Contains Nonbinding Recommendations

Real-Time Premarket Approval Application (PMA) Supplements

Guidance for Industry and Food and Drug Administration Staff

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For questions regarding this document, contact the ORP: Office of Regulatory Programs/Division of Regulatory Programs 1: Submission Support at 301-796-5640. For questions regarding submissions to the Center for Biologics Evaluation and Research, contact CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2017-D-5971. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 673 and complete title of the guidance in the request.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., WO71, Room 3128, Silver Spring, MD 20903, or by calling 1-800-835-4709 or 240-402-8010, by email, ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

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Real-Time Premarket Approval Application (PMA) Supplements

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

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.

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 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

[1] 68 FR 5643

[2] Public Law 107-250

[3] The PMA User Fees guidance is superseded by the following guidances: "User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications"

PMA Supplements. FDA received no comments on Real-Time PMA Supplements in either docket.

This guidance outlines 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.

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

According to section 737(4)(D) of the act,[4] 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 [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.[5]

(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications); "Bundling Multiple Devices or Multiple Indications in a Single Submission" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bundling-multiple-devices-or-multiple-indications-single-submission); and "Real-Time Premarket Approval Application (PMA) Supplements" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-time-premarket-approval-application-pma-supplements).

[4] As amended by the Medical Devices Technical Corrections Act (Public Law 108-214).

[5] A review from a single scientific discipline may be, for example, an electrical engineering, mechanical

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 Assistant Director (AD) in the appropriate Review Division in CDRH or the applications division in the appropriate CBER office to discuss whether the modification to your device is appropriate for a Real-Time PMA Supplement.[6]

2. Your Request

After you and FDA agree that the review can be achieved in a "real-time" setting, we recommend you email[7],[8] your request for a Real-Time review to the appropriate CDRH AD or CBER applications division. 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 email or fax within 14 days of receipt of Real-Time review requests. 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 generally agree to review your proposed change as a real-time supplement.

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 (e.g., face-to-face meeting, teleconference, written responses) based on the information in your request. If you and FDA agree a meeting is appropriate, FDA's response will also

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engineering, chemical engineering, material engineering, microbiology, or biocompatibility review.

[6] For assistance in identifying the appropriate Review Division in CDRH, the applicant may contact the Division of Industry and Consumer Education (DICE). Please see https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice 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 https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/center-biologics-evaluation-and-research.

[7] For additional information about email communications with CBER, please see SOPP 8119: Use of Email for Regulatory Communications, available at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm

[8] CBER will accommodate the use of faxes.

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 email, fax, or phone.[9] 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, and a valid electronic copy (eCopy) has been received. See https://www.fda.gov/medical-devices/premarket-submissions/medical-device-user-fees for information on remitting user fees.

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

FDA requires all applicants to provide an eCopy of the Real-Time PMA supplement.[10] The eCopy must be accompanied by a single paper copy of your signed cover letter submitted to the appropriate Center:

- For devices regulated by the CDRH, send it to the current address displayed on the website http://www.fda.gov/cdrhsubmissionaddress.

- For devices regulated by the CBER, send it to the current address displayed on the website https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm385240.htm.

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.

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

[10] Please refer to the FDA guidance, "eCopy Program for Medical Device Submissions" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions), for additional information on the eCopy program.

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 assessment to support the continued safety and effectiveness of the modified device. Your risk assessment should include a thorough review 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 assessment 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) via mail or email to the primary correspondent identified by the applicant.

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
- ☐ Other (Explain)