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FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals

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Guidance for Industry and Food and Drug Administration Staff

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This document supersedes "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals" issued October 15, 2012.

For questions about this document regarding CDRH-regulated devices, contact the Premarket Approval Staff at 301-796-5640.

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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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Preface

Public Comment

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Identify all comments with the docket number FDA-2003-D-0378. 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 Food and Drug Administration Staff

I. Introduction

The Medical Device User Fee Amendments of 2017[1] (MDUFA IV), 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, 2017, 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[2] for PMAs received in FY 2003-2007 (now referred to as MDUFA I). New performance goals and process improvements were incorporated in the Medical Device User Fee Amendments of 2007[3] for PMAs received in FY 2008-2012 (now referred to as MDUFA II), and subsequently in the Medical Device User Fee Amendments of 2012 (MDUFA III)[4] for PMAs received during FY 2013-2017 (MDUFA III). For PMAs received during FY 2018-2022, the revised performance goals and process

[1] See Title II of the FDA Reauthorization Act of 2017 (Public Law 115-52).
[2] See the Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250).
[3] See Title II of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85).
[4] See Title II of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144).

improvements are outlined in the letter from the Secretary of Health and Human Services to Congress[5] (MDUFA IV Commitment Letter) and are further described below.

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 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 III (for PMAs received in FY 2012 - 2017);
- the effect each action has on goals under MDUFA IV (for PMAs received in FY 2018 - 2022; and
- the different industry actions that may be taken on PMAs.

III. FDA Actions

The PMA regulation outlines the various actions FDA may take on an original PMA or PMA supplement during the course of our review.[6] For original PMAs, panel-track supplements, and 180-day supplements,[7] the following responses are considered FDA actions:

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

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[5] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

[6] See 21 CFR 814, Subpart C.

[7] For more detailed information, 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" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089730.pdf) or the guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM270606.pdf).

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" (also referred to as "MDUFA decision") under FDA's commitment letters and are measured against a MDUFA I/II/III/IV goal. 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,[8] which are identified in the approvable letter (21CFR 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)(iii). 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

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

response to an approvable letter, we will restart the clock with a new FDA response timeframe.

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, or if we have attempted to resolve all deficiencies via interactive review and have not received adequate responses, 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)(4) 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. FDA expects that a denial will normally 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. 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. PMA Performance Goals for MDUFA III

The performance goals for PMA applications received in FY 2013 through FY 2017 (the time frame defined for MDUFA III) were defined in the MDUFA III Commitment Letter.[9] Table 1 below summarizes the decision and performance goals in effect for PMA applications under MDUFA III. Performance goals are applied to the MDUFA III cohort of PMA

[9] See 158 CONG. REC. S8277-S8281 (daily ed. Corrected December 20, 2012) (Letters from the Secretary of Health and Human Services Re: Medical Device User Fee Program), also available at https://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf.

submissions and include goals for Substantive Interaction, MDUFA decision, and Total Time to Decision.

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 filed. FDA Days begin on the date of receipt of the submission or the amendment to the submission that enables the submission to be filed.

The shared outcome goal of Total Time to Decision was a new performance goal for which FDA and industry performance were reported during MDUFA III. FDA and applicants shared responsibility for this goal, which was 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 a filed 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 1: MDUFA III Decision 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						
	FDA Days	FY'13	FY'14	FY'15	FY'16	FY'17
Original PMAs and Panel-Track Supplements - Without Panel	180	70%	80%	80%	90%	90%
Original PMAs and Panel-Track Supplements – With Panel	320	50%	70%	80%	80%	90%
180-Day Supplements	180	85%	90%	90%	95%	95%
Real-Time Supplements	90	90%	90%	95%	95%	95%

Average Total Time to Decision						
		FY'13	FY'14	FY'15	FY'16	FY'17
Original PMAs and Panel-Track Supplements		395	395	390	390	385

V. PMA Performance Goals for MDUFA IV

The performance goals for PMA applications received in FY 2018 through FY 2022 are defined in the MDUFA IV Commitment Letter. Performance goals and associated changes introduced under MDUFA III and retained in MDUFA IV include:

- most PMA submissions are subject to a user fee, and all PMA submissions need a valid eCopy[10] in order to initiate review;
- original PMAs and panel-track supplements will undergo an acceptance review that precedes the filing review[11];
- 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 MDUFA decision goals (modular PMAs no longer have a MDUFA performance goal);
- the terms "expedited" and "priority" will now be referred to as "breakthrough devices" (to be consistent with the statutory language in the 21st Century Cures Act[12]) 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;
- there is a shared outcome goal for the total time from receipt of a submission accepted for filing review 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.

[10] For additional information, refer to the guidance document, "eCopy Program for Medical Device Submissions" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf) for more details.

[11] For additional information on the acceptance and filing reviews, refer to the guidance document, "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf) for more details.

[12] See the 21st Century Cures Act (Public Law 114-255).

Performance goals and associated changes introduced under MDUFA IV include:

- for submissions that require Advisory Committee input, FDA will issue a MDUFA decision within 60 days from the Advisory Committee recommendation, as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations; and

- for submissions that receive a MDUFA decision of Approvable, FDA will issue a decision within 60 days of the sponsor's response to the Approvable letter, as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations.

A. Submission

Many PMA submissions will be subject to a user fee[13] and all PMA submissions (originals, supplements, reports, and amendments) will be subject to the requirement for the appropriate number of copies, including an eCopy. 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. For additional information, please refer to the guidance "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm313368.pdf).

[13] See " User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM345633.pdf).

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 IV goal. After a Substantive Interaction, FDA intends to work with the applicant via Interactive Review to reach a MDUFA decision.

D. MDUFA IV Goals

MDUFA IV includes goals for Substantive Interaction, MDUFA decision, and Total Time (see Tables 2 and 3).

The goals for Substantive Interaction and MDUFA decision are in terms of FDA Days, which are defined in the MDUFA IV 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 filed.

The shared outcome goal of Total Time to Decision was retained for MDUFA IV, and is defined as the time spent by FDA reviewing the application as well as the time spent by the applicant responding to questions from FDA. For MDUFA IV, the Total Time to Decision is the number of calendar days from the date of receipt of a filed 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 Time to Decision for applications (for example, for FY2018, the average Total Time to Decision for PMA applications would be the average of FY2016 through FY2018) 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.

MDUFA IV includes the following performance goals:

Table 2: MDUFA IV Decision Goals

Substantive Interaction		
	FDA Days	FY'18 – FY'22
Original PMAs, Panel-Track Supplements, and 180-Day Supplements	90	95%

MDUFA Decision		
	FDA Days	FY'18 – FY'22
Original PMAs and Panel-Track Supplements - Without Panel	180	90%
Original PMAs and Panel-Track Supplements - With Panel	320	90%
180-Day Supplements	180	95%
Real-Time Supplements	90	95%

Table 3: MDUFA IV Total Time Goals

Average Total Time to Decision					
	FY' 18	FY' 19	FY' 20	FY' 21	FY' 22
Original PMAs and Panel-Track Supplements	320	315	310	300	290

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 a missed MDUFA decision communication, which is 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 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)[14]. 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.

As with the original PMA, any amendment to a PMA or a request to withdraw a PMA will need to include an eCopy as part of the submission to the appropriate Document Control Center for the submission to be processed as described in the guidance document, "eCopy Program for Medical Device Submissions," available at

[14] See 21 CFR 814.37.

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313794.pdf.

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 original or panel-track supplement 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).

Unsolicited major amendments should not be used to add new device models or components of the device 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 decision as defined MDUFA III and IV Commitment Letters) 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; 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

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. 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.

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 III.F 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.