Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals

U.S. Food & Drug Administration

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This document supersedes "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals" dated June 30, 2008.

For questions regarding submissions to the Center for Devices and Radiological Health (CDRH), contact the Premarket Approval Staff 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 at 1-800-835-4709 or 301-827-1800.

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

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Identify all comments with Docket No. 2003D-0434. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov [3] to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number (1208) to identify the guidance you are requesting.
Additional copies of this guida nce d ocu ment are also availa b le 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/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm [4].

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Guidance for Industry and Food and Drug Administration Staff

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This guidance document represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not

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I. Introduction

The Medical Device User Fee Amendments of 2012[1] [11] (MDUFA III), amended the Federal Food, Drug, and Cosmetic Act (the act) to authorize FDA to collect user fees for the review of certain premarket submissions received on or after October 1, 2012, including premarket approval applications (PMAs). The additional funds obtained from user fees will enable FDA, with the cooperation of industry, to improve the device review process to meet certain performance goals and implement improvements for the medical device review process.

Performance goals were initially negotiated and agreed to under the Medical Device User Fee and Modernization Act (MDUFMA) of 2002 (Public Law 107-250) for PMAs filed in FY 2003-2007 (now referred to as MDUFA I). New performance goals and process improvements were incorporated in the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110-85) for PMAs filed in FY 2008-2012 (now referred to as MDUFA II). For PMA applications received during FY 2013-2017, the performance goals and process improvements are outlined in the letter from the Secretary of Health and Human Services (the Secretary) to Congress (MDUFA III Commitment Letter[2] [12]) and are further described below.

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.

II. Scope

This guidance document describes:

- the different FDA actions that may be taken on premarket approval applications (PMAs);
- the effect each action has on goals under MDUFA I (for PMAs received in FY 2003-2007);
- the effect each action has on goals under MDUFA II (for PMAs received in FY 2008-2012);
- the effect each action has on goals under MDUFA III; and

- the different industry actions that may be taken on PMAs.

III. FDA's Actions

The PMA regulation outlines the various actions FDA may take on an original PMA or PMA supplement during the course of our review.[3] [13] For original PMAs, panel-track supplements, and 180-day supplements,[4] [14] the following responses are considered FDA actions:

- approval order;
- approvable letter;
- major deficiency letter;
- not approvable letter; and
- denial order.

For Real-time supplements, all of the above responses apply with the exception of a major deficiency letter.

Furthermore, of these FDA actions, all but a major deficiency letter are an "FDA decision" under FDA's commitment letters and are measured against a MDUFA I/II/III goal.[5] [15]

These FDA actions are described below.

A. Approval Order

FDA will issue an approval order (letter) informing the applicant that the PMA is approved and that the applicant may begin commercial distribution of the device in accordance with any prescribed conditions of approval after we have completed our review and:

- none of the reasons listed in 21 CFR 814.45 for denying approval applies;
- there is reasonable assurance the device is safe and effective (using the criteria provided in 21 CFR 860.7) for its intended use as prescribed in the product labeling; and
- the device manufacturing facilities, methods, and controls were inspected and found to be in compliance with the Quality System regulation (21 CFR Part 820).

When FDA issues an approval order, we shut off the FDA review clock. An approval order marks the end of FDA's review, as this is a final action.

B. Approvable Letter

FDA will issue an approvable letter informing the applicant that we have completed our review of the application and determined that there needs to be:

- resolution of minor deficiencies,[6] [16] which are identified in the approvable letter (21 CFR 814.44(e)); and/or
- completion of an FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with the Quality System (QS) regulation, 21 CFR Part 820, and, if applicable, verifies records pertinent to the PMA as per 21 CFR 814.44(e)(1)(ii). When this is the case, the approvable letter states that the device is “approvable pending GMP inspection.”

When FDA issues an approvable letter pending resolution of minor deficiencies, we stop the FDA review clock and place the application on hold. When FDA receives a complete response to an approvable letter, we will restart the clock with a new FDA response timeframe. Although not a performance goal, FDA intends to review a complete response to an approvable letter within 30 days.

When FDA issues an approvable pending GMP inspection letter, we stop the FDA review clock. Once FDA determines that the GMP issues are resolved, we will issue an approval order.

C. Major Deficiency Letter

FDA will issue a major deficiency letter informing the applicant that the PMA lacks significant information necessary for FDA to complete our review and requests the applicant to amend the application to provide the necessary information regarding the device (21 CFR 814.37(b)), such as:

- a detailed re-analysis of previously submitted data (e.g., alternative statistical method);
- additional test data to demonstrate safety and effectiveness of the device (e.g., electromagnetic compatibility, electrical safety; biocompatibility, reliability, software, labeling, animal testing, sensitivity and specificity in a certain population);
- scientific rationale for test data provided in the submission; or
- new validation data and analyses (e.g., due to device modifications made during the course of the PMA review).

When FDA issues a major deficiency letter, we stop the FDA review clock and place the application on hold. Because a major deficiency letter is not a MDUFA decision, when FDA receives a complete response to a major deficiency letter, we will resume the clock and our review with a goal of reaching a MDUFA decision within the remaining time of the application’s review track (e.g., 180 FDA days).

D. Not Approvable Letter

FDA will issue a not approvable letter informing the applicant that we have completed our review and that we do not believe that the application can be approved because of significant deficiencies. The not approvable letter will describe the deficiencies in the application, including each applicable ground for not

approving and, where practical, will identify measures required to place the submission in approvable form (21 CFR 814.44(f).

Generally, before FDA issues a not approvable letter, we will first issue a major deficiency letter to provide the applicant with an opportunity to address our concerns. However, if an applicant fails to provide an adequate response to a major deficiency letter, FDA will issue a not approvable letter.

When FDA issues a not approvable letter, we stop the review clock and place the application on hold. When FDA receives a complete response to a not approvable letter, we will restart the clock with a new FDA response timeframe. Although not a performance goal, FDA intends to review a complete response to a not approvable letter within 180 days.

E. Denial Order

FDA will issue a denial order (letter) when we need to inform the applicant that we have denied approval of the application. The denial order will identify all deficiencies in the application, including each applicable ground for denial under section 515(d)(2) of the Act and, where practical, will identify measures required to place the application in approvable form (21 CFR 814.45). The denial order will include a notice of an opportunity to request review under section 515(d)(3) of the Act. In addition, FDA may deny approval of a PMA for any of the reasons identified in 21 CFR 814.45(a).

When FDA issues a denial order, we shut off the FDA review clock if a prior action has not already done so.[7] [17] A denial order marks the end of FDA's review, as this is considered a final action.

F. Acknowledgement of Voluntary Withdrawal

Under the PMA regulation, FDA considers an original PMA or PMA supplement to have been voluntarily withdrawn if an applicant fails to respond to an approvable, major deficiency, or not approvable letter within 180 days. (See 21 CFR 814.44(g).) However, upon request, FDA intends to allow one 180-day extension to respond to one of these three FDA action letters, increasing the time to provide a complete response to the FDA action letter to a total of 360 days. FDA intends to notify the applicant when 360 days have elapsed with a letter acknowledging voluntary withdrawal of the PMA or PMA supplement, and any amendment submitted in response to an FDA action letter after 360 days will be considered a resubmission of the PMA. As such, it will be assigned a new PMA number, will be subject to the requirements of 21 CFR 814.20, and the applicant must pay a new user fee.

IV. PMAs Filed in FY 2003-2007 and FY 2008-2012

The performance goals for PMA applications filed from FY 2003 through FY 2007 (MDUFA I) were defined in a November 14, 2002, letter from then DHHS Secretary Tommy G. Thompson to Congress.[8] [18]

The performance goals for PMA applications filed from FY 2008 through FY 2012 (MDUFA II) are defined in a September 27, 2007, letter from then DHHS Secretary Michael O. Leavitt to Congress.[9] [19]

Where the table shows a dash (-), there is no performance goal in effect for that action and fiscal year.

Table 1 below summarizes the decision and performance goals in effect for PMA applications under MDUFA I and MDUFA II. MDUFA I included decision and performance goals for Original PMAs, and panel-track and 180-day supplements. Performance goals were phased in over five years. Cycle goals were also included, but these were abolished in FY 2007 and are not listed in the table.

MDUFA II included two-tier decision goals for all PMA submissions with performance goals and performance goals that remained constant for the five-year duration. The use of a major deficiency letter for 180-day supplements was also initiated under MDUFA II.

Table 1 - MDUFA I & II Decision Goals

	MDUFA I					MDUFA II		
	Tier	FDA days	FY'05	FY'06	FY'07	Tier	FDA days	FY'08-FY'12
Original and Panel-track supplements (non expedited)	1	180	-	-	50%	1	180	60%
	2	320	-	80%	90%	2	295	90%
Original and Panel-track supplements (expedited)	-	300	70%	80%	90%	1	180	50%
						2	280	90%
180-day supplements	-	180	80%	80%	90%	1	180	85%
						2	210	95%
Real-time PMA supplements	-	-	-	-	-	1	60	80%
						2	90	90%
PMA Modules	-	-	-	-	-	1	90	75%
						2	120	90%

V. PMAs Filed in FY 2013-2017

The performance goals for PMA applications filed from FY 2013 through FY 2017 (MDUFA III) are defined in the MDUFA III Commitment Letter. Performance goals and associated changes under MDUFA III include:

- most PMA submissions are subject to a user fee, and all PMA submissions need a valid eCopy[10] [20] in order to initiate review;
- original PMAs and panel-track supplements will undergo an acceptance review that precedes the filing review;
- original PMAs, panel-track supplements and 180-day supplements are subject to a substantive interaction (SI) goal;
- original PMAs, panel-track supplements, 180-day supplements, and real-time supplements are subject to one-tier decision goals (modular PMAs no longer have a MDUFA performance goal);
- the term expedited will now be referred to as priority (to be consistent with the statutory language) and PMAs with that designation will no longer be analyzed as a separate cohort; instead the cohorts will be based on whether or not a panel meeting occurs;
- the performance goals ramp up from year to year instead of remaining constant as they did under MDUFMA II;
- there is a shared outcome goal for the total time from filing to decision for originals and panel track supplements; and
- for original PMAs and Panel-Track PMA supplements for which the MDUFA Decision is exceeded by 20 days, FDA will send a Missed MDUFA Decision (MMD) communication to the applicant.

A. Submission

Many PMA submissions will be subject to a user fee[11] [21] and all PMA submissions (originals, supplements, reports, and amendments) will be subject to the requirement for the appropriate number of copies, including an eCopy.[12] [22] PMA submissions will not be completely processed and distributed and the review clock will not start without confirmation of user fee payment, if applicable, and a validated eCopy.

B. Acceptance and Filing Review for original PMAs and panel-track supplements

FDA will conduct an administrative review to determine whether the required elements are present in the application. If not present, the PMA review process will not continue and the applicant will be notified in writing that the PMA is incomplete. This finding will be communicated to the applicant within 15 calendar days of receipt of the application. This communication represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle. The application will be placed on hold and the review clock will not start until the required elements are provided. The date FDA receives the amendment containing the required elements will be the new PMA receipt date for purposes of placing the application under review so that a filing review can proceed.

The filing review will take place within 45 days of receipt of the accepted application.[13] [23]

C. Substantive Interaction for original PMAs, panel-track supplements and 180-day supplements

Once the application is filed, FDA should conduct the substantive review and communicate with the applicant through a Substantive Interaction within 90 calendar days of the filing date. The Substantive Interaction communication can be a major deficiency letter or an email indicating that FDA will continue to resolve any outstanding deficiencies via Interactive Review. An approval or approvable letter issued prior to the Substantive Interaction goal date will also qualify as a Substantive Interaction for purposes of meeting the MDUFA III goal. After a Substantive Interaction, FDA intends to work with the applicant via Interactive Review to reach a MDUFA decision.

D. MDUFA III Goals

MDUFA III includes goals for Substantive Interaction, MDUFA decision and Total Time (see Table 2).

In MDUFA I and MDUFA II, the cohorts for reporting performance for PMA original and panel-track supplements were delineated by whether or not these submissions were designated to be expedited (now priority). In MDUFA III, the cohorts for original PMAs and Panel-Track PMA supplements will be delineated by whether or not a panel (advisory committee) meeting is held.

The goals for Substantive Interaction and MDUFA decision are in terms of FDA Days, which are defined in the MDUFA III Commitment Letter as those calendar days when a submission is considered to be under review at the Agency for submissions that have been accepted. FDA Days begin on the date of receipt of the submission or the amendment to the submission that enables the submission to be accepted.

The shared outcome goal of Total Time to Decision is a new performance goal for which FDA and industry performance will be reported during MDUFA III. FDA and applicants share responsibility for this goal, which is intended to achieve an objective of a reduced average total time to a MDUFA decision. This goal measures the total time to decision which includes the time spent by FDA reviewing the application as well as the time spent by the applicant responding to questions from FDA.

The Total Time to Decision is the number of calendar days from the date of receipt of an accepted submission to a MDUFA decision. The average Total Time to Decision for PMA applications is calculated as the three-year rolling average of the annual Total Times to Decision for applications (for example, for FY2015, the average Total Time to Decision for PMA applications would be the average of FY2013 through FY2015) within a closed cohort, excluding the highest 5% and the lowest 5% of values. A cohort is closed when 95% of the applications have reached a decision.

Table 2 - MDUFA III Goals

Substantive Interaction

	FDA Days	FY'13	FY'14	FY'15	FY'16	FY'17
Original PMAs, Panel-track Supplements and 180-day supplements	90	65%	75%	85%	95%	95%

MDUFA Decision Goals

Original PMAs and Panel-track Supplements without panel
Original PMAs and Panel-track Supplements with panel
180-day Supplements
Real-time Supplements

Total Time Goal
Average Total time to decisions

	FY'13	FY'14	FY'15	FY'16	FY'17
Originals and Panel-track Supplements	395	395	390	390	385

E. Missed MDUFA Decision Communication for original PMAs and panel-track supplements

For all PMA original and panel-track supplements that do not reach a MDUFA decision by 20 days after the applicable FDA Day goal, FDA will provide written feedback to the applicant to be discussed in a meeting or teleconference, including the major outstanding review topic areas or other reasons that are preventing FDA from reaching a decision as well as an estimated date of completion.

VI. Applicant's Actions

Actions taken by an applicant may include the submission of an unsolicited major amendment, submission of a solicited major amendment, submission of a minor amendment, or withdrawal of the application (either by letter or by not responding to an FDA request). *See* 21 CFR 814.37(a) and (d). The information below clarifies the basis for each action an applicant may take and the effect each action has on the FDA review clock and review goals.

A. Unsolicited Major Amendment

An unsolicited major amendment is a submission of substantial new data by the applicant, on an applicant's own initiative, to be added to a pending PMA

submission. Typical situations that may prompt an applicant to submit an unsolicited major amendment include:

- the applicant obtains additional test data related to the safety or effectiveness of the device, or the applicant becomes aware of data that was omitted from the original application (e.g., electromagnetic compatibility, electrical safety, biocompatibility, reliability, software, labeling, animal testing);
- the applicant obtains significant new clinical data from a previously unreported study, or obtains updated data from a previously reported study; or
- the applicant obtains new validation data and analyses (e.g., concerning device modifications made by the applicant during the course of the PMA review).

The submission of an unsolicited major amendment by the applicant extends the time allotted to reach a FDA decision goal (i.e., MDUFA III decision) as follows:

- if the applicant submits an unsolicited major amendment prior to the Substantive Interaction, the FDA decision goal date is extended by the number of FDA days that have elapsed, i.e., between receipt of the application and receipt of the amendment;[14] [24] or
- if the applicant submits an unsolicited major amendment after the Substantive Interaction, the FDA decision goal date is extended by the number of days equal to 75% of the difference between the filing date and the date of receipt of the amendment, i.e., 75% of the FDA days as of the receipt of the amendment.

B. Solicited Major Amendment[15] **[25]**

A solicited major amendment is the formal submission of information by the applicant, at the request of the FDA (i.e., in response to a major deficiency or not approvable letter). The applicant submits a major amendment to FDA when the applicant receives:

- a major deficiency letter requesting additional information; or
- a not approvable letter that identifies the deficiencies to which the applicant must satisfactorily respond in order to place the PMA in approvable form.

The submission of a solicited major amendment that is a complete response restarts the FDA review clock upon receipt. A partial response to an action letter does not restart the FDA review clock.

C. Unsolicited Minor Amendment

A minor amendment is an amendment that contains clarification of previously submitted data or additional information of a minor nature. It is submitted by an applicant on its own initiative. The submission of a minor amendment has no effect on the review clock.

D. Response to Interactive Review Request

All responses to Interactive Review requests should be submitted via email; however, in circumstances where that is not possible (e.g., due to electronic file size limitations), a response to an interactive review request that is submitted formally will have no effect on the review clock. A response to an interactive review request should only be submitted once.

E. Withdrawal of an Application

An applicant may, on its own initiative, withdraw a PMA submission at any time prior to approval, and for any reason, by submitting an amendment informing FDA of its intent to remove the application from FDA's review. A withdrawal action will stop the review clock on the receipt date of the amendment. FDA will treat the withdrawal as a final FDA action that satisfies the decision goal for that submission.

In addition, as stated in Section II above, FDA considers an original PMA or PMA supplement to have been voluntarily withdrawn if an applicant fails to respond to an approvable, major deficiency, or not approvable letter within a total of 360 days.

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[1] See the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-114).

[2] FDA, "MDUFA Performance Goals and Procedures [26]" (April 18, 2012) (attachment to letter dated July 16, 2012 from Secretary of Health and Human Services Kathleen Sebelius to The Honorable Fred Upton, Chairman, U.S. House of Representatives Committee on Energy & Commerce.

[3] See 21 CFR 814, Subpart C.

[4] For more detailed infor mation, see FDA's guidance document, "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 [27]" or the guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process [28]"

[5] The definition for the term "FDA decision" is provided in the MDUFA III Commitment Letter. See footnote 2.

[6] Minor deficiencies may include, for example, clarifications of previously submitted information, revisions to the labeling, and revisions/development of a post approval study protocol.

[7] FDA expects that a denial will nor mally be preceded by another FDA action that stops the review clock, such as a not approvable letter. There is, however, no statutory requirement for any prior FDA action, and FDA may, in appropriate circumstances, proceed directly to issue a denial order.

[8] See 148 CONG. REC. S1 1549-S1 1551 (daily ed. Nove m ber 18, 2002) (Performance Goals for the Medical Device User Fee and Modernization Act of 2002).

[9] See 153 CONG. REC. S1 2420-S1 2421 (daily ed. October 2, 2007) (Performance Goals for the Medical Device User Fee Amendments of 2007).

[10] For additional information, refer to the draft guidance document entitled, "eCopy Program for Medical Device Submissions [29]" for more details. Once final, this document will represent the Agency's current thinking on this topic.

[11] For additional information, refer to the draft guidance document entitled "User Fees and Refunds for Premarket Approval Applications [30]". Once final, this document will represent the Agency's current thinking on this topic.

[12] For additional information on the appropriate number of hard copies and eCopies, refer to the draft guidance entitled "eCopy Program for Medical Device Submissions [29]". Once final, this document will represent the Agency's current thinking on this topic.

[13] For additional information, please refer to the draft guidance entitled, "Acceptance and Filing Review for Premarket Approval Applications (PMAs) [31]" Once final, this document will represent the Agency's current thinking on this topic.

[14] For MDUFA II, if the applicant submitted an unsolicited major amendment during the first review cycle, the FDA decision goal date was extended by the number of days equal to 75% of the difference between the filing date and the date of receipt of the amendment.

[15] Although a response to an approvable letter is not considered a major amendment because the issues are minor in nature, it will restart the FDA review clock upon receipt. A partial response to an approvable letter will not restart the review clock.

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[25] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments#ft15
[26] http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf

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