Guidance for Industry and FDA Staff

Real-Time Premarket Approval Application (PMA) Supplements

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This document supersedes and replaces, the "Real-Time" Review Program for Premarket Approval Application (PMA) Supplements document last updated April 22, 1997 and Section II C, "PMA Supplements Definitions – Real Time Supplements" of the February 2003 guidance entitled, "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA"

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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

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. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/ode/guidance/673.pdf, or by phone at (301) 827-2000 or (800) 835-4709, 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 (**673**) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

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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.

I. Purpose

This guidance provides information about the real-time review process for premarket approval application (PMA) supplements and outlines the procedures for requesting and submitting these types of documents. This guidance supersedes the document entitled "Real-Time" Review Program for Premarket Approval Application (PMA) Supplements, issued April 22, 1997 (the 1997 document) and Section II C, "PMA Supplements Definitions – Real Time Supplements" of the February 2003 guidance entitled, "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA.**"**

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.

II. Background

On February 4, 2003, FDA published a Federal Register notice entitled, "Medical Device User Fee and Modernization Act of 2002, Establishment of a Public Docket"[1] to provide an opportunity for interested persons to share information and views on the

[1] 68 FR 5643

implementation of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).[2] Subsequently, FDA issued a guidance entitled "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products"[3] and invited comments on its topics, which included Real-Time PMA Supplements. FDA received no comments on Real-Time PMA Supplements in either docket.

In revising the 1997 document, FDA considered the comments submitted on it and other comments about Real-Time review presented at the MDUFMA Annual Stakeholder Meetings.[4] Our revision incorporates the criteria for Real-Time PMA Supplements set forth in section 737(4)(D) of the Federal Food, Drug, and Cosmetic Act (the act) and clarifies the kinds of device modifications we believe are appropriate for real-time review. We continue to invite comments on this guidance.

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 or CBER 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 and CBER's Ombudsman can be reached at (301) 827-0379.

III. Which modifications are appropriate for a Real-Time PMA Supplement?

According to section 737(4)(D) of the act,[5] a Real-Time PMA Supplement is defined as:

> "a supplement to an approved premarket application or premarket report under section 515 that requests a minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant

[2] Public Law 107-250
[3] Issued on February 25, 2003, see www.fda.gov/cdrh/mdufma/guidance/1201.html.
[4] Held December 3, 2003, November 18, 2004, and November 17, 2005.
[5] As amended by the Medical Devices Technical Corrections Act (Public Law 108-214).

> [PMA holder] has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement."

In general, we believe a Real-Time PMA Supplement is appropriate for a minor change that can be expected within a product line, which includes changes to:

- device design
- software
- instructions for use, warnings, or precautions or other labeling that does not affect the indications or contraindications
- sterilization and packaging methods.

In addition, a minor change should be one that is:

- expected for that device type
- validated according to scientific principles we have relied on in previous reviews and accepted test methods or procedures for devices of that type, wherever applicable, such as an FDA-recognized standard or guidance document
- adequately supported by pre-clinical or animal testing, with no new clinical data
- typically involving review within a single scientific discipline, rather than a multidisciplinary review.[6]

We also believe that for a Real-Time PMA Supplement to be an effective route to market, FDA and the PMA holder should agree that the review can be achieved in a "real-time" setting before either initiates the process.

IV. How do I request a Real-Time review?

The typical request for a Real-Time review will follow these 4 steps.

1. Preliminary Discussion

Before submitting your request, we recommend you contact the branch chief in the appropriate review division in CDRH or the applications division in the appropriate

[6] A review from a single scientific discipline may be, for example, an electrical engineering, mechanical engineering, chemical engineering, material engineering, microbiology, or biocompatibility review.

CBER office to discuss whether the modification to your device is appropriate for a Real-Time PMA Supplement.[7]

2. Your Request

After you and FDA agree that the review can be achieved in a "real-time" setting, we recommend you fax your request for a Real-Time review to the appropriate CDRH branch chief or CBER applications division and follow with a hard copy to the Document Mail Center of the appropriate Center. We recommend that your request include the information outlined in the Sample Real Time Review Request in Attachment I.

3. FDA's Response

FDA plans to respond by fax within 14 days of receipt of Real-Time review requests to the Document Mail Center. Generally, if the information in your request is consistent with your preliminary discussion with FDA, and FDA, after evaluating the information, believes the modification is "minor" as defined in section III, FDA will grant your request.

4. Type of Interaction

We intend the review process for a Real-Time PMA Supplement to be interactive, although a face-to-face meeting may not always be part of the process. We will work with you to determine the type of interaction appropriate based on the information in your request. If you and FDA agree a meeting is appropriate, FDA's response will also confirm a meeting date, which should be within 30 days of the proposed submission date of the supplement or the earliest date that both you and FDA personnel are available to meet.

V. Is there a user fee for a Real-Time PMA Supplement?

Yes. As with all fee-paying submissions, the fee for a Real-Time PMA Supplement is due upon submission of the supplement. If FDA receives the supplement prior to payment, we will place the file on hold until we receive payment and notify you by

[7] For assistance in identifying the appropriate review branch in CDRH, the applicant may contact the Division of Small Manufacturers, International, and Consumer Assistance (DSMICA). Please see http://www.fda.gov/cdrh/devadvice/36f.html for contact options. For assistance in identifying the appropriate division in CBER, please contact the Office of Communication, Training and Manufacturers Assistance at 1-800-835-4709 or please see http://www.fda.gov/cber/inside/orgover.pdf.

facsimile.[8] FDA begins its review when the Office of Financial Management notifies CDRH or CBER that payment has been received and we have received the PMA submission. See http://www.fda.gov/oc/mdufma for information on remitting user fees.

VI. How do I submit a Real-Time PMA Supplement?

We recommend you submit at least 3 copies of your Real-Time PMA Supplement to the appropriate Center at the address below.

Each copy should be labeled "**REAL-TIME REVIEW REQUEST GRANTED**" and contain a copy of FDA's response granting your request for a Real-Time review.

If we have scheduled a meeting with you, we recommend you submit your Real-Time PMA Supplement sufficiently in advance to allow FDA reviewers to adequately prepare their reviews. If we have not received your submission at least 3 weeks before the meeting, we will typically reschedule to assure reviewers have adequate preparation time in order to avoid an unproductive meeting.

CDRH Review

PMA Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850

CBER Review

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center, HFM-99, Suite 200N
Rockville, MD 20852-1448

VII. What should a Real-Time PMA Supplement contain?

A Real-Time PMA Supplement should identify all modifications planned for the device and labeling. We recommend you include testing and results, along with a detailed risk

[8] Section 102 of MDUFMA authorizes FDA to put the submission on hold until payment is received.

analysis to support the continued safety and effectiveness of the modified device. Your risk analysis should include a thorough assessment of all potential hazards associated with device use, taking into account the (incremental) modification proposed in your submission and the (cumulative) effects of any preceding modifications made since the approval of the original PMA. Your risk analysis should also identify the steps you have taken to minimize any additional risks that may be created by incremental or cumulative modifications.

VIII. What is the format of a Real-Time review meeting?

If a Real-Time review meeting is part of the process, the meeting generally proceeds as follows:

1. You present the changes to your device, results of testing to support those changes, and your risk analysis.

2. You and FDA discuss any questions or comments about the changes, testing, or risk analysis.

3. The meeting briefly adjourns to allow for discussion amongst FDA staff.

4. FDA generally gives you verbal feedback that day.

After the meeting, FDA will typically send our decision letter (i.e., approval, approvable, or not approvable letter) by fax, with a hard copy to follow.

Attachment I. Sample Real-Time Review Request

PMA Contact Information and Submission Information Date:

Name:
Address
Company:
Phone Number:
Fax Number:

PMA Document Number:
Target Date for submitting to FDA:
Proposed Meeting Date(s):

Reason(s) for submission (check one or more)

- ❑ Minor design changes
- ❑ Material changes to another known material
- ❑ Minor labeling changes
- ❑ Software change
- ❑ Sterilization changes to another known method
- ❑ Packaging changes
- ❑ Other

We recommend that you attach a one-page or less explanation for the requested change(s) including:

- the test methods identified in FDA guidance or recognized standard, if applicable
- identify under what submission we have previously reviewed these test methods, if applicable
- a summary of your risk analysis

Specify the type of meeting you are requesting (check one or more)

- ❑ Face-to-face
- ❑ Telephone conference
- ❑ Video conference
- ❑ Other (Explain)