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FDA and Industry Actions on De Novo Classification Requests: 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

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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 De Novo classification requests (De Novo requests). 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 De Novo requests received in FY 2023-2027. These performance goals are outlined in the MDUFA V Commitment Letter from the Secretary of Health and Human Services (the Secretary) to Congress[2] and are further described below.

[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.

On October 5, 2021, FDA issued a final rule on the De Novo Classification Process.[3] This final rule added new regulations at 21 CFR Part 860, Subpart D--De Novo Classification that describe the procedures and criteria FDA uses in assessing whether a request for an evaluation of automatic class III designation (De Novo classification request or De Novo request) contains the information necessary to permit a substantive review.

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 use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Scope

This document describes:

- the different FDA actions that may be taken on De Novo requests;
- the effect each action has on goals under MDUFA IV for De Novo requests received in FY 2018-2022;
- the effect each action has on goals under MDUFA V for De Novo requests received in FY 2023-2027; and
- the different industry actions that may be taken on De Novo requests.

III. FDA Actions

FDA will begin substantive review of a De Novo request after the request is accepted under 21 CFR 860.230. After FDA conducts a substantive review of the submission, FDA may take any of the following actions (21 CFR Part 860, Subpart D):

- issue an order granting a De Novo request for classification (granting order);
- issue an order declining a De Novo request for classification (decline order); or
- issue a request for additional information (AI request).

Further, in accordance with 21 CFR 860.250(a), the Agency may consider a De Novo request to be withdrawn if additional information is not provided within 180 calendar days following issuance of an AI request. In this instance, FDA may issue a notice of withdrawal to the requester (21 CFR 860.250(b)). A notice of withdrawal is sometimes referred to as a

[3] "Medical Device De Novo Classification Process" (86 FR 54826) at https://www.federalregister.gov/d/2021-21677

"deletion letter." The term "deletion" is used to differentiate a lack of timely response (under 21 CFR 860.250(a)(1)-(2)) from a request to withdraw a pending De Novo request by the requester (21 CFR 860.250(a)(4)).

Of these FDA actions, issuing a granting order, issuing a decline order, and withdrawing a De Novo request are considered MDUFA decisions, as defined in the MDUFA V Commitment Letter.

The following sections describe the actions FDA may take on an accepted De Novo request, explain when these actions may be appropriate, and discuss the effect that each action has on the review clock.

A. Issue an Order Granting the Request to Classify the Device

An order granting the De Novo request to classify the device (granting order) is a letter issued to the De Novo requester stating that FDA has determined that the device meets the criteria for classification into either class I or class II.[4] A granting order authorizes marketing of the device in the United States (U.S.), subject to specific statutory and regulatory requirements.

The criteria for granting a De Novo request are described in section 513(f)(2) of the FD&C Act and 21 CFR Part 860. The grounds on which FDA may decline a De Novo request are described in 21 CFR 860.260. If none of the reasons apply, then FDA will issue an order granting a De Novo request. Such an order shuts off the review clock, marks the end of FDA review, and is considered a final action.

B. Issue an Order Declining the Request

An order declining the De Novo request (decline order) is a letter issued to a De Novo requester (21 CFR 860.260(b)) stating that FDA has determined that either: a) the device is not eligible for De Novo classification; or b) the device is eligible for De Novo classification, but the requester has not demonstrated that the device described in the De Novo request meets the criteria under section 513(a)(1) of the FD&C Act and 21 CFR 860.260. Therefore, the request is declined and the device remains in class III (Premarket Approval).

FDA will issue a decline order in the following situations (21 CFR 860.260(c)):

- the device does not meet the criteria under section 513(a)(1) of the FD&C Act and 21 CFR 860.3 for classification into class I or II (21 CFR 860.260(c)(1));

- the De Novo request contains a false statement of material fact or there is a material omission (21 CFR 860.260(c)(2));

[4] See section 513(f)(2) of the FD&C Act.

- the devices's labeling does not comply with the requirements in 21 CFR parts 801 or 809, as applicable (21 CFR 860.260(c)(3));

- the product does not meet the definition of a device under section 201(h) of the FD&C Act and is not a combination product as defined at 21 CFR 3.2(e) (21 CFR 860.260(c)(4));

- the device is of a type which has already been approved in existing applications for PMAs (21 CFR 860.260(c)(5));

- the device is of a type which has already been classified into class I, class II, or class III (e.g., it is probable that the device could be determined to be substantially equivalent (SE) to a predicate device (i.e., a device that has already been classified within an existing class I or class II classification regulation or an unclassified preamendments device)) (21 CFR 860.260(c)(6));

- an inspection of a relevant facility under 21 CFR 860.240(c) results in a determination that general or general and special controls would not provide reasonable assurance of safety and effectiveness (21 CFR 860.260(c)(7));

- a nonclinical study subject to 21 CFR part 58 that is described in the De Novo request, and that is essential to show there is reasonable assurance of safety, was not conducted in compliance with 21 CFR part 58 and no reason for the noncompliance is provided or, if a reason is provided, the practices used in conducting the study do not support the validity of the study (21 CFR 860.260(c)(8));

- a clinical investigation described in the De Novo request involving human subjects that is subject to the institutional review board regulations in 21 CFR part 56, informed consent regulations in 21 CFR part 50, or good clinical practice (GCP) described in 21 CFR 812.28(a), was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable (21 CFR 860.260(c)(9));

- a clinical or nonclinical study necessary to demonstrate that general controls or general and special controls provide reasonable assurance of safety and effectiveness: (i) has not been completed per the study protocol, or (ii) deficiencies related to the investigation and identified in any request for additional information under 21 CFR 860.240(b)(1) have not been adequately addressed (21 CFR 860.260(c)(10)); or

- After the De Novo request is accepted for review under 21 CFR 860.230(b), the requester makes significant unsolicited changes to the device's indications for use or technological characteristics (21 CFR 860.260(c)(11)).

FDA's decision to decline a De Novo request will be based on review of the totality of the information provided to support the De Novo request, and may therefore be a combination of multiple issues outlined above. A device that is eligible for De Novo classification will be declined if the totality of the information provided, including performance data, is insufficient (e.g., data that were inadequate or inconclusive) to demonstrate that the device is of low to moderate risk. A De Novo request will also be declined if, based on the totality of the information provided, including performance data, FDA determines that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

A decline order will inform the requester of the deficiencies in the De Novo request, including each applicable ground for declining (21 CFR 860.260(d)). A decline order shuts off the review clock, marks the end of FDA review, and is considered a final action.

C. Request for Additional Information

FDA issues a request for additional information (AI request) when the De Novo request lacks information necessary for the Agency to complete its review and determine whether to grant or decline the De Novo request (21 CFR 860.240(b)(1)). AI requests are issued by email with an attachment document identifying deficiencies.[5] These requests inform the requester that the De Novo is being placed on hold pending receipt of a complete response to all of the identified deficiencies. The hold starts on the issue date of the AI request.

FDA generally issues an AI request when FDA believes the additional information needed from the requester is not suitable for interactive review and/or cannot be provided within a reasonable timeframe (i.e., such that the review would be unduly delayed if the submission were not placed on hold).

An AI request is an interim action that stops the review clock and marks the end of an FDA review cycle. The review clock will resume upon the receipt of a complete response to the AI request. Any additional information submitted to FDA must include the reference number assigned to the original De Novo request and, if submitted on the requester's own initiative, the reason for submitting the additional information (21 CFR 860.240(b)(2)).

D. Issue a Notice of Withdrawal

A notice of withdrawal informs the De Novo requester that FDA considers the De Novo request to be withdrawn. The notice of withdrawal represents an FDA decision to discontinue its review of the De Novo request.

In accordance with 21 CFR 860.250(a), FDA considers a De Novo request to have been withdrawn if:

[5] Please note that AI requests from CBER will be issued according to "SOPP 8119: Use of Email for Regulatory Communications," available at https://www.fda.gov/media/108992/download.

- FDA does not receive a complete response in a submission to a request for additional information pursuant to 21 CFR 860.240(b)(1) within 180 calendar days after the date FDA issues such request (21 CFR 860.250(a)(1));

- FDA does not receive a response, after refusing to accept the De Novo request or a technical screening hold, within 180 calendar days of the date notification was issued by FDA (21 CFR 860.250(a)(2));

- FDA is not permitted an opportunity to inspect relevant facilities, pursuant to 21 CFR 860.240(c), at a reasonable time and in a reasonable manner, and to have access to copy and verify all records pertinent to the De Novo request (21 CFR 860.250(a)(3)); or

- The requester submits a written notice to FDA that the De Novo request has been withdrawn (21 CFR 860.250(a)(4)).

If a De Novo request is withdrawn while the submission is on hold, an FDA notice of withdrawal does not affect the review clock. Issuance of a notice of withdrawal shuts off the review clock, marks the end of FDA review, and is considered a final action. The notice will include the De Novo request reference number and the date FDA considered the De Novo request withdrawn (21 CFR 860.250(b)).

IV. De Novo Performance Goals for MDUFA IV

The performance goals for De Novo requests received from FY 2018 through FY 2022 (the time frame defined for MDUFA IV) were defined in the MDUFA IV Commitment Letter.[6] Performance goals and associated changes that were implemented in MDUFA IV include:

- most De Novo requests became subject to user fees;

- FDA issued draft and final guidance that includes a submission checklist to facilitate a more efficient and timely review process;

- De Novo requests became subject to a one-tier MDUFA decision goal (there are no "cycle" (or review cycle) goals for interim actions); and

- for De Novo requests for which a MDUFA decision has not been rendered within 180 FDA days,[7] at the requester's request and resources permitting, but not to the detriment of meeting the quantitative review timelines, FDA will discuss with the

[6] Available at https://www.fda.gov/media/102699/download.

[7] As described in Section VII.D of the MDUFA IV Commitment Letter and 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 accepted. See Section VIII.C of the MDUFA V Commitment Letter, available at https://www.fda.gov/media/158308/download.

requester all outstanding issues with the submission preventing FDA from reaching a decision.

V. De Novo Performance Goals for MDUFA V

The performance goals for De Novo requests received from FY 2023 through FY 2027 (the time frame defined for MDUFA V) are defined in the MDUFA V Commitment Letter.[8] Most of the performance goals and associated changes included in Section IV of this guidance are also retained in MDUFA V. To fulfill the submission checklist requirement, FDA issued a final guidance document "Acceptance Review for De Novo Classification Requests"[9] in 2019, and updated the guidance in 2021 in conjunction with the issuance of a final rule for the De Novo classification process,[10] which took effect on January 5, 2022.

Relative to MDUFA IV, the only significant change in MDUFA V are the performance goals for De Novo requests. De Novo request performance goals will increase for FY 2026 and FY 2027 if performance goals for FY 2023 and FY 2024 are met, respectively, as outlined in the MDUFA goals section below.

A. Submission

Most De Novo requests will be subject to a user fee as described in the guidance document entitled "User Fees and Refunds for De Novo Classification Requests,"[11] and all De Novo requests 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)).[12,13,14] FDA is authorized by section 745A(b)(1) of the FD&C Act to implement eCopy requirements for De Novo requests after the issuance of final guidance 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 "eCopy Program for Medical Device Submissions,"[15] for more information about eCopy requirements and the guidance entitled "Providing Regulatory Submissions for Medical Devices in Electronic

[8] https://www.fda.gov/media/158308/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-review-de-novo-classification-requests
[10] "Medical Device De Novo Classification Process" (86 FR 54826) at https://www.federalregister.gov/d/2021-21677
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-de-novo-classification-requests
[12] 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.
[13] eSTAR is the only type of electronic submission template that is currently available to facilitate the preparation of De Novo requests as eSubmissions. For simplicity, the electronic submission created with this electronic submission template is often referred to as an eSTAR.
[14] https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper-format-cber-regulated-products
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions

Format — Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act"[16] for more information about eSubmission requirements.

De Novo requests will not be processed and distributed to the appropriate Office for review without confirmation of user fee payment (or applicability of a user fee exception), and a valid eCopy or eSTAR.

B. Acceptance Review

In accordance with 21 CFR 860.230, within 15 calendar days of receipt, FDA intends to conduct an acceptance review to make a threshold determination that the De Novo request contains the information necessary to permit a substantive review.[17] If FDA refuses to accept a De Novo request, FDA will notify the requester within 15 calendar days that the submission has not been accepted. The notification will identify those items that are the basis for the refuse to accept (RTA) decision and are therefore necessary for the submission to be considered accepted. The submission will be placed on hold and the review clock will not start until the missing elements are provided. For additional information, please refer to the guidance, "Acceptance Review for De Novo Classification Requests."[18]

This communication represents an administrative review of the submission and is not indicative of deficiencies that may be identified later in the review cycle.

When submitting an eSTAR, the RTA requirements of 21 CFR 860.230, have been automated within the eSTAR.[19] However, FDA intends to employ a virus scanning and technical screening process for an eSTAR. The technical screening process is anticipated to occur within 15 calendar days of FDA receiving the De Novo eSTAR. FDA intends to begin the technical screening for De Novo electronic submissions after confirmation of user fee payment. After receipt, FDA may seek to verify that the submission type is correct during the technical screening period. If this initial verification reveals that the submission is an incorrect type (e.g., a De Novo was received for a device type already approved as a PMA), FDA will place the submission on hold in order to allow for withdrawal of the submission, if appropriate. If the eSTAR does not pass the technical screening process due to an inaccurate response or at least one obviously irrelevant attachment, FDA will notify the submitter via email[20] and identify the inaccurate or irrelevant information, and the De Novo will be placed

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

[17] 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 submitter 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 De Novo requester.

[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-review-de-novo-classification-requests

[19] For more information on the RTA process, please see "Acceptance Review for De Novo Classification Requests," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-review-de-novo-classification-requests.

[20] For additional information about email communications with CBER, please see the "SOPP 8119: Use of Email for Regulatory Communications," available at https://www.fda.gov/media/108992/download.

and remain on hold until a complete replacement eSTAR is submitted to FDA. The technical screening review time does not impact the review clock for files that pass the technical screening. For a submission that passes technical screening, the review clock starts on the day the submission was received by FDA.

C. Substantive Review

Once the submission has been accepted for review (i.e., after the acceptance or technical screening phase of review), FDA will conduct a substantive review (21 CFR 860.240(a)). During the substantive review, FDA will generally communicate with the requester through a Substantive Interaction. The Substantive Interaction communication can be an AI request (which stops the clock) or an email stating that FDA will attempt to resolve any outstanding deficiencies interactively in real-time, without stopping the review clock (Interactive Review).

Following a Substantive Interaction, FDA intends to work with the requester via Interactive Review to reach a MDUFA decision.

D. MDUFA V Goals

MDUFA V includes a goal for a MDUFA decision (see Table 1 below), defined in terms of FDA Days, which are 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 (i.e., user fee is paid and a valid eCopy or eSTAR is provided).

Table 1. De Novo Performance Goals

Action	Review Time (FDA days)	Fiscal Year	Performance Level
MDUFA Decision (grant/decline/ withdraw)	150	FY 2023	70%
		FY 2024	70%
		FY 2025	70%
		FY 2026	70% (80% if FY 2023 goal is met)[21]
		FY 2027	70% (80% if FY 2023 goal is met/ 90% if FY 2024 goal is met)[22]

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

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

E. Missed MDUFA Decision Communication

At Industry's request and as resources permit, but not to the detriment of meeting the quantitative review timelines, if a final decision has not been rendered within 180 FDA days, FDA will discuss with the requester, in a meeting or teleconference, all outstanding issues with the submission preventing FDA from reaching a decision. This discussion will reflect appropriate management input and approval, and will include action items for FDA and/or the requester, as appropriate, with an estimated date of completion for each party to complete their respective tasks.

VI. Requester Actions

Actions taken by the requester of a pending De Novo request may include submission of a response to FDA's AI request (i.e., not a request made via interactive review) or withdrawal of the De Novo request (either by submission of a request for withdrawal or by not responding to an FDA AI request within 180 calendar days) (see 21 CFR 860.250(a)). The information below describes the actions a requester may take and the effect each action has on the review clock.

As with the original De Novo request, any amendment or supplement to a De Novo request or a request to withdraw a De Novo request will need to be submitted via eCopy or eSTAR for the submission to be processed as described in the guidance documents "eCopy Program for Medical Device Submissions"[23] and "Providing Regulatory Submissions for Medical Devices in Electronic Format — Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act."[24]

A. Response to an AI Request

A response to an FDA AI request is the submission of additional information, addressing all of the deficiencies identified in that AI request, that allows FDA to continue or complete the substantive review and reach a decision on the De Novo request (21 CFR 860.240(b)).

The requester should provide a complete response to an AI request from FDA. The response should address all of the deficiencies identified by FDA in its AI request to be considered a complete response.

The requester's submission of a response to an AI request is an action that, upon receipt by FDA, resumes the review clock (i.e., the 150-day review clock resumes upon receipt of the additional information).

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

If FDA determines that the requester has not addressed one or more of the deficiencies identified in the AI request, the review cycle will be terminated until FDA receives a response addressing the remaining deficiencies. In such a case, FDA informs the requester by email that the response is incomplete and the De Novo request will be placed back on hold as of the date of the original AI request; therefore, the review clock has not resumed. The requester will have 180 calendar days from the date of the original AI request in which to submit a complete response, or the De Novo request will be considered to be withdrawn (21 CFR 860.250(a)(1)).

B. Request for Withdrawal of the De Novo Request

A request to withdraw a De Novo request informs FDA of the requester's intent to discontinue its pursuit of FDA review of the De Novo request (21 CFR 860.250(a)(4)).

The De Novo requester may request withdrawal of the pending De Novo request at any time, and for any reason, after it is submitted for review but before FDA renders its final decision. FDA does not consider requests for withdrawal after a final decision has been rendered.

The request to withdraw a pending De Novo request shuts off the review clock, marks the end of FDA review, and is considered a final action. If the De Novo request is under review at the time FDA receives the withdrawal request, the review clock will stop on that date. If the De Novo request is on hold at the time FDA receives the withdrawal request, the review clock will remain stopped as of the date the De Novo request was last placed on hold.