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FDA Guidance Documents for De Novo Classification Requests

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Our staff includes former FDA and Notified Body personnel and industry experts with an in-depth functional knowledge of medical devices, IVDs, combination products, and biotechnology. Compliance requires the navigation of a complex maze of requirements. MEDIcept can provide state-of-the-art interpretation of those regulations, guidance documents, and standards and provides our clients with the information they need to comply safely and cost-effectively.

We use our expertise to quickly identify the root cause, coalesce corrective actions, and provide easy to understand structured solutions or recommended improvements. Since we know corrective action implementation is where many projects fail, we do not just write an action list. We make sure all stakeholders understand why the solutions were chosen and why they are needed. We work hand-in-hand with clients to implement the solutions, so the solutions have been culturally absorbed when the project is done.

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FDA Guidance Documents for De Novo Classification Requests

EXECUTIVE SUMMARY

The De Novo classification process is a risk-based approach for classifying novel medical devices that had previously been automatically placed in Class III, the highest United States device classification.

On October 4, 2021, the US Food and Drug Administration (FDA) issued a final rule to set requirements for the medical device De Novo classification process. On October 5, 2021, FDA issued new versions of four Guidance Documents related to the De Novo Classification Process to align with the final rule. These Guidance Documents attempt to provide additional transparency regarding the De Novo classification process regarding user fees and refunds, expectations on content submission, and MDUFA review goals. This paper summarizes the content of each of the Guidance Documents.

INTRODUCTION

On October 4, 2021, the US Food and Drug Administration (FDA) issued a final rule to set requirements for the medical device De Novo classification process. Alongside the publication of the final rule, FDA issued revisions to the following four FDA Guidances on the De Novo Classification Process on October 5, 2021. This paper provides a summary of each of the four guidances listed below.

1. User Fees and Refunds for De Novo Classification Requests,
2. De Novo Classification Process (Evaluation of Automatic Class III Designation),
3. Acceptance Review for De Novo Classification Requests, and
4. FDA and Industry Actions on De Novo Classification Requests: Effect on FDA Review Clock and Goals.

USER FEES AND REFUNDS FOR DE NOVO CLASSIFICATION REQUESTS

This Guidance describes in detail the different situations under which user fees are required and the circumstances under which the FDA will or will not issue refunds of user fees.

A user fee is required for original De Novo requests and for De Novo requests for a device for which a previous De Novo was declined. It is important to note that no user fee is required if a device is intended solely for a pediatric population. ***Table 1*** summarizes the MDUFA user fees for Fiscal Year 2022 (October 1, 2021, through September 30, 2022).

Application Type	Standard Fee	Small Business Fee
513(g) - *FDA Product Classification Request*	$5,061	$2,530
De Novo Classification Request	$112,457	$28,114

Table 1 - Applicable Medical Device User Fees
(https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa)

FDA will refund a user fee if the submitter qualified for a fee exception, such as a humanitarian device exemption, or if the device was for a pediatric population, and they will do so upon request if the submitter did not submit a valid eCopy before the original De Novo request was accepted for review or the FDA determines the submission does not meet the acceptance criteria during acceptance review.

Attachment 1 of the Guidance summarizes the different situations and is replicated here for convenience in ***Tables 2 to 4***.

De Novo Request Submission Type	De Novo Fee Required
Original De Novo Request	Yes
Additional information for a De Novo request that has not yet been accepted	No
Additional information for a pending De Novo request	No
De Novo request intended solely for a pediatric population	No
De Novo request for a device for which the previous De Novo request was declined	Yes

Table 2 - When Is a De Novo Request Subject to a User Fee?

FDA Determination or Submitter Action	Will FDA Refund Fee Payment?
I qualify for a fee exception provided by section 738(a)(2)(B)(v) of the FD&C Act. (This exception is for pediatric conditions of use.)	Yes
FDA declines my De Novo request.	No
I withdraw my De Novo request after acceptance for review.	No
FDA considers my De Novo request to be withdrawn after acceptance for review.	No
I fail to submit a valid eCopy before my Original De Novo request is accepted for review.	Yes, upon request
I fail to submit a valid eCopy for a De Novo amendment or supplement.	No
FDA determines my submission does not meet the acceptance criteria during acceptance review.	Yes, upon request

Table 3 - When Will FDA Refund a De Novo User Fee?

Submission Type	Must I Pay a Fee?
New De Novo Request	Yes. You must pay applicable fee for a De Novo Request.
510(k)	Yes. You must pay applicable fee for a 510(k).
Reclassification petition	No
PMA	Yes. You must pay applicable fee for a PMA.
HDE	No

Table 4 - What Fee Must I Pay for a New Device Submission Following a De Novo "Decline" Determination?

DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III DESIGNATION)

The De Novo classification process is utilized for Class I or Class II devices for which no legally marketed predicate device exists. On October 5, 2021, FDA issued a final rule on the De Novo classification process, which describes the procedures and criteria FDA will use in assessing whether or not a De Novo classification request (aka a De Novo request) contains the information necessary to permit a substantive review. FDA updated the "De Novo Classification Process" Guidance to reflect the De Novo final rule.

De Novo requests may be submitted for devices that do not fall within any existing classification regulation, for those for which there is no predicate device, or after your device receives an NSE (Not Substantially Equivalent) determination from FDA on a 510(k) submission. FDA will only consider De Novo requests if the reason for the NSE determination was:

- the lack of an identifiable predicate device,
- a new intended use, or
- different technological characteristics that raise different questions of safety and effectiveness.

If a device was found to be NSE due to inadequate performance data to demonstrate substantial equivalence, it is generally not eligible for the De Novo classification process. A De Novo request may be submitted with or without a preceding 510(k) premarket notification.

If you are considering submitting a De Novo request, FDA strongly recommends submitting a Pre-Submission prior to preparing the De Novo submission. While not required, it is a way to obtain early feedback from FDA on whether the device may be eligible for the De Novo classification process and to gather a preliminary perspective on the likely controls that will be necessary and on the data that will be required to support the De Novo request.

The Guidance details the information that should be included in the Pre-Sub, namely:

- the recommended content for all Pre-Subs (refer to FDA Guidance *"Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program"*).
- the proposed class (I or II) including a rationale for why general or general and special controls are adequate to provide a reasonable assurance of safety and effectiveness
- the searches, including search terms, used to establish that no predicate device and no classification regulation for the same device type exists and
- specific questions regarding review issues relevant to a planned De Novo request*

**The Guidance lists the information necessary for FDA to be able to consider specific questions such as risk to health and mitigations and ongoing or planned protocols or studies. The Guidance also provides sample questions to pose to FDA in the De Novo Pre-Sub.*

The required De Novo format and content can be found at

- 21 CFR 860.210, *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=860.210*, and
- 21 CFR 860.220 *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=860.220.*

FDA recommends reviewing information for recently granted De Novo requests, including classification orders, which are publicly posted on their website.

The FDA review process is detailed in ***Table 5***.

Stage	Description	Timing and Potential Outcomes
Acceptance Review	FDA reviews submission to ensure the De Novo request contains the information necessary to permit a substantive review (Refer to the next section of this white paper for a summary of the FDA Guidance "Acceptance Review for De Novo Classification Requests")	Within 15 calendar days one of the following will happen: • FDA will send notification of acceptance • FDA will send notification that the review is on hold pending receipt of additional information. If the requested information is not received by FDA within 180 days, FDA will consider the De Novo request withdrawn If FDA cannot complete the acceptance review within 15 days, FDA will accept the De Novo Request for review and notify the requester.

Substantive Review	FDA reviews the submission, including conducting a classification review of legally marketed device types to analyze whether an existing legally marketed device of the same type exists, including whether a predicate was established through the De Novo classification process.	Within 120 calendar days one of the following will happen:
		• FDA will decline the De Novo Request:
		  ○ if there is a likely predicate, and tell requester to submit a 510(k), unless the device is 510(k) exempt, for Class I or Class II devices or to submit a PMA for Class III devices; or
		  ○ if there is insufficient data to support safety and effectiveness and the device remains in Class III. A PMA may be submitted or a new De Novo may be submitted with the required additional information
		• FDA will send notification that the review is on hold pending receipt of additional information. If the requested information is not received by FDA within 180 days, FDA will consider the De Novo request withdrawn
		• FDA will grant the De Novo request

Table 5 - FDA Review Process

ACCEPTANCE REVIEW FOR DE NOVO CLASSIFICATION REQUESTS

This Guidance provides detail on the types of information FDA believes are necessary to conduct a substantive review for a De Novo request as well as recommendations regarding the acceptance review process and is intended to provide De Novo requesters with additional transparency regarding the types of information FDA believes are necessary for a substantive review.

Appendix A of the Guidance is an Acceptance Checklist that details the elements and objective criteria essential to the FDA's substantive review of the De Novo request.

The Acceptance Checklist begins with a section of Preliminary Questions to ensure the request is with the appropriate Center and the device on its face is eligible for De Novo classification.

After the Preliminary review is complete, as long as the device appears eligible for the De Novo classification and is with the appropriate Center, the reviewer will continue with the checklist to ensure that all applicable elements of a complete De Novo are present in the submission.

The Acceptance Checklist is 19 pages of questions with explanatory information and covers the items identified in ***Figure 1*** on page 5.

Figure 1 - Items Included in Appendix A, Acceptance Checklist

The possible FDA actions discussed in this Guidance are the same as those described in the "De Novo Classification Process" Guidance and summarized in this paper in the previous section.

FDA AND INDUSTRY ACTIONS ON DE NOVO CLASSIFICATION REQUESTS: EFFECT ON FDA REVIEW CLOCK AND GOALS

This FDA Guidance describes the different FDA and industry actions that may be taken on De Novo requests and the effect each action has on the FDA goal of issuing a decision within 150 FDA days of receipt for 70% of De Novo requests received in FY 2022 under MDUFA IV.

The Guidance describes the possible FDA Actions, as shown in ***Table 6***, below, and possible Requester Actions, as shown in ***Table 7***, on page 6.

Action	Description	Effect on Review Clock
Issue a Granting Order	Grants the De Novo request to classify the device. The granting order is a letter to the requester stating that FDA has determined the device meets the criteria for classification as either a Class I or a Class II device.	The review is complete and the manufacturer can now market the device.
Issue a Decline Order	Declines the De Novo request to classify the device. The decline order is a letter to the requester stating that either the device is not eligible for De Novo classification or it is eligible but the requester has not demonstrated that the device meets the criteria for low to moderate risk or other criteria for a Class I or Class II device, and therefore the device remains in Class III and requires Premarket Approval (PMA).	Shuts off the review clock and is considered a final action.
Issue an AI Request	This is an additional information request issued via email with a document attached that identifies the deficiencies.	The De Novo request is placed on hold as of the date of the email and stays on hold until FDA receives a complete response from the submitter. Submitter typically has 180 days to respond.
Issue a Notice of Withdrawal	Indicates the FDA has decided to discontinue its review of the De Novo request. FDA considers a De Novo request to be withdrawn if: i. FDA does not receive a complete response to a request for additional information within 180 calendar days of issuing the request; ii. FDA does not receive a response to an FDA refusal to accept (RTA) the De Novo request within 180 calendar days of the date the RTA was issued; iii. FDA is not permitted to inspect relevant facilities or given access to all records pertinent to the De Novo request; or iv. The requester submits a written notice to FDA that the De Novo request has been withdrawn.	Shuts off the review clock and is considered a final action.

Table 6 - FDA Actions

Action	Description	Effect on Review Clock
Response to an AI Request	This is the submission of additional information that addresses all the deficiencies identified by FDA.	FDA 150-day review clock resumes upon receipt of the additional information. De Novo Request is considered withdrawn if response is not received within 180 calendar days from the date of the AI request.
Request for Withdrawal	Request to withdraw the pending De Novo request. This must be submitted before FDA renders its final decision.	Shuts off the review clock and is considered a final action.

Table 7 - Requester Actions

CONCLUSION

In the new versions of four Guidance Documents related to the De Novo classification process, FDA has attempted to provide additional transparency regarding the De Novo classification process with regard to user fees and refunds, expectations on content submission, and MDUFA review goals. FDA expectations of what constitutes a complete submission are clearly defined and detailed, and the expectations for review times and what actions impact the review clock have been delineated. Any manufacturer with a device that is eligible for the De Novo classification process should become very familiar with these guidance documents and seek assistance from industry experts when needed.

Guidance Document Links

1. User Fees and Refunds for De Novo Classification Requests: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-de-novo-classification-requests*
2. De Novo Classification Process (Evaluation of Automatic Class III Designation): *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation*
3. Acceptance Review for De Novo Classification Requests: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-review-de-novo-classification-requests*
4. FDA and Industry Actions on De Novo Classification Requests: Effect on FDA Review Clock and Goals: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-de-novo-classification-requests-effect-fda-review-clock-and-goals*