Guidance for Industry and FDA Staff

The Review and Inspection of Premarket Approval Applications under the Bioresearch Monitoring Program

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The information collection provisions in this guidance have been approved under OMB control number 0910-0231]. This approval expires September 30, 2007.* An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
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*****The collection of information for "Premarket Approval of Medical Devices," under 21 CFR Part 814 (OMB 0910 – 0231), has been submitted to the Office of Management and Budget (OMB) for review and clearance. (See **Federal Register** notice for September 17, 2007 [72 FR 52882]) Under the Paperwork Reduction Act of 1995 (the PRA), previously approved collections of information under review for clearance by OMB for an extension remain in effect until the review process is completed and OMB approves the collection of information. FDA will publish notice in the **Federal Register** announcing approval for this collection of information.

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. When submitting comments, please refer to Docket No.2006D-0228. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff

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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.

Introduction

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) amended the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) (the Act) to allow for the collection of user fees for the review of certain marketing applications. A portion of the fee collected for the review of a premarket approval application (PMA) will help cover the costs associated with the bioresearch monitoring (BIMO) program review of the PMA and any clinical or non-clinical preapproval inspections. In a letter to Congress that accompanied the user fee legislation, the Secretary of Health and Human Services committed to "improve the scheduling and timeliness of preapproval inspections."[1]

This guidance explains BIMO's process for reviewing PMAs and assigning, scheduling, and evaluating related clinical or non-clinical preapproval inspections. This guidance also applies to the BIMO review of certain PMA supplements and associated BIMO inspections, as discussed below. This guidance does not address premarket notification (510(k)) submissions because BIMO does not ordinarily conduct inspections for this type of submission. FDA believes that the procedural information outlined in this guidance should help applicants and FDA schedule and complete their work in a timely manner.

FDA will address the following in this guidance:

[1] This letter can be found at: www.fda.gov/cdrh/mdufma/pgoals.html

- The sequence of events as the BIMO program within the Office of Compliance (OC) completes review of your PMA;
- The administrative process and the projected timeframes involved with each step; and
- How the BIMO review of clinical or non-clinical inspection results may influence approval decisions for PMAs.

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/ombudsman/.

The Premarket Review Process Overview

A. Premarket Approval Applications

The usual path to approval of a device is submission of a PMA, which may be traditional or modular, and expedited or non-expedited.[2] When seeking premarket approval for your device, you should select the appropriate type of PMA submission based on the following:

1. Traditional PMA

In this PMA format, you would submit all the elements required for a PMA, e.g., complete scientific and technical information about the device, manufacturing information, non-clinical study information, and statistically valid and reliable data from clinical studies, at the same time in a single application, so we can determine whether there is a reasonable assurance that the device is safe and effective for its intended use. For guidance on the type

[2] The Product Development Protocol and, for devices that meet narrow criteria, the Humanitarian Device Exemption, provide alternate approval mechanisms. This guidance does not apply to these application types.

of information needed for FDA to file your PMA, see "Premarket Approval Application Filing Review."[3]

2. Modular PMA

This PMA format consists of sections or modules submitted separately that together become a complete application. Each module includes elements, tests, or other information that constitute a component of a complete PMA, such as manufacturing information or clinical data. For more information on the Modular PMA Program, see the guidance entitled "Premarket Approval Application Modular Review."[4]

3. Expedited PMA (Traditional and Modular)

We give priority to PMAs for devices under certain circumstances. The Office of Device Evaluation (ODE) and the Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD) determine, using criteria defined in section 515(d)(5) of the Act, whether a PMA qualifies for expedited status. For more information on expedited PMAs, see the guidance entitled, "Expedited Review of Premarket Submissions for Devices."[5]

B. Types of PMA Supplements

You must submit a PMA supplement for review and approval if you make a change affecting the safety or effectiveness of a device for which you have an approved PMA. (See 21 C.F.R. 814.39(a).) Some changes do not require a supplement and some changes may be made using alternative forms of submission, as specified in FDA regulations. MDUFMA added definitions to the FDC Act of several types of PMA supplements, including: panel-track supplements, 180-day supplements, and real-time supplements. See FDC Act § 737, 21 U.S.C. § 379.

Panel-track and 180-day supplements generally include clinical and non-clinical information. A BIMO inspection may be required, depending on the proposed change. When a review of the BIMO information or an inspection are needed, the review process and timelines described in this guidance apply. Real-time supplements are not subject to BIMO inspections, so they will not be addressed in this guidance.

In addition to real-time supplements, the following types of applications typically do not involve a BIMO review or inspection and, therefore, they will not be addressed in this guidance:

- 30-day notices

[3] This guidance can be found at: www.fda.gov/cdrh/ode/guidance/297.html
[4] This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/835.html
[5] This guidance can be found at: www.fda.gov/cdrh/mdufma/guidance/108.html

- 135-day supplements
- Special PMA Supplements-Changes Being Affected
- Express PMA supplements
- PMA annual reports

1. Panel-track Supplements

Section 737(4)(B) of the Act, which was added by section 102 of MDUFMA, defines a "panel-track supplement" as "a supplement to an approved premarket application or premarket report under section 515 that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness." (21 U.S.C. 379i (4)(B)).

Panel-track supplements for changes in device design or performance that may significantly affect clinical outcome may require the submission of manufacturing information and an inspection.

We give priority review to panel-track supplements meeting the criteria defined in section 515(d)(5) of the Act. Therefore, in the discussion below, references to expedited and non-expedited PMAs include expedited and non-expedited panel-track supplements.

2. 180-Day Supplements

Under section 737(4)(C) of the Act, which was added by section 102 of MDUFMA, a "180-day supplement" is defined as:

"a supplement to an approved premarket application or premarket report under section 515 that is not a panel-track supplement and requests a significant change in components, materials, design, specification, software, color additives, or labeling." (21 U.S.C. 379i(4)(C)).

Read in conjunction with section 515(d)(6) of the Act, this language means that submission of a 180-Day Supplement is required for certain types of significant changes to the approved device that affect safety and effectiveness of the device. In general, in order for a change to be submitted as a 180-Day Supplement, the clinical data provided in support of the original device approval should still be applicable in supporting the approval of the modified device. In most cases, for such modifications, only new pre-clinical testing is needed to demonstrate reasonable assurance of safety and effectiveness of the modified device. In some instances, however, additional limited confirmatory clinical data may be necessary to provide a bridge between the clinical data set for the original device and the expected clinical performance of the modified device. Although additional clinical data may be necessary, the data collected

are usually from a limited number of patients. Changes to devices that may require a 180-Day Supplement include changes to:

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

If the 180-day supplement involves new clinical data, a BIMO review may be conducted.

C. The Review Process in Brief

The premarket review process begins when you, as an applicant, send six copies[6] of a fileable PMA or three copies[1] of a fileable PMA supplement to the CDRH Document Mail Center (DMC) in ODE. The Division of Bioresearch Monitoring (DBM) completes the review of a PMA's clinical and non-clinical sections, directs the BIMO inspections, receives and analyzes inspection results, and makes final recommendations on the quality and reliability of this data within the timeframes identified by the MDUFMA performance goals.

D. Performance Goals

During negotiations between FDA and industry that preceded passage of MDUFMA, the Center for Devices and Radiological Health (CDRH) and the Center for Biological Evaluation and Research (CBER) agreed to "performance goals," or goals that, while not codified in MDUFMA, "accompany the authorization of medical device user fees [and] represent a realistic projection of what FDA can accomplish with industry cooperation."[2] The original MDUFMA performance goals appear in the *Congressional Record* of November 19, 2002 and can be accessed on the CDRH web page: http://www.fda.gov/cdrh/mdufma/pgoals.html.

Bioresearch Monitoring Review of Clinical and Non-clinical Sections and Process

[6] See 21 CFR 814.20(b)(2).
[7] See 21 CFR 814.39(c).
[2] Congressional Record, November 19, 2002, p. S11549 (statement of Senator Kennedy). The Medical Device User Fee Amendments of 2007 (MDUFMA II) reauthorized user fees for fiscal years 2008-2012. During reauthorization negotiations, FDA agreed to modest changes to some of the goals agreed to during the 2002 legislation but these changes do not affect the timeframes discussed in this guidance document.

A. What process does FDA use to complete a bioresearch monitoring review of the PMA clinical and non-clinical sections?

When a fileable PMA submission arrives at the DMC, the DMC processes the application as follows:

1. Logs in, tracks, and distributes copies as appropriate to the CDRH offices involved, including OC's Field Operations Branch (FOB) (see number 4).
2. Assigns due dates for the CDRH offices based on the date of receipt, i.e., 180 days.
3. Alerts the ODE Program Operations Staff (POS) to the incoming PMA.
4. Sends one complete copy of the PMA to OC/FOB within seven calendar days of receipt.
5. Files one copy in the DMC.

The POS further processes the application administratively, prepares a coversheet, and attaches it as a request for review by the appropriate ODE review division or OIVD.

When OC/FOB receives its copy of the PMA, it forwards the coversheet and the PMA to DBM for review:

1. DBM assigns an internal tracking number to the PMA submission, establishes an initial goal date for the DBM reviewer, and forwards it to the Program Enforcement Branch (PEB) for assignment and review.

    - For both PMAs and PMA supplements, the initial goal date for the issuance of inspection assignments is day 30.

2. After the PEB Chief assigns the PMA submission to a DBM reviewer, the DBM reviewer notifies the lead reviewer within ODE or OIVD that the DBM reviewer serves as the point of contact for the BIMO review of the PMA. The DBM reviewer participates in discussions and deliberations with staff from other FDA offices, i.e., the review team, regarding the review of the PMA submission.

3. The DBM reviewer performs an initial review of the PMA submission prior to the meeting to decide whether the submission is fileable. The review may include the description of the function and operation of the device; summaries, conclusions, or results of any clinical investigations, including the study protocol, informed consent document, sample case report forms, or tabulations of data; non-clinical laboratory studies; and the compliance history of the applicant, sponsor, or clinical investigators. Any unusual observations should be discussed with the ODE or OIVD lead reviewer.

    - BIMO inspections are typically assigned for each fileable original PMA and panel-track supplement.
    - FDA does not make filing decisions on 180-day supplements, and BIMO inspections are assigned for such supplements only at the request of ODE or

OIVD. The milestones for the BIMO review of 180-day supplements begin when the request for consultation is received from ODE or OIVD, instead of when the submission is received.

4. Based upon discussions with the review team, the DBM reviewer identifies sites to inspect. Sites selected for inspection may include the sponsor, monitor, contract research organization, clinical investigator, or laboratory conducting non-clinical studies. Sites may be selected based upon their contribution to the pivotal trial data (e.g., large number of subjects), their compliance history, concerns identified by the review team, adverse effects reported in the PMA, or other considerations.

5. Once the sites for inspection are identified, the DBM reviewer creates a memorandum of inspection assignment, with supervisory clearance, and forwards to OC/FOB for processing and issuance to the FDA District Office within the Office of Regulatory Affairs (ORA). If the inspection involves a firm located in a foreign country, then the memorandum of inspection assignment is sent to the Division of Field Investigations, International Operations Branch (DFI/IOB) within ORA. When possible, the DBM reviewer provides early notification to ORA when a site is selected for inspection. This early notification is especially important for foreign sites because these inspections take longer to organize and complete than domestic inspections due to scheduling, travel logistics, and coordination with the U.S. State Department and foreign governments. To facilitate a timely review of the PMA submission, ORA completes these inspection assignments as follows:

   - For a PMA that is undergoing expedited review, the goal date for the completion of the inspection is day 80.
   - For a PMA that is <u>not</u> undergoing expedited review and for a 180-day supplement, the goal date for the completion of the inspection is day 90.

   When the inspections are complete, observations, if any, are listed on a Form FDA-483 issued to the inspected entity and sent to the DBM reviewer. The DBM reviewer conveys these preliminary inspection findings or observations to the ODE or OIVD lead reviewer for discussion by the review team.

6. Generally, BIMO inspections are pre-announced to ensure the appropriate records and personnel will be available during the inspection. FDA field investigators within ORA schedule and conduct the inspections, draft an inspection report, referred to as an establishment inspection report (EIR), and forward the EIR, including any responses to the Form FDA-483 from the site, through their immediate supervisor, back to DBM. ORA sends the complete EIR to the DBM reviewer according to the following time frames:

   - For a PMA that is undergoing expedited review, the goal date for completion of the EIR is day 100.

- For a PMA that is not undergoing expedited review and for a 180-day supplement, the goal date for completion of the EIR is day 120.

7. The DBM reviewer completes a review of each EIR associated with the PMA, plus any responses to the Form FDA-483, and conveys, with supervisory concurrence, the inspection results in the form of a Final BIMO Recommendation to the ODE or OIVD lead reviewer for discussion by the review team. The review team assesses the results of the BIMO inspections as they relate to the reliability and integrity of data contained in the PMA. To facilitate a timely review of the PMA, DBM intends to send the inspection summary to the review division according to the following time frames:

   - For a PMA that is undergoing expedited review, the goal date for the DBM reviewer to send the Final BIMO Recommendation to the review division is day 120.
   - For a PMA that is not undergoing expedited review and for a 180-day supplement, the goal date for the DBM reviewer to send the Final BIMO Recommendation to the review division is day 150.

   In addition to the Final BIMO Recommendation and review team discussion described above, the DBM reviewer also completes, with supervisory concurrence, a compliance review and final classification of the EIR, taking into consideration any responses to the Form FDA-483. As part of the compliance review, DBM normally issues an information letter to the inspected site or firm, although if significant deviations are identified during the inspection, DBM may issue an untitled or warning letter, detailing any violations of regulatory requirements. Inspections that reveal serious compliance problems may lead to administrative, civil, or criminal action against the regulated entity.

8. OC's goal is to complete its BIMO review of the PMA clinical and non-clinical sections within the projected time frames indicated below in Table 1:

Table 1

BIMO Review Milestone	Expedited PMA or Panel-Track Supplement	Non-expedited PMA or Panel-Track Supplement or 180-Day Supplement[7]
DMC Receipt	Day 0	Day 0
BIMO Receipt of PMA	Day 7	Day 7
BIMO Inspection Assignments Issued	Day 30	Day 30

[7] The milestones for the BIMO review of 180-day supplements begin when the request for consultation is received from ODE or OIVD, instead of when the submission is received.

BIMO Receipt of Preliminary Inspection Findings (e.g., form FDA 483)	Day 80	Day 90
BIMO Inspection Report Completed	Day 100	Day 120
Final BIMO Recommendation to ODE or OIVD	Day 120	Day 150

B. How does the BIMO review of inspection results influence the approval decisions for PMAs and their supplements?

Throughout the application review process, the DBM reviewer interacts with other PMA review team members while providing updates on proposed, ongoing, or completed inspections. In most situations, inspection results are supportive and have little adverse effect on the approval decision. However, in some situations, the inspection results could have an impact on the analysis of the data that supports approval (e.g., labeling changes may be warranted based on the BIMO findings). In rare situations, the inspection results may reveal a significant issue regarding the reliability or integrity of the data, in which case FDA may take one of the following actions:

1. Issue a deficiency letter. If the review division determines that the PMA's clinical or non-clinical sections are significantly deficient or the results of the inspection warrant a deficiency letter, FDA may send a letter identifying the kind of information that should be submitted to complete the review of these sections of the PMA or to address the inspectional findings. Examples of inspection results that may lead to the issuance of a deficiency letter include human subjects being enrolled into the study who failed to meet the inclusion criteria, underreporting of unanticipated adverse device effects, or failure to obtain informed consent. The ODE or OIVD reviewer communicates frequently with the applicant to resolve deficiencies.

2. Issue an Application Integrity Policy (AIP)[8, 9] Letter. If the inspectional findings reveal a pattern or practice of wrongful acts that raise a significant question regarding the reliability of data in an application(s), the Center may issue an AIP letter stopping the review of one, some, or all of the submissions from the applicant that are affected, either directly or indirectly, by the reliability questions and requiring data and system audits and a corrective action plan.

C. How long does the BIMO inspection process take?

[8] See 56 FR 46191: Fraud, Untrue Statement of Material Fact, Bribery, and Illegal Gratuity; Final Policy at http://www.fda.gov/ora/compliance_ref/frn/fraud_ill_grat.html
[9] See: http://www.fda.gov/ora/compliance_ref/aip_procedures/

Typically, ORA schedules and conducts the inspection within 50 to 60 calendar days after the receipt of the inspection assignment based upon whether the PMA is undergoing expedited or non-expedited review. As noted above, a DBM reviewer provides early notification to ORA when a site is identified to facilitate timely scheduling and coordination. ORA contacts the site to pre-announce the inspection which permits the site to ensure that site staff and all required records will be available during the inspection. The inspection at the site usually takes several days; however, depending on the inspectional findings and the complexity of the study, the inspection may take longer. An additional 20 to 30 calendar days is allotted for the completion of the EIR. From ORA's receipt of the inspection assignments, the entire inspection process, which includes scheduling, the inspection itself, and writing the inspection report, ordinarily takes between 70 and 90 calendar days.

D. What are the most common factors that delay the BIMO review of a PMA?

An applicant's failure to submit certain information in the PMA can delay the BIMO review of a PMA. Information that is commonly missing is complete contact information for clinical investigators or Institutional Review Boards (IRBs), the IRB-approved informed consent documents, the location of where clinical study records are maintained, the study protocol including history of any changes with corresponding date of changes, sample case report forms, or tabulations of data, commonly referred to as "line data," that support key safety and effectiveness endpoints for each subject entered into the pivotal study(ies). This data should be sorted by site, then subject, and provided in a standard acceptable electronic format, such as SAS XPORT file format, or a file format mutually acceptable to you and FDA.

Another factor that can delay review is the lack of the sponsor's or investigators' availability to permit the BIMO inspection. When a PMA or PMA supplement is submitted there is a presumption of site readiness for inspection so a timely BIMO review can be completed. FDA should be able to validate the data submitted in your PMA through an on-site inspection or other appropriate means.[10] This is especially important for sites located outside of the United States, where FDA may have limited access to review and copy records due to privacy restrictions in the foreign country's laws and regulations. In these situations, you should take steps to ensure that FDA will have access to these records.

[10] See 21 CFR 814.15(d)(3).