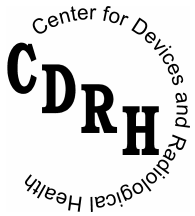
Guidance for Industry and FDA Staff

Premarket Approval Application Filing Review

Document issued on: May 1, 2003

This document supersedes PMA Filing Decisions (P90-2), dated May 18, 1990 and PMA Refuse to File Procedures (P94-1), dated May 2, 1994.

For questions regarding this document, contact Nicole Wolanski at 301-594-2186. For questions regarding biologics, contact Sayah Nedjar at 301- 827-3524.



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Please refer to the exact title of this guidance document when submitting comments. Comments may not be acted upon by the Agency until the document is next revised or updated.

In addition, we are soliciting comments on the following issues related to the Premarket Approval Application (PMA) filing process. Please submit all comments to the above address.

> **#1**: Comment on your experience with the PMA filing process and provide suggestions for how the Center for Devices and Radiological Health (CDRH) could improve the filing process. Based on your experience with the PMA filing process, describe what you have learned about it that is not adequately explained in the guidance document.
>
> **# 2**: When CDRH makes a "not filing" decision, we issue a letter stating the specific reasons for our decision. Please comment on the adequacy and clarity of the information that CDRH provides in a "not filing" decision, both in written and verbal correspondence.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/ode/297.pdf , or to receive this document by fax, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number (**297**) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Premarket Approval Application Filing Review

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

Purpose

As discussed in more detail below, the PMA regulation identifies the criteria that, if not met, may serve as a basis for refusing to file a PMA. These criteria have been the subject of two previous ODE Blue Book Memoranda (i.e., "PMA Filing Decisions #P90-2," dated May 18, 1990, and "PMA Refuse to File Procedures #P94-1," dated May 2, 1994) and are captured in the "Checklist for Filing Decisions for PMAs." These documents have been used by CDRH staff for over 10 years to help elucidate the broad preclinical and clinical issues that need to be addressed in a PMA and the key decisions to be made during the filing process. Although these documents were developed for internal use, industry has also referred to these documents for when preparing their PMA submissions.

The agency recognizes, however, that there is still room for improvement in the consistency with which filing decisions have been made across the reviewing divisions. Moreover, with the enactment of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), the filing process takes on additional importance in helping the Center to meet its performance goals. Therefore, the purpose of the current guidance document is to further clarify the filing criteria to enhance the consistency of our filing decisions and to help applicants understand the types of information FDA will need to determine if a PMA should be "filed."

CDRH staff and industry should note that the current guidance is not significantly different from the previous Blue Book Memoranda and PMA filing checklist as the PMA filing criteria defined in the regulation have not changed. The "preliminary questions" and the "filing review questions" remain the same. The focus of this guidance is to provide additional explanation and examples whenever possible to help clarify questions that

reviewers have identified as needing more specificity. For example, original PMAs have been submitted with required information missing. This document explains that if the missing information can be quickly provided (e.g., within 30 days) by the PMA applicant without impeding the review process, the application may be filed. Also, there have been cases in which a PMA has been submitted before the planned enrollment for the study has been achieved. This guidance provides examples of when such a situation would not be problematic, such as when the change in protocol was the result of a recommendation of a Data Monitoring Committee. This type of situation has been discussed in previous FDA guidances, such as in the Least Burdensome guidance,[1] but is reiterated here, since it could affect the filing process.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html.

Introduction

The purpose of the PMA filing review is to make a threshold determination about whether an application is sufficiently complete for the Agency to undertake a substantive review. The PMA regulation (21 CFR 814.42(e)) states that FDA may refuse to file a PMA if **any** of the following applies:

[1] The complete title of this guidance is: "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles" and can be found at: http://www.fda.gov/cdrh/modact/leastburdensome.html#2
.

(1) The PMA is incomplete because it does not on its face contain all the information required under section 515(c)(1)(A)-(G) of the Federal Food, Drug, and Cosmetic Act (the act).

(2) The PMA does not contain each of the items required under section 814.20 and justification for omission of any item is inadequate.

(3) The applicant has a pending premarket notification under section 510(k) of the act with respect to the same device, and FDA has not determined whether the device falls within the scope of section 814.1(c).

(4) The PMA contains a false statement of material fact.

(5) The PMA is not accompanied by a statement of either certification or disclosure as required by 21 CFR Part 54.

Section 814.20 of the regulation further specifies that PMAs must include, among other things, "*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*" (21 CFR 814.20(b)(6)). The key issue here is that the phrase "data and information in sufficient detail" sometimes leads to subjective interpretations. Because of this, CDRH staff has frequently expressed the need for more specific guidance in applying this regulatory standard to the PMA application filing decision-making process.

The previous Blue Book Memoranda relating to PMA filing have focused on defining broad issues or principles that should be used in deciding whether a PMA should be filed. These memoranda have only been partially successful in clarifying the filing criteria. The goal of this document is to clarify the criteria for filing a PMA, thereby enhancing the consistency of our filing decisions. The decision-making process presented in this document is captured in a checklist (Attachment 1), which CDRH staff will use during the filing review process.

Scope

The information presented in this document is intended to provide CDRH staff with a clear, consistent approach to making filing decisions on original PMA applications and panel-track PMA supplements. (Modular PMAs are not addressed in this document as they will be covered in a separate guidance.)

In addition, it should be noted that this document is focused on the regulatory and scientific criteria for making a "File" or "Not File" decision for a PMA. It specifically does not alter the following administrative aspects of the PMA filing process: the time frame for the filing review phase (i.e., 45 days); the processes for document tracking, distribution, and handling; and the procedures for assembling the review team and setting up the filing meeting.

This document does not discuss the statutory criteria for expedited designation or the requirements for an expedited submission to be tracked in accordance with the MDUFMA performance goals. FDA will be issuing additional guidance on Expedited PMAs at a later time. Also, this document does not address the monetary aspects associated with PMAs. Information pertaining to the fees and payment procedures for submission of a PMA can be found at http://www.fda.gov/oc/mdufma. Information pertaining to the amount that will be refunded when the agency makes a not filing decision or determines that the submitted PMA is not required will be addressed in additional guidance at a later time.

Presubmission Interaction

Prior to interacting with review staff, applicants should consult the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) for general information regarding the PMA regulations. Before submitting a PMA, we encourage applicants to interact with CDRH review staff. Such presubmission interaction is an important way of improving the quality and completeness of a PMA and, thus, increases the likelihood of the PMA being filed. Also, we encourage applicants to meet face to face with CDRH staff before preparing the PMA to discuss issues related to their specific device and PMA.

In addition, CDRH's Device Advice, http://www.fda.gov/cdrh/devadvice/, as well as other applicable CDRH device-specific guidance documents, provide valuable information for preparing PMAs; all of which are available on the Internet http://www.fda.gov/cdrh/guidance.html and through DSMICA.

Basic Review Policies and Procedures

In order to use this guidance appropriately, FDA staff should review the following basic assumptions about the Center's review policies and procedures.

PMA is the appropriate regulatory mechanism

In accordance with the Least Burdensome provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), the filing review should verify that PMA is the appropriate regulatory mechanism for the device. If the product is not a device, or the device can be properly regulated by other means, staff should determine this during the filing review and convert the PMA as appropriate.

Some required elements can be submitted interactively during review

The PMA should contain the basic administrative and scientific elements listed in 21 CFR 814.20 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=814.20),

acknowledging that some of these elements, if missing, can be submitted interactively[2] without impeding our filing review.

The contents of the PMA should allow substantive review

PMA contents should not be so disorganized or inadequate so as to prevent proceeding with substantive review.

The filing decision is not based on a substantive review of the studies in the PMA

In determining whether a PMA should be filed, studies should not be categorized as "grossly inadequate" based on a substantive evaluation of the reported data/results (i.e., we should not refuse to file a PMA because we have reviewed its data and believe that it is ultimately not approvable).

Staff will consider the applicant's justifications for any alternate approaches

Consistent with the Least Burdensome provisions of FDAMA, staff will consider the applicant's justifications for any alternate approaches to demonstrating reasonable assurance of safety and effectiveness.[3]

PMA review team will hold a division-level filing meeting

The decision to "File" or "Not File" a PMA is made at the division level. It should be made in collaboration with the PMA review team, the Chief of the reviewing branch, and the Director of the reviewing division. These discussions should occur during a division-level filing meeting, held approximately 30 days after receipt of the PMA. The Program Operations Staff (POS) should be informed of the meeting and consulted when necessary.

The Checklist – Preliminary Questions

Within 2 weeks of receipt of the PMA and prior to the formal filing review, the PMA team leader (or other office-designated personnel) should answer a set of preliminary questions. These preliminary questions are included on the first page of the checklist (Attachment 1 of this document). This checklist will be filled out for each PMA, and included as part of the review documentation.

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[2] Staff should follow the procedures described in **Blue Book Memo: Fax & E-mail Communication with Industry about Premarket Files Under Review A02-01**, http://www.fda.gov/cdrh/ode/a02-01.html, for phone, fax, and email communication with PMA applicants during the review process.

[3] The presence of a justification is particularly relevant in the filing stage while the in-depth review of such justifications falls within the scope of the substantive review phase.

Depending upon the answers to these preliminary questions, the remainder of the filing review may or may not be required. If the responses to the preliminary questions and subsequent consultation with the Center personnel identified below indicate that the PMA filing review should not continue,[4] the PMA team leader should promptly:

- inform the PMA review team to halt further review of the application until further notice; and
- notify the applicant using proper administrative procedures.

The preliminary questions are:

1. **Is the product a device (per 201(h) of the act)?**

   If the product does not appear to meet the definition of a device, as stated in Section 201(h) of the act, the PMA team leader will consult with the ODE Jurisdictional Officer to determine the appropriate action and will inform division management. If CDRH staff determines that the product is not a device, the PMA review team will stop the review.

2. **Is the device subject to review by CDRH?**

   If the device is either subject to review in a different Center (e.g., CBER), or if the device is a combination product and CDRH does not have the lead, the PMA team leader will consult with the ODE Jurisdictional Officer to determine the appropriate action and will inform division management. If CDRH staff determines that the device is not subject to CDRH review, the PMA review team will stop the review.

3. **Is class III/PMA review required for the device?**

   Our goal is to apply the appropriate level of regulation to ensure device safety and effectiveness. Therefore, early in the filing review process, FDA should consider the regulatory burden and the available mechanisms to apply the proper degree of regulation. In making this determination, staff will consider how similar devices are being regulated.

   Class III/PMA review is required if the device is:

   - a transitional device,
   - the subject of a 515(b) "call for PMA" regulation,

[4] There are two additional criteria for not accepting a PMA for review: i) the application is not submitted with the required user fee and ii) the application is not signed or counter-signed by a U.S. representative. Since any PMA not meeting these two criteria will not be processed by the Document Mail Center, they are not included in the checklist.

- comparable in technology and intended use to a device subject to PMA requirements,
- novel technology with no apparent means of regulation in Class I or II (see below), or
- Class III by virtue of a 510(k) Not Substantially Equivalent (NSE) determination with no apparent means of regulation in Class I or II (see below).

Regulation under PMA as a Class III device is not appropriate, if the device:

- was previously identified as a possible de novo candidate in an NSE letter,
- is the subject of a NSE decision due to lack of industry responsiveness,
- is similar to other 510(k)-cleared devices and believed to be Class I or II, or
- is not currently subject to premarket requirements, i.e., under enforcement discretion.

If regulation under PMA is not appropriate, the PMA team leader will inform division management and POS to determine the appropriate action. If the review division determines that class III/PMA review is not required, the PMA review team will stop the review.

4. **Is there a pending 510(k) for the same device with the same indications for use?**

   The regulations do not allow FDA to file a PMA if a 510(k) for the same device is pending (21 CFR 814.42(e)(3)). If there is a pending 510(k), the review team will stop the review. The applicant should either withdraw the 510(k) or the PMA. The PMA team leader will consult division management and POS to determine the appropriate action.

5. **Is the submitter the subject of the Application Integrity Policy (AIP)?**

   The lead reviewer will refer to the AIP list. If the applicant is on the list, the reviewer will consult the ODE Integrity Officer to determine the appropriate action.

The Checklist – Filing Review

If the answers to the above preliminary questions indicate that PMA review should continue, the formal filing review should proceed by answering questions in the "Filing Review" section of the checklist. This section of the checklist collects information regarding the completeness of the PMA (i.e., "Inventory of Organizational and Administrative Elements"), assesses the basic adequacy of the technical elements (i.e., "Filing Assessment of Technical Elements"), and guides CDRH staff through the process necessary to arrive at a decision to "File" or "Not File" a PMA (i.e., "Filing Decision Questions").

The specific issues that are critical to the PMA filing decision-making process (i.e., the "Filing Decision Questions") are individually discussed below. The numbering scheme used

for these decision questions corresponds to that of the checklist. Each Filing Decision Question should be answered "YES" for the PMA application to be filed.

We do not anticipate that any single member of the PMA review team will be able to answer all of these questions. Rather, we expect that the PMA team leader will complete this checklist in consultation with the team members at the conclusion of the division-level filing meeting.

Decision 1: Is the PMA sufficiently organized to permit substantive review?

If the PMA has one or more organizational problems that appear to be minor **or** can be remedied by contacting the applicant[5] by phone, fax, or email[6] and requesting additional information, the answer to the above question is "YES" and the PMA team leader will note the specific problem(s) on the checklist. Examples of such minor organizational problems include: missing Table of Contents and omission of section dividers (provided the PMA appears to be organized into discrete sections). If such minor organizational problems exist, the problems do not preclude the review division from filing the PMA.

If the PMA has one or more organizational problems that will specifically hamper substantive review **and** cannot be remedied through communication with the applicant by phone, fax, or email, the answer to the above question is "NO" and the PMA team leader will note the specific problem(s) on the checklist. Examples of such major/significant organizational problems include: sections/information cannot be easily located, contents are not organized into discrete sections, and information is placed in the wrong section or is improperly distributed among multiple sections. If such major organizational problems exist and can't be remedied by a call to the applicant, the review division should not file the PMA.

Decision 2: Is PMA sufficiently complete to permit substantive review?

If the PMA is missing one or more of the sections required in 21 CFR 814.20, but this omission either does not prohibit initiating the substantive review process **or** can be remedied by interactively contacting the applicant[5] by phone, fax, or email and requesting additional information,[6] the answer to the above question is "YES" and the PMA team leader will note the specific omission(s) on the checklist. Examples of information that would typically be categorized as minor omissions include:

[5] The applicant's anticipated time frame for providing this additional information should not exceed 30 days.

[6] Staff should follow the procedures described in Blue Book Memo: **Fax & E-mail Communication with Industry about Premarket Files Under Review A02-01**, http://www.fda.gov/cdrh/ode/a02-01.html, for phone, fax, and email communication with PMA applicants during the review process.

- bibliography,
- device sample,
- summary of the PMA,
- single-investigator justification,
- financial certification or disclosure, and
- claim of categorical exclusion for an environmental assessment (if the device would qualify).

Additionally, for filing purposes only, the applicant may submit the manufacturing section later (within 90 days) during the substantive review period. If such minor omissions exist, it does not preclude the review division from filing the PMA.

If, on its face, the PMA is missing one or more required sections, and this omission prohibits substantive review **and** cannot be readily supplied through interactive communication with the applicant, the answer to the above question is "NO" and the PMA team leader will note the specific omission(s) on the checklist. Examples of information that would typically be categorized as major omissions include:

- device description section,
- description of the principles of operation of the device (including components) and properties relevant to clinical function,
- reports of key nonclinical studies,
- clinical studies section,
- clinical protocol,
- statistical analyses,
- basic labeling elements (statement of indications for use, contraindications, warnings, precautions, and instructions for use), and
- environmental assessment (if the device does not qualify for a claim of categorical exclusion).

Additionally, if any major section is not in English **and** not accompanied with an English translation, the answer to the above question is "NO." If such major omissions exist, the review division should not file the PMA.

Decision 3: From only an administrative review, do the data submitted in the PMA appear to constitute valid scientific evidence?

If the data do not constitute valid scientific evidence, the division should not file the PMA. However, answer "NO" only if, it is **clear** that the PMA is supported solely by information that 21 CFR 860.7 identifies as **not** regarded as valid scientific evidence, i.e., "isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions."

Decision 4: Were the clinical study data collected and analyzed per the protocol?

If the clinical data submitted in support of PMA approval were collected and analyzed consistent with the major elements of the clinical protocol (i.e., objectives, study population, endpoints, study design, hypothesis, sample size, and follow-up duration), **or** the applicant provides a scientific or clinical justification for the use of an alternate approach, the answer to the above question is "YES" and the PMA team leader will note any specific deviations or justifications on the checklist. In addition, if the sample size is smaller or the follow-up duration is shorter than specified in the clinical protocol, but such changes are supported by either: (i) the recommendation of a Data Monitoring Committee (DMC) or (ii) statistical plans that incorporate interim stopping rules, substantive review of the PMA may proceed. That is, these cases do not preclude the division from filing the PMA.

If the study deviated from the clinical protocol with respect to the major elements identified in the paragraph above **and** the applicant provided no justification, the answer to the above question is "NO" and the PMA team leader will note the specific deviation(s) on the checklist. In these cases, the division should not file the PMA.

As discussed above, occasionally, applicants have submitted PMAs with incomplete clinical data, i.e., the sample size is smaller or follow-up duration is shorter than specified in the clinical protocol. If no justification is provided and/or the applicant indicates they intend to update the PMA with necessary additional clinical data, we will consider such PMAs to be submitted prematurely and therefore incomplete. If the PMA is viewed as a premature submission, the answer to the above question is "NO." In these cases, the review division should not file the PMA.

Decision 5: Were the nonclinical and clinical data collected on the final design of the device (i.e., the device design intended to be marketed)?

If the nonclinical and pivotal clinical data submitted in support of PMA approval were collected on the final device design, or the differences between the study device and final device clearly do not affect safety or effectiveness of the device and/or clinical outcome, the answer to the above question is "YES" and any device changes will be noted on the checklist. Furthermore, if the clinical data were collected on an earlier design of the device **and** the applicant provides a detailed scientific or clinical justification describing why the study results on the earlier device design apply to the proposed design, the answer to the above question is "YES" and the justification will be noted on the checklist. These cases do not preclude the review division from filing the PMA.

If changes were made to the device design either during or after the pivotal nonclinical and clinical studies and these changes could potentially impact safety and/or effectiveness **and** no justification is provided as to why these data are

applicable to the new design, the answer to the above question is "NO." In this case, the PMA team leader will note the specific device change(s) on the checklist, and the review division should not file the PMA.

Decision 6: Were the patient population and endpoints selected appropriately?

If, upon an administrative review, the patient population (as defined by the inclusion and exclusion criteria) in the pivotal study matches the device's indications for use and the endpoints that were selected appear to be clinically relevant, the answer to the above question is "YES." Additionally, if FDA has questions regarding the appropriateness of patient population and/or endpoints **and** the applicant provides a detailed scientific or clinical justification for this approach, the answer to the above question is "YES." These cases do not preclude the review division from filing the PMA.

If the patient population and/or endpoints of the pivotal study, **on their face**, do not match the proposed indications for use **and** no justification is provided for this alternate approach, the answer to the above question is "NO." In addition, if the pivotal study was conducted outside the U.S. and the local medical practice and/or patient population do not match those of the U.S., answer "NO" to the above question. In these cases, the PMA should not be filed.

Decision 7: Does the PMA address the key nonclinical and clinical issues identified by FDA prior to submission of the PMA application, OR has the applicant provided a detailed scientific or clinical justification for the alternate approach?

If the PMA application addresses each of the key nonclinical and clinical issues identified by FDA in either prior regulatory submissions, interactions regarding the proposed device (e.g., prior PMA application, prior "Not Substantially Equivalent" decision on a 510(k), IDE letters, pre-IDE comments, Determination or Agreement meeting(s), or other meetings or teleconferences), or a guidance document, the answer to the above question is "YES." Furthermore, if some of these key issues previously identified by FDA are not addressed, but the PMA application contains a detailed scientific or clinical justification for the omission or deviation, the answer to the above question is "YES." These cases do not preclude the review division from filing the PMA.

In this context, the term "key issues" is meant to refer to issues that are central to our review of device safety and effectiveness. Examples of key issues include: long-term nonclinical studies (e.g., biocompatibility, carcinogenicity, or other animal studies), sample size, patient population, statistical hypothesis, study design, and endpoints. These key issues typically are device-specific. As a result, the decision of the review division to "Not File" a PMA application based on this criterion can only be made after carefully considering these questions:

Are the types of necessary nonclinical and clinical studies well-known in the scientific and medical communities for the particular device?

For an "established" device type, the types of nonclinical and clinical studies that we would expect in a PMA are likely to be well-known both within FDA and in the scientific and medical communities and, as such, are often included as part of an FDA guidance document and/or consensus standard. On the other hand, similar issues for a novel medical device may be the subject of ongoing scientific discussion or debate and typically need to be assessed by the PMA review team during the substantive review process. Therefore, we expect that the review division will only consider refusing to file based on a "NO" response to "Decision 7" for PMAs for established device types.

Were the issues conveyed to the manufacturer as part of a documented regulatory process?

Examples of a documented regulatory process include:

- prior PMA application,
- prior "Not Substantially Equivalent" decision on a 510(k),
- IDE letters, or
- letter(s) issued as a result of Determination or Agreement meetings.

Issues conveyed in this manner typically carry more weight than recommendations made in more informal situations (e.g., pre-IDE comments, meetings or teleconferences). Therefore, we expect staff will reserve refusing to file based on a "NO" response to "Decision 7" to instances where the key issues were identified by staff as part of a documented regulatory process.

Concerns raised by the agency during the filing review regarding **results and outcomes** of nonclinical and clinical studies **should not preclude filing**. Since the interpretation of study results typically involves a thorough risk/benefit assessment, which is often interdisciplinary in nature, these issues inherently need to be weighed during the substantive review process. Examples of information that would typically fall into this category include:

- demographic information for the study population,
- conclusions regarding statistical analyses,
- report or assessment of protocol deviations, and
- reports of device failures or malfunctions.

Attachment 1

Checklist for Filing Decision for PMAs

Identification: ***PMA Number: _____*** ***Date Received: _____***

Device: _____ ***Procode: _____***

Company Name/ Address: _____

_____

Contact Name/Phone numbers:_____

_____

Decision: ***Review Team Recommendation: File ___*** ***Not File ___***

Expedited review requested: ***Yes___*** ***No___***

Does device meet expedited criteria, outlined in the expedited review guidance (*hyperlink to be constructed*)***:*** ***Yes___*** ***No___***

Expedited Review Granted: ***Yes___*** ***No___***

Team Leader Signature: _____ Date: _____

Supervisory Signature: _____ Date: _____

Preliminary Questions		
Answers in the shaded blocks indicate consultation with Center advisor is needed.	Yes	No
1. Is the product a device (per 201(h) of the act)? If no, consult with the ODE Jurisdictional Officer to determine the appropriate action and inform your division management.		
2. Is the device subject to review by CDRH (i.e., device is not subject to review by a different Center, and device is not a combination product for which another Center has the lead, etc.)? If no, consult with the ODE Jurisdictional Officer to determine the appropriate action and inform your division management.		
3. Is class III/PMA review required for the device? For example, a class III review is not required if the device could be properly regulated as class I or class II via 510(k), de novo classification, enforcement discretion, etc.		
4. Is there a pending 510(k) for the same device with the same indications for use? The regulations do not allow the FDA to file a PMA if a 510(k) for the same device is pending (21 CFR 814.42(e)(3)).		
5. Is the applicant the subject of an Application Integrity Policy (AIP)? If yes, consult with the ODE Integrity Officer to determine the appropriate action.		

Only proceed to the "Filing Review" section if the above preliminary questions indicate PMA review should continue.

Filing Review

Bolded items under "Inventory of Organizational and Administrative Elements" and "Filing Assessment of Technical Elements" feed into Filing Decision Questions 1-7

Inventory of Organizational and Administrative Elements (21 CFR 814.20)

Check "Yes" if item is present in application, "No" if it is not, "N/A" if it is not needed.

		Yes	No	N/A
A.	PMA Content			
1.	**Are all required sections in English or accompanied with an English translation?**	☐	☐	☐
2.	Is there a table of contents? (CFR 814.20(b)(2))	☐	☐	☐
3.	Is a bibliography provided? (21 CFR 814.20(b)(8)(i))	☐	☐	☐
	• Have copies of key articles been provided and are English translations included, if appropriate?	☐	☐	☐
4.	If a device sample is needed, has it been provided? (21 CFR 814.20(b)(9))	☐	☐	☐
5.	Is there a summary of the contents of the PMA?	☐	☐	☐
6.	Device Characteristics			
a.	**Is a description of device included? (21 CFR 814.20(b)(4)(i))**	☐	☐	☐
i.	pictorial representations	☐	☐	☐
ii.	materials specifications	☐	☐	☐
	• Is there a color additive present that 1) is intended solely to impart color and 2) contacts the body for a significant period of time? (Is the device subject to 21 CFR 70.5 General restrictions for use of color additives?)	☐	☐	☐

		Yes	No	N/A
b.	**Is a description of the principles of operation of the device (including components) and properties relevant to clinical function present? (21 CFR 814.20(b)(4)(iii))**	☐	☐	☐
7.	Device Manufacturing Sections (Note: for filing purposes it may be submitted later during the substantive review period.) (21 CFR 814.20(b)(4)(v) and Guidance for the Preparation of PMA Manufacturing Information)			
•	Has a description of the methods, facilities, and controls used in the manufacture, processing, packing, storage, and installation of the device been provided? (21 CFR 814.20(b)(4)(v))	☐	☐	☐
8.	**Is a summary of the nonclinical laboratory studies and results provided? (21 CFR 814.20(b)(6)(i))**	☐	☐	☐
a.	Sterilization	☐	☐	☐
b.	Biological/Microbiological	☐	☐	☐
c.	Immunological	☐	☐	☐
d.	Toxicological/Biocompatibility	☐	☐	☐
e.	Engineering (Stress, Wear, etc.)	☐	☐	☐
f.	Chemistry/Analytical (for IVDs)	☐	☐	☐
g.	Shelf life	☐	☐	☐
h.	Animal Modeling	☐	☐	☐
i.	Other essential laboratory testing	☐	☐	☐
9.	**Is a summary of the clinical investigations and results provided?**	☐	☐	☐
a.	**Are clinical protocols included?**	☐	☐	☐
b.	Is a description of study population demographics provided?	☐	☐	☐
c.	Is a description of adverse events, e.g. adverse reactions, complaints, discontinuations, failures, replacements, etc. given?	☐	☐	☐
d.	Have report forms for patients who died or were discontinued been provided, i.e., to resolve potential bias?	☐	☐	☐

		Yes	No	N/A
10.	**Are statistical analyses of the clinical investigations provided?**			
11.	Has appropriate draft labeling been submitted?	☐	☐	☐
	a. Physician Labeling	☐	☐	☐
	i. **Are indications for use included?**	☐	☐	☐
	ii. **Are contraindications, warnings, and precautions included?**	☐	☐	☐
	iii. **Are instructions for use included?**	☐	☐	☐
	b. Patient Labeling (OHIP/ODE Memorandum of Understanding)	☐	☐	☐
	c. Technical/operators manual	☐	☐	☐
12.	Statements/Certifications/Declarations of Conformity			
	a. Has the applicant provided documentation to establish conformance with applicable performance standards and/or voluntary standards? (21 CFR 814.20(b)(5))	☐	☐	☐
	b. Has the applicant provided documentation to establish conformance with applicable FDA guidance/guidelines?	☐	☐	☐
	c. Has the applicant complied with the requirements of 21 CFR Part 54 regarding financial disclosure of clinical investigators?	☐	☐	☐
	d. Environmental Assessment under 21 CFR 25.20(n)	☐	☐	☐
	i. If claiming a categorical exclusion, information to justify the exclusion, OR	☐	☐	☐
	ii. An environmental assessment (<u>ONLY</u> required for devices that present new environmental concerns)	☐	☐	☐

Filing Assessment of Technical Elements – Nonclinical and Clinical Studies

Check "Yes" if the information submitted is considered adequate to permit substantive review, "No" if it is not, "N/A" if it is not needed.

		Yes	No	N/A
A.	Consistency of study with protocol and study completeness			
1.	**sample size/number of patients completing the study**	☐	☐	☐
2.	**follow-up duration**	☐	☐	☐
3.	**follow-up evaluations**	☐	☐	☐
4.	**objectives**	☐	☐	☐
5.	**study population/enrollment criteria**	☐	☐	☐
6.	**endpoints**	☐	☐	☐
7.	**study design**	☐	☐	☐
8.	**hypothesis**	☐	☐	☐
9.	**statistical analysis**	☐	☐	☐
B.	Appropriateness of key aspects of the protocol			
1.	**Does the patient population match the intended use?**	☐	☐	☐
2.	**Have clinically significant endpoints been selected?**	☐	☐	☐
3.	Is the primary study based on foreign clinical data? (21 CFR 814.15(b) and 814.15(d))	☐	☐	☐
•	**Are data justified (i.e., do the population and medical practices match those in the U.S.)?**	☐	☐	☐

	Yes	No	N/A
C. Prior history of the applicant with this device			
1. If this device has been the subject of an NSE decision, does the PMA address the NSE issues (e.g., new material, energy source, etc.)?	☐	☐	☐
2. Has a previously submitted PMA for this device been withdrawn?	☐	☐	☐
• **If yes, does the current PMA address any historical issues related to safety or effectiveness?**	☐	☐	☐
3. Is reference to applicable IDEs given? IDE# _____	☐	☐	☐
• **Has the data presented in the PMA taken into account the staff concerns addressed in the IDE correspondence (e.g., "future considerations")?**	☐	☐	☐
4. Were any pre-submission meetings held with applicant? (e.g., Teleconference, Informal face-to-face, Agreement, Determination)	☐	☐	☐
• **If yes, were all staff concerns previously presented to the applicant addressed in the PMA or has the applicant provided a detailed scientific or clinical justification for the alternate approach?**	☐	☐	☐

Filing Decision Questions

The Filing Decision Questions are shaded and bolded. Some Filing Decision Questions are preceded by introductory questions (denoted by suffixes "a" and "b") to ensure that those Filing Decision Questions are answered appropriately.

		Yes	**No**
Decision 1a	Are there any organization problems? -If "no," answer "yes" to Decision 1 below. -If "yes," describe and continue on to Decision 1b. Comments:	☐	☐
Decision 1b	Can the organization problems be remedied through interactive communication with the applicant? -If "yes," answer "yes" to Decision 1 below. -If "no," describe and answer "no" to Decision 1 below. Comments:	☐	☐
Decision 1	**Is the PMA sufficiently organized to permit substantive review?**	☐	☐
Decision 2a	Are there any missing elements/sections (identified above)? -If "no," answer "yes" to Decision 2 below. -If "yes," describe and continue on to Decision 2b. Comments:	☐	☐

		Yes	No
Decision 2b	Can the missing section(s)/element(s) be supplied interactively by the applicant? -If "yes," answer "yes" to Decision 2 below. -If "no," describe and answer "no" to Decision 2 below. Comments:	☐	☐
Decision 2	**Is the PMA sufficiently complete to permit substantive review?**	☐	☐
Decision 3	**From only an administrative review, do the data submitted in the PMA appear to constitute valid scientific evidence? Only answer "no" if, it is clear that the PMA is supported solely by information that 21 CFR 860.7 identifies as not regarded as valid scientific evidence:** **-isolated case reports** **-random experience** **-reports lacking sufficient details to permit scientific evaluation** **-unsubstantiated opinions** **Comments:**	☐	☐

		Yes	No
Decision 4a	Was each study completed and analyzed per the protocol (answers to A1-9 under "Filing Assessment of Technical Elements")? -If "yes," answer "yes" to Decision 4 below. -If "no," describe and continue on to Decision 4b. Comments:	☐	☐
Decision 4b	If any study was not completed per the protocol, did the applicant provide a detailed scientific or clinical justification for this alternate approach, without the intention of updating the PMA with additional data? -If "yes," describe and answer "yes" to Decision 4 below. -If "no" (i.e., no justification is provided, or a clinical update is intended), describe and answer "no" to Decision 4 below. Comments:	☐	☐
Decision 4	**Were the clinical study data collected and analyzed per the protocol?**	☐	☐
Decision 5a	Were the studies performed using the final device design (i.e., the device design intended to be marketed)? -If "yes," answer "yes" to Decision 5 below. -If "no," describe and continue on to Decision 5b. Comments:	☐	☐

		Yes	No
Decision 5b	If the studies were performed using an earlier device design, did the applicant provide a detailed scientific or clinical justification? -If "yes," describe and answer "yes" to Decision 5 below. -If "no" (i.e., device changes were made that could impact safety OR effectiveness and no justification is provided), describe and answer "no" to Decision 5 below. Comments:	☐	☐
Decision 5	**Were the nonclinical and clinical data collected on the final design of the device (i.e., the device design intended to be marketed)?**	☐	☐
Decision 6a	Does the patient population match the device's indication for use, are the endpoints clinically relevant, and (if the pivotal study was conducted outside the U.S) do the foreign data/patient population and medical practice match those of the U.S.? -If "yes," answer "yes" to Decision 6 below. -If "no," describe and continue on to Decision 6b. Comments:	☐	☐

Decision 6b	If "no" to question 6a, did the applicant provide a detailed scientific or clinical justification? -If "yes," describe and answer "yes" to Decision 6 below. -If "no", describe and answer "no" to Decision 6 below. Comments:	☐	☐
Decision 6	**Were the patient population and endpoints selected appropriately?**	☐	☐

Decision 7	**Does the PMA address the key nonclinical and clinical issues identified by FDA prior to PMA application, or has the applicant provided a detailed scientific or clinical justification for the alternate approach?** ***See the guidance document (*Premarket Approval Application Filing Review*) for interpretation of this criterion.***	☐	☐

For general review documentation purposes, please complete the following table.

Recommendations

Do the PMA team members and division management recommend filing?	**Yes**	**No**	**N/A**
1. Clinician (refer to clinician's memo for details)	☐	☐	☐
2. Statistician (refer to statistical checklist and statistician's memo for details)	☐	☐	☐
3. Preclinical reviewers			
a. Engineer	☐	☐	☐
b. Toxicologist	☐	☐	☐
c. Veterinarian	☐	☐	☐
d. Other: _____.	☐	☐	☐
e. Other: _____.	☐	☐	☐
f. Other: _____.	☐	☐	☐
g. Other: _____.	☐	☐	☐
4. Team leader	☐	☐	☐
5. Division Management			
a. Branch Chief	☐	☐	☐
b. Chief Medical Officer	☐	☐	☐
c. Deputy Division Director	☐	☐	☐
d. Division Director	☐	☐	☐