document is incorporated by reference, e.g., a master file, please include the original letter of authorization as an attachment to this cover letter.*

The existence of this PMA supplement and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(l), 5 USC 552, and other applicable laws is hereby claimed. *[Note: confidentiality claims cannot be made unless the applicant has complied with the applicable requirements.]*

If there are questions regarding this submission, *[name]* may be contacted at *[give telephone number including area code]*.

Sincerely yours,

*[Signature]*  
*[Name and title of applicant's representative]*

### **"Special PMA Supplement - Changes Being Effectuated" Cover Letter**

SUBJECT: Special PMA Supplement-Changes Being Effectuated" to *[original PMA reference number]* for *[present device trade name]*

*[Applicant's name]* is submitting this "Special PMA Supplement-Changes Being Effectuated" to our approved Premarket Approval application to place into effect the following change(s) described in 21 CFR 814.39(d)(2) that enhance(s) the *[safety of/safety in the use]* of *[device trade name]*.

*[As required by 21 CFR 814.39(d)(1), provide a full explanation of the basis for the changes and the date that such changes are being effectuated.]*

### **30-day Notice PMA Supplement Cover Letter**

SUBJECT: 30-day Notice PMA supplement to *[original PMA reference number]* for *[present device trade name]*

*[Applicants name]* is submitting this 30-day Notice PMA supplement to our approved Premarket Approval application for the *[present device trade name]* to request approval to *[identify the manufacturing change or modification to be made in the device]*.

Note: Two copies should be sent to CDRH's Office of Device Evaluation. At the same time, a duplicate copy should be sent directly to CDRH's Office of Compliance, Field Programs Branch, HFZ-306, ATTN: 30-day Notice, 9200 Corporate Blvd., Rockville, MD 20850. The duplicate copy should be flagged: "Office of Compliance Copy."

### **Express PMA Supplement Cover Letter**

SUBJECT: Express PMA supplement to *[original PMA reference number]* for *[present device trade name]*

*[Applicant's name]* is submitting this Express PMA supplement to our approved Premarket Approval application for the *[present device trade name]* to request approval for a new *[manufacturing or sterilization]* facility.

Note: Two copies should be sent to CDRH's Office of Device Evaluation. At the same time, a duplicate copy should be sent directly to CDRH's Office of Compliance, Field Programs Branch, HFZ-306, 9200 Corporate Blvd., Rockville, MD 20850. The duplicate copy should be flagged: "Office of Compliance Copy."

### **30-day PMA Supplement Cover Letter**

SUBJECT: 30-day PMA supplement to *[original PMA reference number]* for *[present device trade name]*

*[Applicant's name]* is submitting this 30-day PMA supplement to our approved Premarket Approval application for the *[present device trade name]* to request approval to *[identify the change or modification to be made in the device]*. As provided in the FDA *[letter/advisory opinion]* dated *[date]*, this change may be reported to FDA in a 30-day PMA supplement and implemented 30 days after FDA files the 30-day PMA supplement under the conditions



described in 21 CFR 814.39(e).

### **Amendment to Original PMA or PMA Supplement Cover Letter**

SUBJECT: Amendment to *[original PMA or PMA supplement reference number]* for *[device trade name]*

### **Unsolicited submission of additional information**

*[Applicant's name]* is submitting this amendment to its *[Premarket Approval application or PMA supplement]* *[original PMA or PMA supplement reference number]* for the *[device trade name]* to provide *[identify the additional information being provided]*.

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### **References**

[21 CFR 814.37](#)

[21 CFR 814.39](#)

When PMA Supplements are Required, #P90-1 (blue book memo)

<http://www.fda.gov/cdrh/p90-1.html>

Modifications to Devices Subject to Premarket Approval - The PMA Supplement Decision Making Process; Draft

<http://www.fda.gov/cdrh/ode/pumasupp.pdf>

Criteria for Panel Review of PMA Supplements #P86-3 (blue book memo)

<http://www.fda.gov/cdrh/p863.html>

Real-Time Review Program for Premarket Approval Application (PMA) Supplements

<http://www.fda.gov/cdrh/ode/realtim2.html>

<http://www.fda.gov/cdrh/ode/realtime.pdf>

30-Day Notices and 135-day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH (Docket 98D-0080); Final

<http://www.fda.gov/cdrh/modact/daypmasp.html>

<http://www.fda.gov/cdrh/modact/daypmasp.pdf>

Draft Guidance: Likelihood of Facilities Inspections When Modifying Devices Subject to Premarket Approval

<http://www.fda.gov/cdrh/comp/likelihood.html>

Guidance to Industry Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review; Final

<http://www.fda.gov/cdrh/modact/evidence.html>

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## **Special Considerations**

### **Biocompatibility**

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials should not, either directly or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or, (iii) produce adverse reproductive and

developmental effects. Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

FDA recognizes the standard ISO 10993 (International Standards Organization) for biological evaluation of medical devices. This standard provides guidance for selecting the tests to evaluate the biological response to medical devices. When selecting the appropriate tests for biological evaluation of a medical device, the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body must be considered.

The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate. Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. Therefore, it may not be necessary to conduct all the tests suggested in the FDA's testing guidance matrix.

Additional information on biocompatibility can be found in the following guidance document:

Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, Blue Book Memo, G95-1  
<http://www.fda.gov/cdrh/g951.html>

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## **Color Additives**

Color additives in medical devices are subject to the same provisions that apply to color additives in foods, drugs, and cosmetics. A color additive is a dye, pigment, or other substance, whether synthetic or derived from a vegetable, animal, mineral, or other source, which imparts a color when added or applied to a food, drug, cosmetic, or the human body. The Food, Drug and Cosmetic (FD&C) Act states that devices containing a color additive are considered unsafe, and thereby adulterated, unless a regulation is in effect listing the color additive for such use. The FD&C Act limits applicability of these provisions to color additives for devices that directly contact the body for a significant period of time. At the present time, the term a "significant period of time" is not defined by FDA regulation.

The color listing regulation may permit use of the color additive in a generic type of device, such as contact lenses, or may place limitations on its use, such as polypropylene nonabsorbable sutures for general surgical use but not for ophthalmic surgical use.

PMA applicants must demonstrate color additives remaining in and on the device are safe. Manufacturers may choose an appropriate color additive approved for medical devices in accordance with its use and restrictions. Color additives listed for use in medical devices are provided in 21 CFR 73 and 21 CFR 74.

- [Part 73, Subpart D](#): Color additives exempt from batch certification
- [Part 74, Subpart D](#): Color additives subject to batch certification

If a color additive has not been previously listed, the manufacturer must submit a color additive petition to FDA. If the PMA is submitted before the color additive petition is approved, the PMA approval will be delayed.

In searching for an appropriate color additive for use in its device, manufacturers should consider color additives listed for use in foods, drugs, or cosmetics as a starting point. However, the safety data of the color additive for a food, drug, or cosmetic may not be relevant to devices. That is, the color additive may be used in a different part of the body or for a longer duration than that approved.

The following provides additional guidance on color additives.

Color Additive  
[http://www.fda.gov/cdrh/dsma/pmaman/appdxe.html#P7\\_2](http://www.fda.gov/cdrh/dsma/pmaman/appdxe.html#P7_2)  
<http://www.fda.gov/cdrh/ode/296.pdf>

Color Additives for Medical Devices

<http://www.fda.gov/cdrh/ode/575.pdf>

Color Additives - Center for Food Safety and Applied Nutrition  
<http://www.cfsan.fda.gov/~dms/col-toc.html>

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## Combination Products

A combination product is a product comprised of two or more regulated components (drug/device or biologic/device) that are combined as a single entity or is a product labeled for use with a specified drug, device, or biologic where both are required to achieve the intended use, indication, or effect.

To ease the regulatory burden of industry, FDA has established Intercenter agreements which establishes the lead FDA Center for review and oversight of certain categories of products. Intercenter agreements with CDRH are referenced below.

Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health.  
<http://www.fda.gov/oc/ombudsman/bio-dev.htm>

Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health.  
<http://www.fda.gov/oc/ombudsman/drug-dev.htm>

Some combination products involve cutting edge, novel technologies that raise not only unique scientific and technical questions, but also regulatory challenges related to where and how they should be regulated in order to ensure adequate and consistent regulatory oversight. The Office of Combination Products assigns review responsibility for combination products. The Office is also responsible for designating the component of FDA with primary jurisdiction for the premarket review and regulation of any product requiring a jurisdictional designation.

Additional information regarding combination products can be found at the following website:

Office of Combination Products  
<http://www.fda.gov/oc/combo/>

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## Electromagnetic Compatibility

PMA applicants must demonstrate that the device is electrically safe and does not interfere with other devices used in the same environment. Electromagnetic compatibility, or EMC, means that the device is compatible with (i.e., no interference caused by) its electromagnetic environment, and that it does not emit levels of electromagnetic energy that cause electromagnetic interference (EMI) in other devices in the vicinity. The wide variation of medical devices and use environments makes them vulnerable to different forms of electromagnetic energy which can cause electromagnetic interference. Additional guidance and information CDRH activities in this area is available on the "CDRH Medical Device Electromagnetic Compatibility Program" website at <http://www.fda.gov/cdrh/emc/>

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## Electronic Submissions

CDRH accepts medical device applications in electronic form. PMA applicants should notify the reviewing division of CDRH of their desire to submit an application in electronic form prior to submission. This lead time is needed to discuss any special considerations with the submitter prior to development of the documents.

The application should be submitted in a PDF (Portable Document Format) format as the PMA review staff will use Acrobat

Exchange to review the submission. This will assure that what a reviewer sees on the screen is the same as what would have been seen on paper. Applications may be submitted on floppy diskettes or CD-ROM. At least one paper copy of the submission is also required.

An electronic application does not change the order in which submissions are reviewed. No preferential treatment will be given to manufacturers who submit an electronic application. Additional copies of some reports may be requested in order to help facilitate the review.

Additional information on electronic copies can be found the Internet at <http://www.fda.gov/cdrh/electsub.html>

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### **Environmental Impact Considerations**

21 CFR 814.20(b)(11) states that an environmental assessment in accordance with 21 CFR 25 must be included in the PMA application. However, PMA applications do not ordinarily require an environmental assessment (EA) or environmental impact statement (EIS). Devices of the same type and for the same use as a previously approved device are categorically excluded from an EA or an EIS [§25.34(d)]. These devices compete for the same market with already approved devices of the same type and use, and therefore, there is no increased environmental impact resulting from the introduction of the device into commercial distribution. A statement requesting a categorical exclusion from an environmental assessment is not required in the PMA application.

If the device causes environmental hazards in the manufacture, use, or disposal of the device, an environmental assessment must be submitted in the PMA. Guidance on environmental assessments can be found in the following guidance document.

Environmental Impact Considerations\*

[http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127\\_59655](http://www.fda.gov/cdrh/dsma/pmaman/sec03.html#P1127_59655)

\*Please note that 21 CFR 25 has been revised after this guidance was published and some references to 21 CFR 25 have changed.

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### **Expedited Review**

FDA believes it is in the interest of the public health to review applications for certain medical devices in an expedited manner. Expedited review will generally be considered when a device offers a potential for clinically meaningful benefit as compared to the existing alternatives (preventative, diagnostic, or therapeutic) or when the new medical device promises to provide a revolutionary advance (not incremental advantage) over currently available alternative modalities.

Granting of expedited review status means that the marketing application would receive priority review before other pending applications, i.e., the application will be placed at the beginning of the appropriate review queue.

The criteria and procedure for expedited review are provided in the following guidance document.

PMA/510(k) Expedited Review

<http://www.fda.gov/cdrh/ode/g98-4.html>

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### **Expiration Dating**

Under 21 CFR 809, In Vitro Diagnostic Products for Human Use, the labeling must provide an expiration date based upon the stated storage instructions. Other devices are not required to have expiration dating, but may be appropriate. If expiration dating is provided in the labeling, it must be based upon the storage instructions provided in the labeling and substantiated through stability testing. Data to support the expiration date must be provided in the PMA and maintained as part of Quality System records under 21 CFR 820. Guidance on shelf life protocols can be found in the following guidance documents.

## 21 CFR 211.166 Stability testing

Guidance for Industry: Q1A Stability Testing of New Drug Substances and Products  
<http://www.fda.gov/cder/guidance/4282fnl.htm>

Evaluation of Stability Data  
<http://www.fda.gov/cder/guidance/4983dft.htm>

Guideline for Submitting Documentation for the Stability for Human Drugs and Biologics  
<http://www.fda.gov/cder/guidance/old028fn.pdf>

Stability Testing of Drug Substances and Drug Products  
<http://www.fda.gov/cder/guidance/1707dft.pdf>

Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products  
<http://www.fda.gov/cder/guidance/ichq5c.pdf>

## **In Vitro Diagnostic (IVD) Products**

### Definition

In vitro diagnostics are medical devices that analyze human body fluids, such as blood or urine, to provide information for the diagnosis, prevention, or treatment of a disease. The device classification for these devices can be found under 21 CFR 862, 21 CFR 864, and 21 CFR 866.

### Labeling

In Vitro Diagnostic Products have special labeling requirements and distribution restrictions under 21 CFR 809, In Vitro Diagnostic Products for Human Use. Additional guidance can be found under "Device Advice Labeling Requirements for In Vitro Diagnostic Devices."

### Clinical Laboratory Improvement Amendments (CLIA) of 1988

In addition to FDA regulation under the Food, Drug, and Cosmetic Act, in vitro diagnostic (IVD) devices are also subject to the Clinical Laboratory Improvement Amendments (CLIA) of 1988. This law established quality standards for laboratory testing and an accreditation program for clinical laboratories.

The requirements that apply vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results. The regulations established three categories of testing on the basis of the complexity of the testing methodology: waived tests, tests of moderate complexity, and tests of high complexity. Laboratories performing moderate- or high-complexity testing or both must meet requirements for proficiency testing, patient test management, quality control, quality assurance, and personnel. These specific requirements do not apply to tests in the waived category.

In January 2000 the categorization of commercially marketed in vitro diagnostic tests under CLIA was transferred from the Center for Disease Control and Prevention (CDC) to FDA. CDRH's Office of of In Vitro Diagnostic Device Evaluation and Safety (OIVD) determines the appropriate complexity categories for clinical laboratory devices as they evaluate premarket submissions. Waived products, devices exempt from premarket notification, and devices under premarket review by other FDA Centers are also processed by OIVD. Responsibilities currently assigned to CDC, including review of test systems, assays, or examinations not commercially marketed as IVD products, will remain with CDC.

Below is a list of CLIA Program Information Resources:

FDA CLIA Website (complexity categorizations, waiver)  
<http://www.fda.gov/cdrh/clia>

CMS CLIA Website (program information, statistics, etc.)  
<http://www.cms.hhs.gov/clia>

CDC CLIA Website (regulations, CLIAC)  
<http://www.phppo.cdc.gov/clia/default.asp>

Additional information on assignment of CLIA categories by FDA can be found on the Internet at  
<http://www.fda.gov/cdrh/clia/>

#### Additional IVD Guidance

For additional information on in vitro diagnostics devices, please visit the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) website at <http://www.fda.gov/cdrh/oivd/>

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#### **Master Files**

A PMA applicant often utilizes another party's product (e.g., material, ingredient, subassembly, or accessory) or facility in the manufacture of the device. Although information regarding the third party's product is pertinent to the review of the PMA, the third party may not want to divulge confidential or trade secret information to the PMA applicant. To preserve the trade secrets of the ancillary medical device industry and at the same time facilitate the sound scientific evaluation of medical devices, FDA allows the third party to submit the confidential information directly to FDA in a device master file. A master file may also be considered when several applications may be submitted for different products which may use a common material or process. However, different uses of the medical device may require additional testing or information to support the evaluation of that particular product.

Please note that a master file is NOT a marketing application. It is not independently reviewed or approved. A master file is only reviewed when a premarket submission [PMA or Premarket Notification 510(k)] under review contains an authorization letter from the third party that permits FDA to review the master file to support the premarket submission. Since the master file may contain additional information than required for the review of the submission, the authorization letter should specify the appropriate sections or pages for review.

Additional guidance on master files can be found in the following guidance document.

CDRH Master Files  
[http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7\\_2](http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2)

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#### **Radiation Emitting Products**

If the medical device also emits electronic product radiation, additional requirements apply under the Radiation Control for Health and Safety Act (RCHSA). Electronic product radiation means

- any ionizing or non-ionizing electromagnetic or particulate radiation, or
- any sonic, infrasonic, or ultrasonic wave, which is emitted from an electronic product as the result of the operation of an electronic circuit in such product.

Examples include lasers, diagnostic x-ray, fluoroscopes, and computed tomography (CT). The requirements are in place to prevent unnecessary exposure to radiation due to the use of these products. Requirements may include submission of reports to FDA, labeling, retention of certain records, and reporting of accidental radiation occurrences. Additional information on requirements for radiation emitting products can be found on the website at <http://www.fda.gov/cdrh/devadvice/311.html>

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## Software

If the device contains software, the PMA submission must contain documentation of software validation appropriate to the level of risk of the device. The following guidance documents provide guidance on software validation and documentation of the validation for submission in the PMA.

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

<http://www.fda.gov/cdrh/ode/57.html>

<http://www.fda.gov/cdrh/ode/software.pdf>

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

<http://www.fda.gov/cdrh/comp/guidance/938.html>

<http://www.fda.gov/cdrh/comp/guidance/938.pdf>

Guidance for Off-the-Shelf Software Use in Medical Devices

<http://www.fda.gov/cdrh/ode/guidance/585.html>

<http://www.fda.gov/cdrh/ode/guidance/585.pdf>

Glossary of Computerized System and Software Development Terminology

<http://www.fda.gov/cdrh/comp/guidance/938.pdf>

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## Standards

Conformance with recognized consensus standards can provide a reasonable assurance of safety and/or effectiveness for many aspects of medical devices. Information submitted on conformance with such standards will have a direct bearing on safety and effectiveness determinations made during the review of premarket submissions. If any premarket submission contains a declaration of conformity to the recognized consensus standards, this will, in most cases, eliminate the need to review the actual test data for those aspects of the device addressed by the standards.

Conformance with recognized consensus standards in and of itself, however, may not always be a sufficient basis for regulatory decisions. For example, a specific device may raise a safety or effectiveness issue not addressed by any recognized consensus standard, or a specific FDA regulation may require additional information beyond what conformity to the recognized consensus standards provides. Under such circumstances, conformity with recognized standards will not satisfy all requirements for marketing the product in the United States.

FDA recognizes certain consensus standards. If the device complies to an FDA recognized standard, the applicant may need only submit a declaration of conformity to the standard without submitting test data. Conformance to FDA recognized standards are voluntary and may be used to demonstrate performance or safety of a device.

Information on FDA's standard program including a database of FDA recognized standards can be found on the following website:

CDRH Standards Program

<http://www.fda.gov/cdrh/stdsprog.html>

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## Sterility

The sterilization method (e.g., steam heat, ethylene oxide, radiation), sterility assurance level (SAL), description of the packaging to maintain the device's sterility, and method of validation must be provided in the PMA. The manufacture may use an FDA recognized validation method or an equivalent method. Additional information on sterilization can be found in the following documents:

Blue book memo: Updated 510(k) Sterility Review Guidance K90-1

<http://www.fda.gov/cdrh/ode/guidance/361.html>

<http://www.fda.gov/cdrh/ode/guidance/361.pdf>

Please note that although this guidance document is specific to the Premarket Notification 510(k) process, the information is also relevant to PMAs.

FDA recognized consensus standards for sterilization validation can be found by searching the CDRH standards database at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

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## Import/Export

### Importing into the U.S.

In order to import medical devices subject to Premarket Approval (PMA) into the U.S., the device must have FDA approval through the PMA process as well as meet all applicable FDA regulatory requirements. At this time, FDA does not recognize regulatory approvals from other countries. [Exporting Medical Devices](#) provides a summary of FDA requirements for foreign manufacturers and importers of medical devices and products that emit radiation.

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### Export of Approved PMA Devices

#### Requirements

Any medical device that is legally in the U.S. may be exported anywhere in the world without prior FDA notification or approval. For a device to be legally in commercial distribution in the U.S., the following requirements must be met:

- The manufacturing facility must be registered with FDA;
- The device must be listed with FDA;
- The device must have an approved Premarket Approval (PMA) application;
- The device must meet the labeling requirements of 21 CFR Part 801 and 21 CFR 809, if applicable;
- The device must be manufactured in accordance with the Quality Systems (QS) Regulation of 21 CFR Part 820 (also known as Good Manufacturing Practices or GMP).

#### Certificates for Foreign Government

While FDA does not place any restrictions on the export of these devices, certain countries may require written certification that a firm or its devices are in compliance with U.S. law. In such instances FDA will accommodate U.S. firms by providing a Certificates for Foreign Government (CFG). These export certifications were formerly referred to as Certificates for Products for Export or Certificates of Free Sale. The CFG is a self certification process that is used to speed the processing of requests. To obtain instructions on how to obtain a CFG, call 240-276-0132. If you are unable to reach a person on the Export Certificate Team, please call 240-276-0130.

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### Export of Unapproved PMA Devices

Export of unapproved devices must meet the requirements under sections 801 or 802 of the FD&C Act. The provisions for unapproved PMA devices are discussed below.



## Exporting PMA Devices under Section 802

### Requirements

Unapproved Class III devices may be exported under section 802 if the firm and the device meet certain criteria. These devices include unapproved devices which would not be able to obtain a PMA or whose PMA has not been approved. In order to qualify for export under 802, devices must meet the four requirements of 801(e)(1) and pass the restrictions set forth in 802(f). That is, the devices must:

- meet the requirements of section 801(e)(1), that is, the device is
  - in accordance with the specifications of the foreign purchaser;
  - not in conflict with the laws of the country to which it is intended for export;
  - labeled on the outside of the shipping package that it is intended for export; and
  - not sold or offered for sale in domestic commerce.
- substantially meet Quality Systems Regulation (also known as Good Manufacturing Practices) or an international quality standard recognized by FDA (currently, none are recognized),
- not be adulterated other than by the lack of marketing approval,
- not be the subject of a notice by Department of Health and Human Services that re-importation would pose an imminent hazard, nor pose an imminent hazard to the receiving country, and
- not be mislabeled other than by possessing the language, units of measure, or any other labeling authorized by the recipient country. In addition, the labeling must comply with the requirements and conditions of use in the listed country which gave marketing authorization, and must be promoted in accordance with its labeling.

In addition to the requirements above, the device must comply with the laws of the receiving country and have valid marketing authorization by the appropriate authority in a listed (Tier 1) country. This means that a firm whose device has received marketing authorization in any of the Tier 1 countries can export that device to any country in the world as long as the device meets applicable requirements of the FD&C Act .

The exporter must submit a "Simple Notification " as per section 802(g) to FDA when the firm begins to export. No approval from FDA is required.

If the firm or device does not comply with the above criteria, the device cannot be exported under section 802. However, the device may qualify for exportation under section 801(e)(2).

### Recordkeeping Requirements

Any person exporting a product under any provision of section 802 must maintain records [section 802(g)] of all devices exported and the countries to which the products were exported. In addition to the requirements in 801(e)(1) noted above, such records include, but are not limited to, the following:

- The product's trade name;
- The type of device;
- The product's model number;
- The consignee's name and address; and
- The date on which the product was exported and the quantity of product exported.

These records must be kept at the site from which the products were exported or manufactured, and be maintained for the same period of time as required for records subject to good manufacturing practice or quality systems regulations applicable to the product. That is, all records must be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer (21 CFR 820.180). The records shall be made available to FDA, upon request, during an inspection for review and copying by FDA.

### Certificate of Exportability

Even though FDA does not require a firm to obtain written permission prior to export, a foreign purchaser may request proof of compliance with U.S. law prior to export. FDA will provide a Certificate of Exportability to the exporter under section 802 (COE) to facilitate export of a medical device under section 802.

#### Additional Information

Exporting Medical Devices provides a list of Tier 1 countries and additional information on simple notifications and Certificates of Exportability.

#### Exporting Unapproved PMA Devices Under Section 801(e)(2)

##### Requirements

Unapproved devices which would not be able to obtain a PMA, or whose PMA has not been approved, that do not meet the criteria under section 802 may qualify for export under section 801(e)(2). Export under section 801(e)(2) is required when exporting an unapproved Class III device in which:

- the importing country will not accept the marketing authorization of a listed (Tier 1) country as described in Section 802; or
- the device is not manufactured in substantial conformance with the Quality System (GMPs).

The device must meet the following criteria to be exported:

- The device must meet the requirements under Section 801(e)(1) of the FD&C Act, that is, the device is;
  - in accordance with the specifications of the foreign purchaser;
  - not in conflict with the laws of the country to which it is intended for export;
  - labeled on the outside of the shipping package that it is intended for export; and
  - not sold or offered for sale in domestic commerce.
- A review by FDA must determine that the exportation of the device is not contrary to public health and safety and;
- The device has the approval of the country to which it is intended for export.

##### Export Permit

To obtain FDA's approval to export these devices in accord with Section 801(e)(2) of the FD&C Act, a request that includes the following information must be submitted to FDA:

- A complete description of the device intended for export;
- The status of the device in the U.S.; e.g., whether it is investigational, banned, unapproved PMA product, etc.; and
- A letter from the appropriate foreign liaison (person with authority to sign a letter of acceptance for the foreign government identified in the CDRH Foreign Liaison Listing , which must be either in English or accompanied by a certified English translation, stating:
  - the device is not in conflict with the laws of the country to which it is intended for export.
  - the foreign government has full knowledge of the status of the device in the U.S.; and
  - import is permitted or not objected to.
  - a statement that the requestor conducted a search of the Medlars database and a summary of the search results, and a summary of safety data to demonstrate that export of the device will not be contrary to the public health and safety.

A notarized certification from a responsible company official in the United States may be provided as an alternative to a letter from the foreign government [Section 1.101(b)(2)]. The letter should state:

- the product is not in conflict with the foreign country's laws.

- the certification must include a statement acknowledging that the responsible company official is making the certification is subject to the provisions of 18 U.S.C 1001. This statutory provision makes it a criminal offense to knowingly and willfully make a false or fraudulent statement, or make or use a false document, in any matter within the jurisdiction of a department or agency of the United States. This statutory provision also makes it a criminal offense to knowingly and willfully falsify, conceal, or cover up by any trick, scheme, or device, a material fact in any matter within the jurisdiction of a department or agency of the United States.

If the manufacturer is exporting to a country within the European Economic Area (EEA) a device that has been awarded the "CE mark," FDA will accept documentation of the "CE mark" in lieu of a letter from the foreign government or responsible company official approving importation.

#### Additional information

Exporting Medical Devices provides additional information on requirements and instructions on how to obtain an export permit under 801(e)(2).

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## Frequently Asked Questions

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- [Is FDA approval required to change the trade name of the device?](#)
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- [Can I obtain a copy of a PMA submission?](#)

### Who can submit a PMA?

The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA approval of the PMA. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. Often times the applicant is the inventor/developer and ultimately the manufacturer. If the applicant does not reside or have a place of business within the U.S., the PMA must be countersigned by an authorized representative who does. [[§814.20](#)]

### Are data from foreign clinical studies accepted by FDA?

A study conducted under an investigational device exemption (IDE) outside the United States and submitted in support of a PMA must comply with the IDE regulation ([21 CFR 812](#)). A study conducted outside the U.S. which was not conducted under an IDE must comply with one of the following:

- Research begun on or after effective date November 19, 1986: FDA will accept studies which have been conducted outside the U.S. and begun on or after November 19, 1986, if the data constitute valid scientific evidence ([§860.7](#)) and the investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research was conducted, whichever offers greater protection to the human subjects. If the standards of the country are used, the applicant must state in detail any differences between those standards and the Declaration of Helsinki and explain why the national standards offer greater protection to the human subjects.

- Research begun before effective date November 19, 1986: FDA will accept studies which have been conducted outside the U.S. and begun before November 19, 1986, if the agency is satisfied that the data constitute valid scientific evidence (§860.7) and that the rights, safety, and welfare of human subjects have not been violated.

A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

- the foreign data are applicable to the U.S. population and medical practice;
- the studies have been performed by clinical investigators of recognized competence; and
- the data may be considered valid without the need for an on site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on site inspection or other appropriate means.

Applicants who seek approval based solely on foreign data are encouraged to meet with FDA officials in a presubmission meeting.

Additional guidance on FDA policy regarding the acceptance of foreign clinical data can be found in the following document.

Acceptance of Foreign Clinical Studies; Guidance for Industry

<http://www.fda.gov/cder/guidance/fstud.htm>

<http://www.fda.gov/cder/guidance/fstud.pdf>

#### **How does the sponsor notify FDA of a change in address of the official correspondent for the PMA under review?**

FDA will send all PMA correspondence only to the designated official correspondent of the PMA. The sponsor can change the name or address of the official correspondent by submitting an amendment to the PMA.

#### **Is FDA approval required to change the trade name of the device?**

Yes, the sponsor must submit a PMA supplement and receive approval before the change in trade name can be implemented.

#### **Can the sponsor sell the PMA to another company? How does the owner notify FDA of a change in ownership?**

Yes, a PMA may be sold to another company. The sponsor must submit a PMA amendment to notify FDA of the new owner. The new sponsor is responsible for complying with the PMA regulatory requirements as well as all other applicable regulations such as registration, listing, quality system, and medical device reporting. The PMA reference number will remain the same.

Ownership of a PMA may be transferred at any time, i.e., before or after FDA approval. At the time of the transfer, the former owner should provide an original and a copy of a letter (preferably on the letterhead of the former owner and signed by an appropriate company official) to be used to notify FDA that all rights of the PMA have been transferred to the new owner.

If the PMA has been approved, the new owner need only report that the transfer of PMA ownership will not result in a change or modification that would require a submission of a PMA supplement (§814.39) or affect the conditions of approval applicable to the PMA. If changes are made that require a PMA supplement (§814.39) or affect the conditions of approval, the new owner must submit an appropriate PMA supplement and obtain written FDA approval before marketing the device.

The above amendment or supplement should also include:

- the effective date of the ownership transfer;

- a statement of the new owner's commitment to comply with all the conditions of approval applicable to the PMA; and
- either a statement that the new owner has a complete copy of the PMA including all amendments, supplements, and reports or a request for a copy from the FDA files. FDA will provide a copy of the PMA under the Freedom of Information fee schedule. [21 CFR 10.42]

A change in manufacturing or product sterilization site and certain changes to the device, labeling, or packaging require prior FDA approval through a PMA supplement. See PMA amendments and supplements for further guidance on when a PMA supplement is required.

If the transfer of ownership occurs before the PMA is approved, the PMA must be amended to include the applicable information and ownership transfer letter described above.

### **Can the PMA holder enter into a licensing agreement with another manufacturer?**

When the holder of an approved PMA enters into an agreement to permit another firm (hereafter referred to as the licensee) to manufacture and distribute a device under the licensee's private label, FDA approval may be obtained by the following procedure:

The licensee may submit an original PMA that includes, or includes by authorized reference to the holder's approved PMA, all appropriate information required by 21 CFR 814.20.

After the licensee's PMA is approved, the original PMA holder may not rescind any authorization permitting the licensee's use of information in the original approved PMA. The licensee may also use that same information in support of changes or modifications later proposed by the licensee. The licensee becomes independent of the original PMA holder and should submit all required PMA supplements and periodic postapproval reports directly to FDA.

The PMA submission must include the following:

- a statement signed by both parties confirming that the original PMA holder has furnished the licensee with a complete copy of all manufacturing information in the approved PMA applicable to the licensee's manufacture of the device;
- a complete description of a licensee's manufacturing facilities and a listing and explanation of all differences between the original PMA holder's and the licensee's methods and controls used in the manufacture, processing, packing, storage, and, when appropriate, installation of the device;
- process validation and expiration dating information, where appropriate;
- copies of all required labeling (draft or final) and a description of all differences between the PMA holder's and the licensee's labeling (e.g., a markup of the PMA holder's approved labeling identifying the revisions incorporated in the licensee's labeling);
- a description and the results of all tests and evaluations which demonstrate that the licensee's device is identical or sufficiently similar to the PMA holder's device to the extent that there is reasonable assurance that the licensee's device is safe and effective for the intended use; and
- the licensee's FDA establishment registration number and, if applicable, the dates of the most recent FDA inspection of the licensee's manufacturing facility.

### **Can the sponsor change the manufacturing site of the PMA approved device?**

Yes, however, the sponsor must receive FDA approval of the new manufacturing site prior to distributing product that was manufactured at the new facility. If the new manufacturing facility has received a Quality System inspection within the last two years, the change may qualify for an Express PMA Supplement for Facilities Change. If Express PMA Supplement requirements are not met, the sponsor must submit a 180-day PMA supplement.

Additional information on the Express PMA Supplement process can be found in the guidance document "Draft Guidance: Likelihood of Facilities Inspections When Modifying Devices Subject to Premarket Approval"  
<http://www.fda.gov/cdrh/comp/likelihood.html>

### Does an extension of product shelf life require a PMA supplement?

If FDA has previously reviewed and accepted a protocol for changes to the expiration date and testing was performed in accordance with that protocol, the change to the expiration date can be made and reported in an annual report. If not, a PMA supplement should be submitted. Additional guidance can be found in "Modifications to Devices Subject to Premarket Approval - The PMA Supplement Decision Making Process; Draft")  
<http://www.fda.gov/cdrh/ode/pumasupp.pdf>

### How can I find more information about a PMA under review?

Before FDA approves or disapproves a PMA, FDA will not disclose the existence of the PMA unless it previously has been publicly disclosed or acknowledged. Even if the existence of the PMA has been publicly disclosed or acknowledged, data or information contained in the file are not available for public disclosure. However, FDA may disclose a summary of portions of the safety and effectiveness data, if disclosure is relevant to public consideration of a specific pending issue. [21 CFR 814, 21 CFR 20]

### Can I obtain a copy of a PMA submission?

Upon approval (or denial of approval) of any PMA, FDA will publicly reveal the existence of the PMA and provide a detailed summary of the information submitted to FDA about the safety and effectiveness of the device. The approval order, summary of safety and effectiveness, and product labeling are available on the Internet and are linked from the searchable PMA database.  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>

In addition, the following types of information in the PMA file are available for public disclosure after deletion of any trade secret, confidential commercial or financial information, or any other information that if disclosed would constitute a clearly unwarranted invasion of personal privacy, e.g., personnel, medical, and similar information. The releasable information includes:

- all safety and effectiveness data and information previously disclosed to the public;
- any protocol for a test or study;
- any adverse reaction report, product experience report, consumer complaint, and other similar data and information;
- a list of components previously disclosed to the public;
- an assay method or other analytical method; and
- all correspondence and written summaries of oral discussion relating to the PMA file.

The following types of information are not available for public disclosure unless they have been previously disclosed to the public, relate to a device for which a PMA has been abandoned, or no longer represent a trade secret or confidential commercial or financial information:

- manufacturing methods or processes including quality control procedures;
- production, sales, distribution, and similar data and information; and
- quantitative or semiquantitative formulas.  
[21 CFR 814 and 21 CFR 20]

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## Regulations

CFR Title 21 Database

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

[21 CFR 814 Premarket Approval of Medical Devices](#)

[21 CFR 54 Financial Disclosure by Clinical Investigators](#)

[21 CFR 801 Labeling](#)

[21 CFR 820 Quality System Regulation](#)

### ***Federal Register Notices***

The *Federal Register* (FR) is the official daily publication for rules, proposed rules, and notices of federal agencies and organizations, as well as Executive Orders and other Presidential Documents. In order to create or revise an existing regulation, FDA will publish a proposed rule in the FR and request comments. FDA will then evaluate all comments received and publish a final rule. Once a proposed rule is finalized, it is published in the Code of Federal Regulations (CFR).

The following list of *Federal Register* notices site the original publication of the PMA regulation and subsequent changes to the regulation. The sections of 21 CFR 814 affected by the Federal Register notice are noted after the Federal Register date. Changes to 21 CFR 814 regarding Humanitarian Use Devices are listed separately.

Premarket Approval

July 22, 1986

Premarket Approval of Medical Devices

November 7, 1986

814.15 - Research conducted outside of the U.S.  
814.20 - Application

December 2, 1986

814.20 - Application  
814.15 - Research conducted outside of the U.S.  
814.39 - PMA supplements  
814.82 - Postapproval requirements  
814.84 - Reports

October 8, 1988

Medical Devices; 30-Day Notices and 135-Day PMA Supplement Review; Final Rule  
814.39 PMA supplements

March 27, 1990

814.20 - Application

December 10, 1992

814.44 - Procedures for review of a PMA

April 5, 1996

814.3 - Definitions  
814.47 - Temporary suspension of approval of a PMA

June 26, 1996

814.3 – Definitions

October 2 1996

814.9 – Confidentiality

July 29, 1997

National Environmental Policy Act; Revision of Policies and Procedures

814.20 - Application

January 30, 1998

Revising the Announcement Procedures for Approvals and Denials of Premarket Approval Applications

814.44 - Procedures for review of a PMA  
814.45 - Denial of a approval of a PMA

February 2, 1998

Financial Disclosure by Clinical Investigators

814.20 - Application  
814.42 - Filing a PMA

March 31, 2000

Medical Devices; Information Processing Procedures; Obtaining, Submitting, Executing, and Filing of Forms:  
Change of Addresses [[Text](#)] [[PDF](#)]

814.20 - Application

September 19, 2000

Administrative Practices and Procedures; Good Guidance Practices [[Text](#)] [[PDF](#)]

814.20 - Application

### **Humanitarian Use Devices**

June 26, 1996

Subpart H - Humanitarian Use Devices

February 2, 1998

Financial Disclosure by Clinical Investigators



814.12 - Filing an HDE

November 3, 1998

Humanitarian Use of Devices [[Text](#)]

- 814.100 - Purpose and Scope
- 814.104 - Original applications
- 814.106 - HDE amendments and resubmitted HDEs
- 814.108 - Supplemental Applications
- 814.112 - Filing an HDE
- 814.114 - Timeframes for reviewing an HDE
- 814.116 - Procedures for review of an HDE
- 814.118 - Denial of approval or withdrawal of approval of an HDE
- 814.120 - Temporary suspension of an approval of an HDE
- 814.124 - Institutional Review Board requirements
- 814.126 - Postapproval requirements and reports

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Updated 12/21/2004

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