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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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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

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. 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

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

The Medical Device User Fee Amendments of 2022[1] (MDUFA V), amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to authorize FDA to collect user fees for the review of certain premarket submissions received on or after October 1, 2022, 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 negotiated and agreed to under MDUFA V for PMAs received in FY 2023-2027. These performance goals and process improvements are outlined in the letter from the Secretary of Health and Human Services to Congress[2] (MDUFA V Commitment Letter) and are further described below.

In general, FDA's guidance documents 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

[1] See Title II of the FDA User Fee Reauthorization Act of 2022 (Public Law 117-180).
[2] See 168 CONG. REC. S5194-S5203 (daily ed. September 28, 2022) (Food and Drug Administration User Fee Reauthorization). The MDUFA V Commitment Letter is also available at https://www.fda.gov/media/158308/download.

use of the word *should* in Agency guidances 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 IV (for PMAs received in FY 2018 – 2022);
- the effect each action has on goals under MDUFA V (for PMAs received in FY 2023 – 2027); 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.[3] For original PMAs, panel-track supplements, and 180-day supplements,[4] 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 a "MDUFA decision" under FDA's commitment letters and are measured against a MDUFA IV/V goal. These FDA actions are described below.

[3] See 21 CFR Part 814, Subpart C.

[4] For more detailed information, see FDA's guidance document, "User Fees and Refunds for Premarket Approval Applications and Device Biologics Licences Applications," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications or the guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process.

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 found to be in compliance with the Quality System regulation (21 CFR Part 820).

An approval order shuts off the review clock, marks the end of FDA review, and is considered 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,[5] 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 review clock and place the application on hold. When FDA receives a complete response to an approvable letter, we will resume the clock with a new FDA response timeframe to reach a final decision. FDA will issue a decision within 60 calendar 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.

When FDA issues an approvable pending GMP inspection letter, we stop the review clock. Once FDA determines that the device manufacturing facilities, methods, and controls are

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

found to be in compliance with the Quality System regulation, 21 CFR part 820, we will issue an approval order.

C. Major Deficiency Letter

FDA will issue a major deficiency letter[6] 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 critical to determining reasonable assurance of safety and effectiveness of the device 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 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[7]).

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)).

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[6] For additional information about deficiencies, see FDA's guidance document, "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-responding-deficiencies-accordance-least-burdensome-provisions.

[7] As described in Section VIII.C of the MDUFA V Commitment Letter, FDA Days are those calendar days when a submission is considered to be under review at the Agency for submissions that have been filed. See Section VIII.C of the MDUFA V Commitment Letter, available at https://www.fda.gov/media/158308/download.

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 resume 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 calendar 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 FD&C 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 FD&C Act. 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 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, not approvable, or not filing letter within 180 calendar days (21 CFR 814.44(g)). FDA will automatically grant one 180-day extension to respond to one of these four FDA action letters, increasing the time to provide a complete response to the FDA action letter to a total of 360 calendar days. FDA intends to notify the applicant when 360 calendar days have elapsed with a letter acknowledging voluntary withdrawal of the PMA or PMA supplement. Any amendment submitted in response to an FDA action letter after 360 calendar 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 IV

The performance goals for PMA applications received in FY 2018 through FY 2022 were defined in the MDUFA IV Commitment Letter.[8] 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[9] in order to initiate review;
- original PMAs and panel-track supplements will undergo an acceptance review that precedes the filing review[10];
- original PMAs, panel-track supplements, and 180-day supplements are subject to a Substantive Interaction 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[11]) 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 calendar days, FDA will send a Missed MDUFA decision (MMD) communication to the applicant.

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 calendar days from the Advisory Committee recommendation, as

[8] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization). The MDUFA IV Commitment Letter is also available at https://www.fda.gov/media/102699/download.

[9] For additional information, refer to the guidance document, "eCopy Program for Medical Device Submissions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions.

[10] For additional information on the acceptance and filing reviews, refer to the guidance document, "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-and-filing-reviews-premarket-approval-applications-pmas.

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

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 calendar 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.

V. PMA Performance Goals for MDUFA V

The performance goals for PMA applications received in FY 2023 through FY 2027 are defined in the MDUFA V Commitment Letter.[12] The performance goals and associated changes included in Section IV of this guidance are also retained in MDUFA V. Performance goals and associated changes introduced under MDUFA V include:

- for original PMA and panel-track supplement submissions received in FY 2023 through FY 2024, the average shared outcome Total Time to Decision goal for FDA and industry is 290 calendar days; and

- for original PMA and panel-track supplement submissions received in FY 2025 through FY 2027, the average shared outcome Total Time to Decision goal for FDA and industry is 285 calendar days.

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 an eCopy or an electronic submission (eSubmission) using an electronic submission template (e.g., eSTAR (electronic Submission Template And Resource)),[14,15] when available. 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 valid eCopy or eSTAR. FDA is authorized by section 745A(b)(1) of the FD&C Act to implement eCopy requirements for PMA submissions and is authorized by section 745A(b)(3) of the FD&C Act to implement requirements for submissions solely in electronic format. Please see the guidance entitled

[12] https://www.fda.gov/media/158308/download
[13] See " User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications.
[14] eSTAR is the only type of electronic submission template that is intended to be available to facilitate the preparation of PMA submissions as eSubmissions. For simplicity, the electronic submission created with this electronic submission template is often referred to as an eSTAR.
[15] See FDA's website regarding the eSTAR program, available at https://www.fda.gov/medical-devices/how-study-and-market-your-device/voluntary-estar-program. This website provides current information regarding the eSTAR program for CDRH and CBER.

"eCopy Program for Medical Device Submissions,"[16] for more information about eCopy requirements and the guidance "Providing Regulatory Submissions for Medical Devices in Electronic Format — Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act"[17] for more information about eSubmission requirements.

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.[18] 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 calendar days of receipt of the accepted application. For additional information, please refer to the guidance "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)."[19]

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

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[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-medical-devices-electronic-format-submissions-under-section-745ab

[18] In the case of a government closure during the 15-day review period, the review period may be extended by a comparable number of business days that the FDA buildings are closed. If the applicant receives an automated notice that the acceptance review was not completed because the screening period has exceeded 15 calendar days, FDA may send a correction notice to the applicant.

[19] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-and-filing-reviews-premarket-approval-applications-pmas

D. MDUFA V Goals

MDUFA V includes goals for Substantive Interaction, MDUFA decision, and Total Time to Decision (see Tables 1 and 2).

The goals for Substantive Interaction and MDUFA decision are in terms of FDA Days, which are defined in the MDUFA V 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 retained for MDUFA V, 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 V, 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 FY 2023, the average Total Time to Decision for PMA applications would be the average of FY 2021 through FY 2023) 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 V includes the following performance goals:

Table 1: MDUFA V Decision Goals

Substantive Interaction		
	FDA Days	FY2023 – FY2027
Original PMAs, Panel-Track Supplements, and 180-Day Supplements	90	95%
MDUFA Decision		
	FDA Days	FY2023 – FY2027
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 2: MDUFA V Total Time Goals

Average Total Time to Decision					
	FY2023	FY2024	FY2025	FY2026	FY2027
Original PMAs and Panel-Track Supplements	290	290	285	285 (275)[20]	285 (275/270)[21]

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 calendar 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).[22] The information below clarifies the basis for each action an applicant may take and the effect each action has on the 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 or eSTAR (when available) for the submission to be processed as described in the guidance documents, "eCopy Program for Medical Device Submissions."[23]

[20] The goal will be adjusted if the conditions of Section III.A of the MDUFA V Commitment Letter are met. For additional information, see Section III.A of the MDUFA V Commitment Letter, available at https://www.fda.gov/media/158308/download.

[21] The goal will be adjusted if the conditions of Section III.A of the MDUFA V Commitment Letter are met. For additional information, see Section III.A of the MDUFA V Commitment Letter, available at https://www.fda.gov/media/158308/download.

[22] See 21 CFR 814.37.

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions

and "Providing Regulatory Submissions for Medical Devices in Electronic Format — Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act."[24, 25]

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 IV and V 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 elapsed 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 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:

[24] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-medical-devices-electronic-format-submissions-under-section-745ab
[25] https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper-format-cber-regulated-products

- 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 resumes the review clock upon receipt. A partial response to an action letter does not resume the review clock. Although a response to an approvable letter is not considered a major amendment because the issues are minor in nature, it will resume the review clock upon receipt. A partial response to an approvable letter will not resume 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 calendar days.