Guidance for Industry and FDA Staff

Expedited Review of Premarket Submissions for Devices

Document Issued on: February 29, 2008

This document supersedes "Expedited Review of Premarket Submissions for Devices" dated November 26, 2003.

For questions regarding the use or interpretation of this guidance in the review of PMAs and PDPs, please contact the PMA Staff at (240) 276-4040.

For questions regarding the use or interpretation of this guidance in the review of 510(k)s, including the Evaluation of Automatic Class III Designation classification actions (de novo review), please contact Heather Rosecrans at (240) 276-4021 or by email at heather.rosecrans@fda.hhs.gov.

For questions regarding the use or interpretation of this guidance in the review of devices regulated by CBER, please contact Sayah Nedjar, Ph.D., at 301-827-3524 or by email at sayah.nedjar@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

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.Regulations.gov. 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 Center for Devices and Radiological Health (CDRH) through the Internet at: http://www.fda.gov/cdrh/mdufma/guidance/108.pdf or http://www.fda.gov/cdrh/mdufma/guidance/. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (**108**) to identify the guidance document you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

Contains Nonbinding Recommendations

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Guidance for Industry and FDA Staff

Expedited Review of Premarket Submissions for Devices

This guidance document 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 document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

I. Introduction

This document has the following purposes: (1) develop a common understanding of the statutory criteria for granting expedited review to premarket submissions for medical devices, and (2) outline standard procedures that should be followed to achieve an efficient expedited review process. Furthermore, this updated version of the guidance document reflects the changes under the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85)[1] and corresponding changes in our expedited review policy for premarket approval applications (PMAs),[2] premarket reports,[3] product development protocols (PDPs), and premarket notification submissions (510(k)s).

An expedited review process for medical devices was first developed in 1994 and explained in a General Program Memorandum (G94-2) entitled, "**PMA/510(k) Expedited Review**." That document was revised and issued as a guidance document on March 20, 1998, to reflect the expedited review criteria in Section 515(d)(5) of the Federal Food, Drug, and Cosmetic Act (the Act).[4] The revised guidance document, known as "**PMA/510(k) Expedited Review – Guidance for Industry and CDRH Staff**," was superseded and replaced by the guidance document entitled, "**Expedited Review of Premarket Submissions of Devices,**" dated November 26, 2003, which reflected a decade of experience from administering an expedited

[1] FDAAA includes the Medical Device User Fee Amendments of 2007 (MDUFMA II).
[2] PMAs involved are traditional PMAs, modular PMAs (after the last module is received), and panel-track supplements.
[3] A premarket report is a PMA application for a reprocessed, single-use device (see section 515(c)(2) of the Federal Food, Drug, and Cosmetic Act (Act); 21 U.S.C. 360e(c)(2)).
[4] While Section 515(d)(5) of the Act only applies to premarket approval applications (PMAs), because of the potential public health importance of devices warranting expedited review status, FDA also has applied the expedited review criteria to all premarket submissions, including devices evaluated under a PDP, the Evaluation of Automatic Class III Designation process (also known as the "*de novo*" or "risk based" classification process),[4] and 510(k)s. For information on the de novo process, refer to Section 513(f)(2) of the Act and the guidance document entitled "Evaluation of Automatic Class III Designation" found at http://www.fda.gov/cdrh/modact/classiii.html.

review program for medical devices, as well as the performance goals set forth in the MDUFMA I Goals Letter. [5]

The 2003 version of this guidance document is superseded by this version, which incorporates changes under FDAAA. More specifically, for PMAs, FDA will no longer require additional conditions in order for an expedited PMA to be measured against MDUFMA expedited performance goals. Therefore, this guidance document no longer includes information specific to the additional conditions described under MDUFMA I for expedited PMAs.[6] In addition, if a PMA or 510(k) is granted expedited status, this status would not be revoked during its review should a device of the same type be approved or cleared.

FDA's guidance documents, including this guidance document, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents 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 regarding premarket device submissions 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 contact information, can be found on the Internet at http://www.fda.gov/cdrh/ombudsman/.

[5] For more information, please refer to the letter from the Secretary of Health and Human Services to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate ("Goals Letter") dated November 19, 2002, http://www.fda.gov/cdrh/mdufma/pgoals.html and referenced in section 101(3) of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA I).

[6] A pre-filing meeting was one of the previous conditions under MDUFMA I for a PMA to have an expedited review status and be subject to MDUFMA performance goals. Although removed as a condition, CDRH intends to develop guidance on meetings with industry, including pre-submission meetings. For CBER submissions, please refer to CBER's meeting procedures webpage at http://www.fda.gov/cber/regsopp/81011.htm.

II. Devices Appropriate for Expedited Review

FDA considers a device, or combination product containing a device,[7] appropriate for expedited review[8] if the device or combination product:

1. **is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and**

2. **addresses an unmet medical need, as demonstrated by one of the following:**

    a. **The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology.** Breakthrough technologies should be demonstrated to lead to a clinical improvement in the treatment or diagnosis of the life-threatening or irreversibly debilitating condition.

    b. **No approved alternative treatment or means of diagnosis exists.**

    c. **The device offers significant, clinically meaningful advantages over existing approved alternative treatments.** The device should provide for a clinically important earlier or more accurate diagnosis or offer important therapeutic advantages in safety and/or effectiveness over existing alternatives. Such advantages may include demonstrated superiority over current treatments for effects on serious outcomes (e.g., morbidity), ability to provide clinical benefit for those patients unable to tolerate current treatments, or ability to provide a clinical benefit without the serious side effects associated with current treatments.

    d. **The availability of the device is in the best interest of patients.** That is, the device provides a specific public health benefit, or meets the need of a well-defined patient population. This may also apply to a device that was designed or modified to address an unanticipated serious failure occurring in a critical component of an approved device for which there are no alternatives, or for which alternative treatment would entail substantial risk of morbidity for the patient.

III. Special Considerations

Manufacturers who are working with a federal agency in the development of medical devices to address a national security issue should include a letter in the premarket submission from the federal agency (e.g., Department of Defense, Department of Homeland Security) identifying the specific device or device type and indicating that commercial availability is of particular importance to our national security. The letter should be printed on official agency letterhead and signed by an individual with appropriate authority for making the request.

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[7] Combination products are eligible for expedited review under the MDUFMA goals when CDRH or CBER has been designated as the lead Center.

[8] FDA is required by statute, section 515(d)(5), to review only PMAs meeting certain conditions on an expedited basis. FDA, however, is using these criteria as guidelines for expedited review of PDPs, 510(k)s, and de novo classifications. For more information on de novo classification, refer to http://www.fda.gov/cdrh/devadvice/314c.html.

To expedite the process, the letter should also be faxed to the Office of Device Evaluation's Program Operation Staff (POS). The early fax to POS will allow for confirmation of the expedited status and will allow for better monitoring of the review status of the expedited submission.

IV. Expedited Review: Its Meaning and Impact

While all device submissions granted expedited review status are subject to priority review, there is no assurance that a device will receive FDA marketing authorization in a more timely manner when compared with submissions not granted expedited status. The reasons for this outcome are varied, such as a device involves new technology or presents complex scientific and regulatory issues that warrant more in-depth review; a failure by the manufacturing facility to be prepared for inspection; or a failure of the applicant to provide adequate scientific data in its submission.

In order to reap a benefit from the expedited review process, the commitment on behalf of the applicant to resolve all scientific and regulatory issues should match that of FDA. It will only be through effective communication (i.e., interactive review) and a total commitment to fulfilling all regulatory and scientific requirements that FDA and the applicant can speed market authorization for safe and effective products.[9]

Although an expedited PMA will be assessed against the MDUFMA II expedited performance goals without a pre-filing meeting, FDA strongly recommends to industry to have such a meeting.[10]

V. Expedited Review Queue

Granting expedited review status means that a marketing application that is determined to be appropriate for expedited review is placed at the beginning of the appropriate review queue and receives additional review resources, as needed. If multiple applications for the same type of device offering comparable advantage over existing approved alternatives have been granted expedited review, they are reviewed with priority assigned on a first-in-first-reviewed (FIFR) basis for each review cycle.

Furthermore, if one of these applications is approved, the remaining expedited applications will retain their expedited status until a final decision is rendered. This is a change from our previous practice in which we would revoke the expedited status from all pending expedited submissions once we approve a submission of the same type. We are implementing this change in order to simplify our review process. Since MDUFMA provides different performance goals for non-expedited and expedited PMAs, switching the status during the review of an application requires the review staff to switch to a different review process and be accountable for meeting a different

[9] FDA has issued a guidance document on interactive review entitled, "Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements," http://www.fda.gov/cdrh/ode/guidance/1655.html.

[10] CDRH intends to develop guidance on meetings with industry, including pre-submission meetings. For CBER submissions, please refer to CBER's meeting procedures webpage at http://www.fda.gov/cber/regsopp/81011.htm.

goal. For this reason, the status of the application should be decided at the time the submission is filed and will continue until the review is completed and a final decision is rendered.

Any new application filed after the approval or clearance of a device of the same type will not be given an expedited status unless covered under Section III (Special Considerations).

VI. Applicability to PMA Performance Goals

Under MDUFMA I, for a traditional PMA, modular PMA, or panel-track supplement to be tracked against the expedited PMA performance goals, the applications/supplement had to meet the statutory expedited criteria described in Section II (Devices Appropriate for Expedited Review) AND the PMA applicant had to meet the following conditions:

- the applicant attended a pre-filing meeting with FDA;
- the PMA was substantively complete as defined at the pre-filing meeting; and
- the manufacturing facilities were prepared for a good manufacturing practice (GMP) inspection at the time of the PMA submission.

If a PMA met the expedited statutory criteria but did not satisfy all three of the conditions above, the application was still considered expedited and FDA prioritized review of the application. However, FDA was not obligated to meet the MDUFMA I expedited PMA performance goals for this application. Thus, there were actually two different categories for expedited review: a "statutory only" category and a "statutory and MDUFMA" category.

Having two different expedited categories led to implementation difficulties, such as how to determine whether a device manufacturing site was ready for inspection at the time a PMA was submitted. While a PMA applicant may have claimed in its PMA submission that its manufacturing site was ready to be inspected, FDA's inspectors often discovered that sites were actually not ready for inspection. Likewise, there were no criteria for deciding whether or not a particular meeting that an applicant had with the FDA, regardless of the topic of discussion, constituted a pre-filing meeting.

Thus, because of the difficulty in implementing the expedited provision under MDUFMA I, FDA and the industry agreed to streamline the process and eliminate the three additional conditions above. Therefore, under FDAAA, FDA will now evaluate the expedited status of each PMA application based solely on the original statutory criteria defined in Section II (Devices Appropriate for Expedited Review) above. Furthermore, all expedited original PMAs and panel track supplements will be assessed against the MDUFMA II expedited performance goals.[11]

[11] See the guidance document entitled, "FDA and Industry Actions of Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment," at www.fda.gov/cdrh/mdufma/guidance/1218.html.

VII. Requesting Expedited Review

The responsibility for identifying devices that are appropriate for expedited review is a responsibility jointly shared by industry and FDA. A primary objective of this guidance document is to promote a common understanding of which device submissions may be granted expedited review status to facilitate an early recognition of devices that merit such review. (Refer to Attachment 1 for suggested timeframes for making expedited review determinations early in the device development process.)

A. Industry Responsibilities

Opportunities to identify a device as a candidate for expedited review occur throughout the device development process. Some of the factors described earlier in this guidance document that indicate that a device should be granted expedited review status may be apparent during the early stage of development, while other factors that indicate a device should be granted expedited review status may not be apparent until there has been an actual assessment of patient outcomes. As an example, a device in the early design stage may qualify for expedited review if, for a certain life-threatening disease or condition, there exists no approved alternative treatment (i.e., see conditions 1 and 2b in Section II (Devices Appropriate for Expedited Review) of this guidance document). Alternatively, a device further along in the development process that has undergone clinical testing may be eligible for expedited review based on significant advances in safety and effectiveness by satisfying conditions 1 and 2c in Section II (Devices Appropriate for Expedited Review).

Regardless of a device's stage of development, we encourage industry to discuss potential devices that may be appropriate for expedited review as early as possible during their interactions with the Center. The following milestones may be good opportunities to assess a device's eligibility for expedited review and to notify FDA of any device that appears to warrant expedited review status:

- pre-investigational device exemption application (IDE) discussions with FDA, including formal agreement and determination meetings;
- IDE meetings where significant findings are presented to FDA; and
- premarket submission meetings, such as those frequently scheduled with review divisions before submitting PMAs, PDPs, and select 510(k)s.

FDA recommends that industry requests for expedited review of a premarket submission be made in writing and accompany any materials submitted in preparation for a meeting or with the application that is to be expedited. The request for expedited review should cite the relevant expedited review criteria described in this guidance document that have been met and include information sufficient to justify the request. In cases where FDA has granted expedited review status in advance of the submission of a marketing application, the applicant should include a copy of the FDA correspondence with the submission.

Once FDA grants expedited review status for a submission, industry responsibilities do not end. If the expedited review program is to function effectively and efficiently, industry should give priority to resolving all scientific and regulatory issues that surface during the review process.

This may involve redistributing resources from other activities to resolving pending issues, or by responding to FDA requests for additional information in as timely a manner as possible. It will only be through a complete and total commitment by all parties involved that expedited review will result in safe and effective devices getting to market in as short a time as possible.[12]

B. FDA Responsibilities

It is the responsibility of FDA staff to consider whether new devices are appropriate for expedited review, regardless of whether a company has identified its device as a potential candidate for this program.

Opportunities for identifying devices that are eligible for expedited review include, but are not limited to:

- pre-IDE discussions with companies, including formal agreement and determination meetings;
- IDE meetings where significant findings may be presented by an applicant;
- pre-PMA, pre-PDP, and pre-510(k) meetings where scientific and regulatory requirements may be discussed;
- the early phase of FDA review of marketing applications (refer to discussion of specific timeframes discussed below); and
- special considerations described in Section III above.

C. FDA Timeframes for Determinations

The Division Director responsible for evaluation of a device is authorized to grant expedited review status for a premarket submission, whether requested by the applicant or initiated by FDA. Given the public health importance of this decision, we will attempt to reach a decision on whether to grant expedited review within the following timeframes:

- **Pre-Submission Communications** - When expedited review is a consideration during pre-submission communications with companies, review divisions should make a prompt determination regarding device eligibility. Whenever possible, FDA expects the review divisions to make a determination within two weeks of the request for, or discussion of, a particular device's eligibility for expedited review status.
- **510(k)s and de novo classification actions** - The decision to expedite the review should be made within two weeks from the receipt date of the submission.

[12] See also FDA's guidance document on interactive review entitled, "Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements," http://www.fda.gov/cdrh/ode/guidance/1655.html.

- **PMAs -** The decision to expedite the review should be made as early as possible during the 45-day filing review.[13] For PMA supplements that are filed upon receipt (e.g., 180-day supplements), the decision should be reached within 30 days of receipt of the submission.

Note: When granting expedited review, the review divisions should consider other pending submissions for the same intended use that may also be appropriate for expedited review. Likewise, the review divisions should monitor incoming submissions for devices of the same type that may also be appropriate for expedited review status. If more than one pending submission is appropriate for expedited review, both submissions should be granted expedited review status.

D. FDA Administrative Procedures

After FDA determines that expedited review is appropriate, the division should complete the *"Expedited Review Form"* (Attachment 2) specifying the basis for its determination. A copy of this form, signed by the Division Director, is to be provided to the appropriate Office Director, and the 510(k) or PMA Staff, or in CBER, to the Regulatory Project Management Branch.

The *Expedited Review Form* also includes certain information regarding resource utilization. In completing the form, review divisions should establish:

- **A Review Team** – The division should designate a team leader and review team, as well as identify resources from outside the division that may be needed to appropriately expedite the review; and

- **A Tentative Timeline for Review of the Application** – The division should establish a timeline for review. Each division should use project management techniques to expedite applications and monitor timeframes. CBER should use the structure of a Regulatory Project Manager (RPM) and Scientific Lead (SL) to achieve these goals.

In CDRH, the division will prepare and issue a letter notifying the applicant of the expedited review status. In CBER, the Office should prepare the letter notifying the applicant of the expedited review status. The notification conveying expedited review status may be incorporated into other outgoing correspondence between the applicant and FDA (e.g., a response to an IDE or a PMA filing letter). A copy of the notification letter should be included in the administrative file according to established procedures, and issuance of this letter should also prompt an update of the database to reflect FDA's granting of a device's expedited review status.

VIII. Expedited Review Procedures for FDA

The review division, along with all other CDRH components that may be participating, incur specific responsibilities upon granting expedited review. The areas below warrant special consideration.

[13] See 21 CFR 814.42(a).

A. Resource Management

The Division Director should ensure that the application is reviewed in the most efficient manner, tracked as an expedited review and completed within the MDUFMA timeframes. Implementation of this policy may have an impact on other review work of the division. Additional resources will likely be necessary for review of the marketing applications granted expedited review. The following should be considered, when appropriate, to accommodate the expedited review process:

- assignment of a team leader/project manager to manage the administrative activities (such as arranging internal and external meetings and teleconferences, taking meeting minutes, etc.);
- shift in the workload within the affected reviewing division;
- scientific experts from outside the Center and/or FDA may need to be consulted to facilitate review of an expedited application; and
- scientists from elsewhere in CDRH may be needed to provide support in areas where the standard review queue is affected by the workload shift.

B. Advisory Panel Review

FDA takes most PMAs that are granted expedited review status to an advisory panel for review. The respective review division should make the decision whether a PMA will go to an advisory panel, in consultation with the applicant, at the time of the filing decision. While most 510(k)s are not taken to panel, the review division should make the decision whether an expedited 510(k) submission will go to an advisory panel for review, in consultation with the applicant, at the time that the expedited review is granted, which is usually within two weeks of receipt of the submission. It is the responsibility of the Division Director to ensure that the decision to bring the application or submission to an advisory panel is made within the appropriate timeframe. The review team and the respective advisory panel's Executive Secretary should be involved in this process. Information about the procedures for advisory panel review is available at http://www.fda.gov/cdrh/modact/amendpan.pdf.

C. Monitoring

On a quarterly basis, the Office should review the progress of submissions granted expedited review status. The purpose of this review will be to provide feedback to the review divisions and to offer suggestions for any encountered difficulties.

D. Public Disclosure

The fact that FDA has determined a device is eligible for expedited review procedures generally will not be disclosed to the public by FDA until the time that marketing authorization has been granted, or until the materials are made available in connection with advisory panel meetings for

those applications or submissions undergoing panel review.[14] Although FDA generally does not comment on the status of pending applications, it may release publicly disclosable information if it becomes necessary to correct misleading statements made by the applicant.

At the time of approval or clearance, a publicly disclosable paragraph may be provided to appropriate media outlets (through FDA's Press Office) and FDA information sources (CDRH web page, DSMICA, etc.) depending on the significance of the approval or clearance. FDA may make public sufficient information to permit interested parties to monitor the agency's implementation of the expedited review program, with the exception of information related to expedited reviews granted for the special considerations described in Section III above.[15]

[14] See http://www.fda.gov/cdrh/ode/guidance/1341.html for information about the public availability of the advisory panel materials.

[15] Any disclosures will be made in accordance with 21 CFR Part 20 and any other applicable laws protecting private, confidential commercial information, and trade secrets.

Attachment 1: Suggested Timeframes for Discussing Expedited Review with FDA

Table 1. Suggested Timeframes for Discussing Expedited Review Status (shown in solid shading)

Expedited Criteria	Pre-Submission Product Development Timeline				
	Concept	Prototype	Pre-clinical	Clinical	Performance Assessment
1 + 2a				opportunities for discussion	
1 + 2b		opportunities for discussion			
1 + 2c				opportunities for discussion	
1 + 2d				opportunities for discussion	

Legend for Table 1:

Criteria for Expedited Review

1. Condition is life-threatening or irreversibly debilitating

AND

2. the device addresses an unmet medical need, demonstrated by **any one** of the following:

   a. breakthrough technology

   b. no approved alternative

   c. significant clinically meaningful advantage

   d. in the best interest of patients.

Pre-Submission Product Development Timeline

Phase	Primary Activity
Concept	Working up the abstract or generic idea
Prototype	Building first functional, full scale, pre-production model
Pre-clinical	Bench testing prototype and subsequent models
Clinical	Conducting human subject trials
Performance Assessment	Evaluating data from preclinical and clinical phases

Attachment 2: Expedited Review Form

Applicant: _____

Device: _____

Use/Indications: _____

Document #: _____

Justification for Expedited Review		**Check if YES (✓)**
1.	Does the device affect a condition that is life-threatening or irreversibly debilitating?	❑
2.	Does the device address an unmet medical need, as demonstrated by any one of the following:[16] a. breakthrough technology b. no approved alternative c. significant clinically meaningful advantage d. in the best interest of patients.	❑ ❑ ❑ ❑
3.	Are the answers to 1 & any one part of 2 a YES response?	❑
		If yes, go to 4.
		If no, skip to 5.
Expedited Review Assessment (check only one)		
4.	The application qualifies for expedited review status and is subject to MDUFMA Performance Goals	❑
5.	The application does not qualify for expedited review status	❑

Identify review team leader & members:

Attach tentative review timeline.

Signature: _____
Division Director & Date

[16] FDA will verify the applicability of any justification proposed.