§ 814.19 Product development protocol (PDP).

A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

Subpart B—Premarket Approval Application (PMA)

§ 814.20 Application.

(a) The applicant or an authorized representative shall sign the PMA. If the applicant does not reside or have a place of business within the United States, the PMA shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) Unless the applicant justifies an omission in accordance with paragraph (d) of this section, a PMA shall include:

(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. A PMA shall include separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects. A PMA shall be submitted in six copies each bound in one or more numbered volumes of reasonable size. The applicant shall include information that it believes to be trade secret or confidential commercial or financial information in all copies of the PMA and identify in at least one copy the information that it believes to be trade secret or confidential commercial or financial information.

(3) A summary in sufficient detail that the reader may gain a general understanding of the data and information in the application. The summary shall contain the following information:

(i) Indications for use. 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.

(ii) Device description. An explanation of 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.

(iii) Alternative practices and procedures. A description of existing alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended.

(iv) Marketing history. A brief description of the foreign and U.S. marketing history, if any, of the device, including 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. The description shall 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.

(v) Summary of studies. An abstract of any information or report described in the PMA under paragraph (b)(6)(ii) of this section and a summary of the results of technical data submitted under paragraph (b)(6) of this section. Such summary shall include a description of the objective of the study, a description of the experimental design of the study, a brief description of how the data were collected and analyzed, and a brief description of the results, whether positive, negative, or inconclusive. This section shall include the following:

(A) A summary of the nonclinical laboratory studies submitted in the application;

(B) A summary of the clinical investigations involving human subjects submitted in the application including a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, 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 shall be identified as such).

(vi) Conclusions drawn from the studies. A discussion demonstrating that the data and information in the application constitute valid scientific evidence within the meaning of § 860.7 and provide reasonable assurance that the device is safe and effective for its intended use. A concluding discussion shall 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.

(4) A complete description of:

(i) The device, including pictorial representations;

(ii) Each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;

(iii) The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;

(iv) The principles of operation of the device;

(v) The methods used in, and the facilities and controls used for, 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 practice can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(5) Reference to any performance standard under section 514 of the act or the Radiation Control for Health and Safety Act of 1968 (42 U.S.C. 263b et seq.) in effect or proposed at the time of the submission and to any voluntary standard that is relevant to any aspect of the safety or effectiveness of the device and that is known to or that should reasonably be known to the applicant. The applicant shall—

(i) Provide adequate information to demonstrate how the device meets, or justify any deviation from, any performance standard established under section 514 of the act or under the Radiation Control for Health and Safety Act, and

(ii) Explain any deviation from a voluntary standard.

(6) The following technical sections which shall contain data and information in sufficient detail to permit FDA to determine whether to approve or deny approval of the application:

(i) A section containing results of the nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear of life, and other laboratory or animal tests as appropriate. Information on nonclinical laboratory studies shall include a statement that each such study was conducted in compliance with Part 58, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

(ii) A section containing results of the clinical investigations involving human subjects with the device including clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, 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 report 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, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. Any investigation conducted under an IDE shall be identified as such. Information on clinical investigations involving human subjects shall include the following:

(A) A statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50, or if the study was not conducted in compliance with those regulations, a
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brief statement of the reason for the
noncompliance.

(B) A statement that each study was
conducted in compliance with Part 812
or Part 813 concerning sponsors of clin-
ical investigations and clinical inves-
tigators, or if the study was not con-
ducted in compliance with those regu-
lations, a brief statement of the reason
for the noncompliance.

(7) For a PMA supported solely by
data from one investigation, a jus-
tification showing that data and other
information from a single investigator
are sufficient to demonstrate the safe-
ty and effectiveness of the device and
to ensure reproducibility of test re-

(B)(i) A bibliography of all published
reports not submitted under paragraph
(b)(6) of this section, whether adverse
or supportive, known to or that should
reasonably be known to the applicant
and that concern the safety or effec-
tiveness of the device.

(ii) An identification, discussion, and
analysis of any other data, informa-
tion, or report relevant to an evalu-
ation of the safety and effectiveness
of the device known to or that should rea-
sonably be known to the applicant
from any source, foreign or domestic,
including information derived from in-
vestigations other than those proposed
in the application and from commer-
cial marketing experience.

(iii) Copies of such published reports
or unpublished information in the pos-
session of or reasonably obtainable by
the applicant if an FDA advisory com-
mittee 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 ap-
plicant shall 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 in-
clude, e.g., instructions for installation
and any information, literature, or ad-
vertising that constitutes labeling
under section 201(m) of the act.

(11) An environmental assessment
under § 25.32(a)(18) prepared in the ap-
plicable format in § 25.31, unless the ac-
tion qualifies for exclusion under
§ 25.24(e) (4) or (5). If the applicant be-
lieves that the action qualifies for ex-
clusion, the PMA shall under § 25.23(c)
provide information that establishes to
FDA’s satisfaction that the action re-
quested is included within the excluded
category and meets the criteria for the
applicable exclusion.

(12) Such other information as FDA
may request. If necessary, FDA will ob-
tain the concurrence of the appropriate
FDA advisory committee before re-
questing additional information.

(c) Pertinent information in FDA
files specifically referred to by an ap-
plicant may be incorporated into a
PMA by reference. Information in a
master file or other information sub-
mitted 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. If a master file is not re-
ferenced within 5 years after the date
that it is submitted to FDA, FDA will
return the master file to the person
who submitted it.

(d) If the applicant believes that cer-
tain information required under para-
graph (b) of this section to be in a PMA
is not applicable to the device that is
the subject of the PMA, and omits any
such information from its PMA, the ap-
plicant shall submit a statement that
identifies the omitted information and
justifies the omission. The statement
shall be submitted as a separate sec-
tion in the PMA and identified in the
table of contents. If the justification
for the omission is not accepted by the
agency, FDA will so notify the appli-
cant.

(e) The applicant shall periodically
update its pending application with
new safety and effectiveness informa-
tion learned about the device from on-
going or completed studies that may
reasonably affect an evaluation of the
safety or effectiveness of the device or
that may reasonably affect the state-
ment of contraindications, warnings,
precautions, and adverse reactions in
the draft labeling. The update report
shall be consistent with the data re-
porting provisions of the protocol. The
applicant shall submit three copies of
any update report and shall include in
the report the number assigned by FDA
to the PMA. These updates are consid-
§ 814.37 PMA amendments and resubmitted PMA's.

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

(b) 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.

(c) 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, as follows:

(1) 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.

(2) 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.

(d) An applicant may on its own initiative withdraw a 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 of the date of the request, FDA will consider the pending PMA or PMA supplement to be withdrawn voluntarily by the applicant.

(e) An applicant may resubmit a PMA or PMA supplement after withdrawing it or after it is considered withdrawn under paragraph (d) of this section, or after FDA has refused to accept it for filing, or has denied approval of the PMA or PMA supplement. A resubmitted PMA or PMA supplement shall comply with the requirements of §814.20 or §814.39, respectively, and shall include the PMA number assigned to the original submission and the applicant's reasons for resubmitting the PMA or PMA supplement.
mission of the PMA or PMA supplement.

§ 814.39 PMA supplements.

(a) After FDA approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA, under paragraph (e) of this section, has advised that an alternate submission is permitted. While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall 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:

(1) New indications for use of the device.
(2) Labeling changes.
(3) The use of a different facility or establishment to manufacture, process, or package the device.
(4) Changes in manufacturing facilities, methods, or quality control procedures.
(5) Changes in sterilization procedures.
(6) Changes in packaging.
(7) Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.
(8) 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 approved, the change shall be reported to FDA under paragraph (b) of this section.

(b) An applicant may make a change in a device after FDA’s approval of a PMA for the device without submitting a PMA supplement if the change does not affect the device’s safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device.

(c) All procedures and actions that apply to an 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 under §814.20(b)(3) is required for only a supplement submitted for 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. The applicant shall submit three copies of a PMA supplement and shall include information relevant to the proposed changes in the device. A PMA supplement shall include a separate section that identifies each change for which approval is being requested and explains the reason for each such change. The applicant shall submit additional copies and additional information if requested by FDA. The time frames for review of, and FDA action on, a PMA supplement are the same as those provided in §814.40 for a PMA.

(d)(1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section 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 under §814.17 of a written FDA order approving the PMA supplement provided that:

(i) The PMA supplement and its mailing cover are plainly marked “Special PMA Supplement—Changes Being Effected”;
(ii) The PMA supplement provides a full explanation of the basis for the changes;
(iii) The applicant has received acknowledgement from FDA of receipt of the supplement; and
(iv) The PMA supplement specifically identifies the date that such changes are being effected.

(2) The following changes are permitted by paragraph (d)(1) of this section:

(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction.
(ii) Labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device.
(iii) Labeling changes that delete misleading, false, or unsupported indications.

(iv) Changes in quality controls or manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device.

(e) FDA will identify a change to a device for which an applicant has an approved PMA and for which a PMA supplement under paragraph (a) is not required. FDA will identify such a change in an advisory opinion under §10.85, if the change applies to a generic type of device, or in correspondence to the applicant, if the change applies only to the applicant’s device. FDA will require that a change for which a PMA supplement under paragraph (a) is not required be reported to FDA in—

(1) A periodic report under §814.84 or

(2) A 30-day PMA supplement under this paragraph.

FDA will identify, in the advisory opinion or correspondence, the type of information that is to be included in the report or 30-day PMA supplement. If the change is required to be reported to FDA in a periodic report, the change may be made before it is reported to FDA. If the change is required to be reported in a 30-day PMA supplement, the change may be made 30 days after FDA files the 30-day PMA supplement unless FDA requires the PMA holder to provide additional information, informs the PMA holder that the supplement is not approvable, or disapproves the supplement. The 30-day PMA supplement shall follow the instructions in the correspondence or advisory opinion. If the 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.

(Amended by the Office of Management and Budget under control number 0910-0231)