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FDA finalizes De Novo Evaluation Guidance and issues associated Refuse to Accept Checklist

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On October 30, 2017, the Food and Drug Administration (FDA or the Agency) released its final De Novo request guidance document entitled, De Novo Classification Process (Evaluation of Automatic Class III Designation) (Final Guidance). This guidance finalizes the draft guidance with the same title that was published on August 14, 2014, and supersedes the related legacy guidance from 1998[1]. The Final Guidance is part of FDA's commitments under the Medical Device User Fee Act (MDUFA IV), where, for the first time, performance goals and submission fees are applied to De Novo requests. Similar to other MDUFA-tracked marketing submissions, De Novo requests will transition to also contain a refuse to accept (RTA) checklist, the draft guidance[2] for which was published concurrently with the Final Guidance.

As background, the Final Guidance comes after years of modification to the De Novo request program aimed at improving its usability. When first implemented, the scope of the De Novo pathway was limited to low risk devices that had been found not substantially equivalent (NSE) via 510(k) premarket notification and required burdensome rulemaking before a De Novo request could be granted. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) improved the De Novo process by expanding it to allow for reclassification of both low- and moderate-risk devices, created the direct De Novo pathway bypassing the requirement that sponsors first submit a 510(k) notice that is found NSE, and requiring only notification in the Federal Register prior to granting a request. Accordingly, the number of De Novo requests submitted and granted per year rose from less than 10 from 2009-2012 to approximately 25 per year in fiscal years 2013-2016. With the formalization of the review process under MDUFA IV, as well as the Agency's increasing reluctance to accept combination predicate/reference device arguments in support of substantial equivalence, this number is expected to continue to rise.

That said, the Final Guidance does little more to update the process other than finalize the draft guidance issued in 2014, and implement a change (as required by the 21st Century Cures Act) wherein sponsors who receive an NSE determination for a device eligible for De Novo reclassification are no longer required to submit a De Novo request within 30 days.

[1] New Section 513(f)(2) – Evaluation of Automatic Class III Designation, Guidance for Industry and Staff (February 19, 1998).
[2] Acceptance Review for De Novo Classification Requests (Draft) (October 30, 2017)

When to Submit a De Novo Request

A device that is not otherwise classified by regulation technically defaults to the highest risk classification (class III). The De Novo process allows FDA to "automatically downclassify" such a device if it is low- to moderate- risk. Thus, the De Novo pathway is appropriate only for devices for which there is no predicate (either due to a new intended use or where the device raises different questions of safety or effectiveness) and there is not an already existing classification regulation or an approved premarket approval (PMA). In addition, the probable risks and benefits of the device must be sufficiently understood such that general and special controls (where appropriate) can be created to provide reasonable assurance of the safety and effectiveness of the device. It is important to note that such special controls typically include the requirement of clinical testing to support a De Novo request.

Continued Encouragement of De Novo Pre-submission

Although not technically required, FDA continues to recommend submitting a De Novo pre-submission prior to submitting a De Novo request. The pre-submission process allows sponsors to obtain feedback on whether the De Novo classification process is likely appropriate for a specific device, and also to help determine the data that will be necessary to support the request. To obtain useful feedback from FDA specific to the planned De Novo request, in addition to including general device information (such as device description, intended use, and planned and completed testing), a De Novo pre-submission should address the following:

— proposed classification for the device;

— a summary of the search performed to determine that the device cannot fit into any previous classification, including a rationale why the device does not fit the closest classifications;

— a description of each identified risk, including studies planned/undertaken to establish the device's risk profile. The Final Guidance provides more detail regarding how FDA performs benefit/risk assessments, consistent with the Agency's guidance entitled, Factors to Consider When Making Benefit Risk Determinations in Medical Device Premarket Approval and De Novo Classifications; and

— proposed mitigation measure(s)/control(s) for each risk that will demonstrate that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness.

De Novo Review Process

FDA's review process of a De Novo request remains largely unchanged, aside from a required user fee, the future addition of a RTA checklist review upon initial submission, and the establishment of an FDA performance goal for a review time of 150 days. More specifically, the review process consists of the following steps.

— FDA will verify that the same device for the same indications for use from the same sponsor is not under review in another submission (pre-submission, 510(k), PMA, etc.). If it is, FDA will not begin review of the De Novo request until the other submission is withdrawn by the submitter.

— Once implemented, FDA will perform a RTA checklist review within 15 days of submission to evaluate completeness of the request. FDA will begin to enforce the RTA review 60 days after the RTA guidance has been finalized. The RTA process is similar to the one currently used for 510(k) premarket notifications where missing a single item resets the FDA review clock. The review is meant to be administrative, not substantive, but each reviewer will have great discretion in this regard as has been seen with the 510(k) RTA checklist.

- FDA will assess whether the De Novo pathway is the appropriate pathway for the device.
    - In the Final Guidance, FDA clarified that if the same device type is being reviewed in a different De Novo request concurrently, when the first De Novo request is granted, FDA intends to notify the submitter of the follow-up De Novo request still under review that a predicate has been established and that the pending De Novo request still under review will be declined as a 510(k) is now required. The company would then be required to submit a 510(k) notice, which could incorporate all information supplied in the pending De Novo request by reference. From a practical matter, FDA has already been following this conversion protocol prior to the release of the Final Guidance.
- FDA will then begin a substantive review of the De Novo request to determine if the supplied data and information demonstrate that general controls or general and special controls are adequate to provide reasonable assurance of safety and effectiveness. If information is missing, FDA can request additional information, which stops FDA's review clock. The company has 180 days to provide the missing information, or withdraw the submission. This is the same as the current 510(k) process.
- Once granted, FDA will publish the a final order in the Federal Register providing public notice of the decision, which will result in codification of the device's identification, classification, and applicable requirements in Title 21 of the Code of Federal Regulations. FDA will also publically publish a summary of their review that will not include company confidential material, which will be available on FDA's website in the De Novo online database.
- Under the MDUFA IV, FDA has committed to completing review of De Novo requests in 150 FDA review days, with the percent of submissions required to meet this goal increasing from 50 to 70 percent over the next several years, as detailed in the table below. This is a change from the statutorily required review timeline of 120 days[3]. If a final decision has not been rendered within 180 total 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.

Action	Review Time (FDA days)	Performance Level (by Fiscal year)				
		FY2018	FY2019	FY2020	FY2021	FY2022
MDUFA Decision (grant/decline)	150	50%	55%	60%	65%	70%

Conclusion

The Final Guidance does not significantly change the content or review process that has been in place since 2012 for De Novo requests. Although the 150-day review time is nominally higher than the statutorily required 120-day review time, FDA has had widespread difficulty adhering to this 120-day review timeline previously. Given that De Novo requests are now MDUFA-tracked, requiring reports from FDA to Congress on review metrics, results may become more consistent with potentially shorter review times. The De Novo process continues to become a more appealing and reliable process for devices that are too novel for the 510(k) premarket notification pathway and it is likely that the annual number of De Novo requests granted will continue to increase.

[3] FDC Act § 513(f)(2)(A)(iii)

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