Hogan Lovells

FDA proposes new regulations to govern De Novo requests – will the process live up to its promise?

12 December 2018

Last week the Food and Drug Administration (FDA) issued a proposed set of new regulations to further define and update the De Novo review process.[1] Although De Novo review has been available for two decades, for the past 20 years, FDA has sought to implement and manage the De Novo review process by reference directly to the statutory language in the Federal Food, Drug, and Cosmetic Act (FDCA) and guidance documents. FDA's new proposed rule, *Medical Device De Novo Classification Process*, (the De Novo proposed rule or the proposed rule) is the first time the agency has issued regulations to clarify the procedural and substantive requirements surrounding the De Novo premarket review pathway. Many of the provisions of the proposed rule are consistent with existing guidance, but a few new recommendations worth noting are discussed below.

The release of the De Novo proposed rule follows a 26 November 2018 FDA announcement of new steps to modernize the 510(k) pathway. In that statement, FDA suggested that new and updated medical devices may present new risks excluding them from review through the 510(k) process and requiring De Novo review, which could lead to increased use of the De Novo pathway going forward. This is consistent with initial plans FDA has released related to the Software Precertification Pilot Program, suggesting that the agency anticipates many, if not most, software as a medical device (SaMD) products will utilize the De Novo review process. The De Novo proposed rule, if finalized, provides greater direction for companies as to the expected content and format for these submissions.

Background

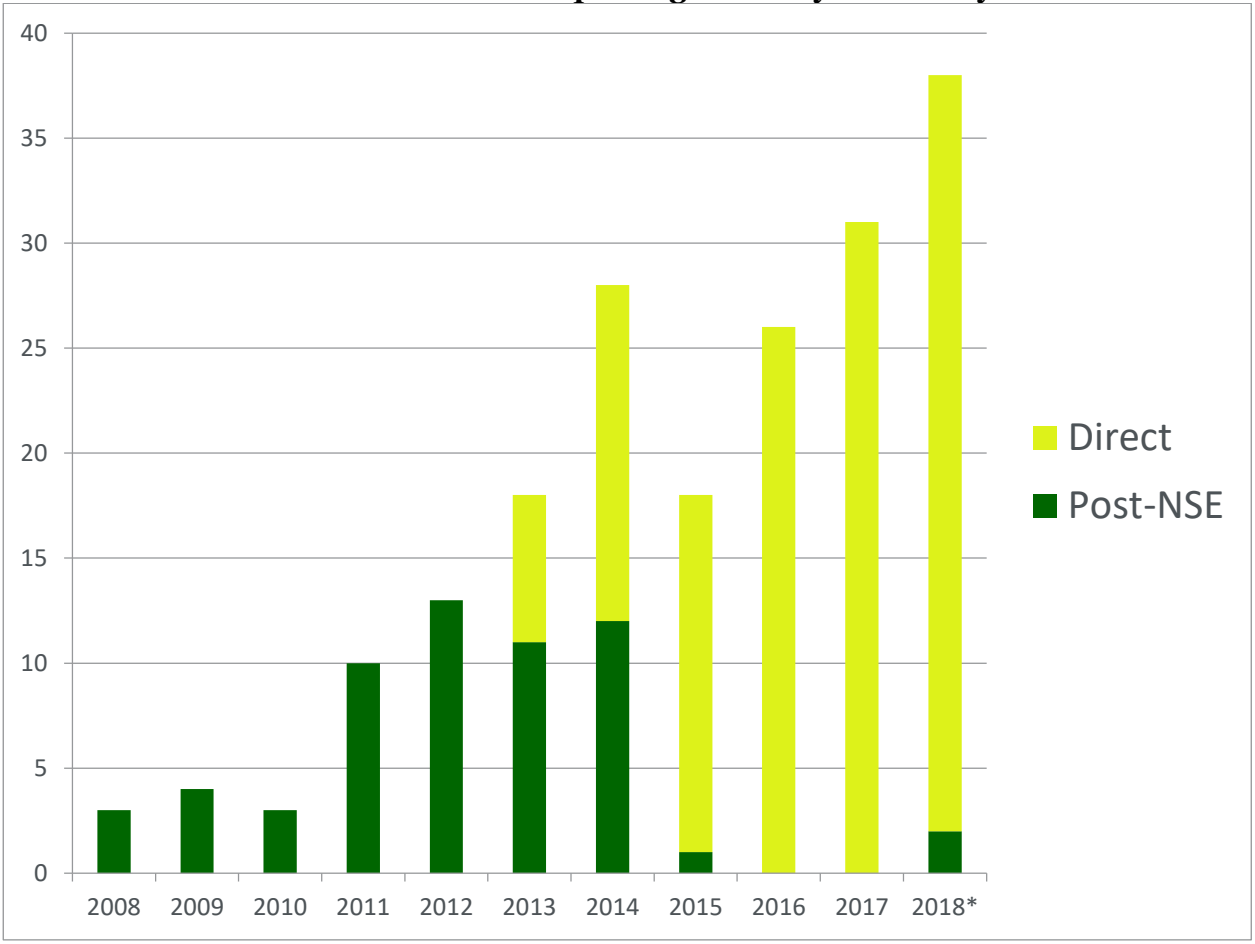
The De Novo pathway for obtaining premarket authorization was originally established in 1997 under the Food and Drug Administration Modernization Act. FDA's granting of a De Novo request allows marketing authorization for an individual device and creates a new classification regulation for the device type. Subsequent devices can then claim substantial equivalence to that device through the 510(k) pathway, subject to specified special controls.

Initially, the De Novo pathway could only be used within 30 days after a medical device had been deemed "not substantially equivalent" (NSE) through the 510(k) process. Subsequently, the FDA

[1] *Medical Device De Novo Classification Process* (7 Dec. 2018), 83 Fed Reg. 63127, available here.

Safety and Innovation Act of 2012 established an alternate direct De Novo pathway, which permits sponsors who believe no suitable predicate device exists to submit a De Novo request without first attempting the 510(k) process. In recent years, the vast majority of De Novo requests have followed this "direct De Novo" pathway. More recently, in 2016, the 21st Century Cures Act eliminated the requirement that a De Novo request be submitted within 30 days of receiving an NSE determination for those sponsors who first submitted a 510(k) notice. This change has little practical impact, however, as less than 3 percent of De Novo requests since 2015 have followed an NSE determination, with the remaining 97 percent following the direct De Novo pathway instead, as shown in the figure below.

Number of De Novo requests granted by calendar year



*Data through 11 December 2018

Proposed rule

The proposed rule would establish a new subpart to the medical device classification regulations (21 C.F.R. Part 860, Subpart D) outlining FDA's expectations for the content of De Novo requests and the criteria the agency intends to use in evaluating them. As drafted, the De Novo proposed rule describes many of the same elements outlined in FDA's final guidance, De Novo Classification Process (Evaluation of Automatic Class III Designation) (30 October 2017) (De Novo guidance), but it also provides additional specifics based on the agency's finding that certain De Novo requests still lack crucial data or information, rendering them incomplete and requiring additional reviews.

In issuing its proposal, FDA acknowledged that the statutory language in FDCA Section 513(f)(2) is vague with respect to what specific information should be included in a De Novo request. This

proposed rule aims to clarify the minimum content requirements and establish clear standards for FDA to follow in its review of such requests. A large part of the proposed rule covers the expected content of a De Novo request, which is largely consistent with the recommendations of the De Novo guidance; however, new requirements not called out in the guidance, such as a sample of the device (or directions about where to access a sample of the device) and information about alternative known practices/procedures for the same indications, which are similar to premarket approval (PMA) requirements for class III devices, are also included.

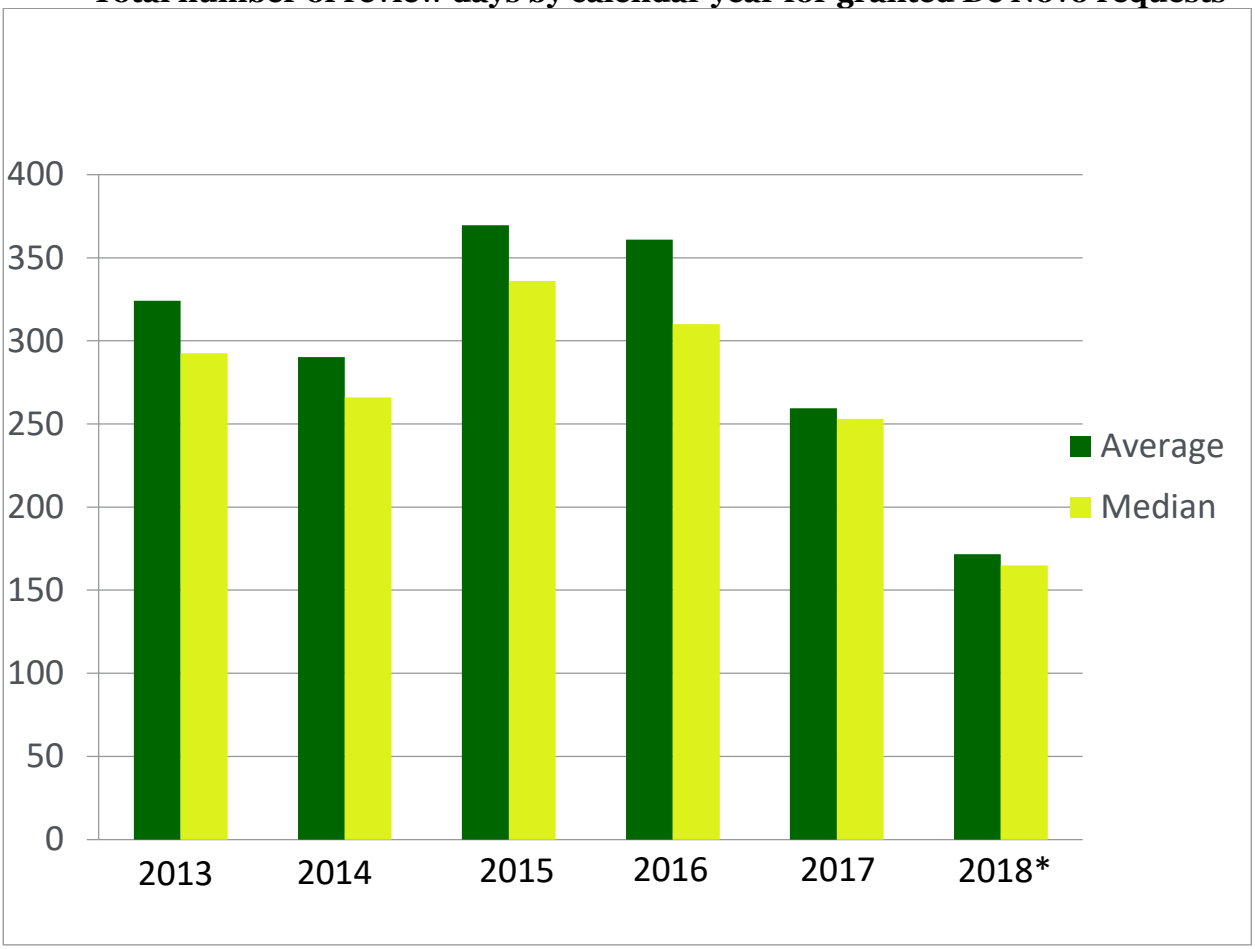
The agency also notes that other information necessary for FDA to determine what types of controls are needed to provide a reasonable assurance of the device's safety or effectiveness should be provided in the De Novo request. For example, medical device reporting (MDR) data—if the device is legally marketed in the United States for a different intended use—may be relevant to an evaluation of the device's safety. Omission of any of the required information must be supported by a justification.

The proposed rule would clarify FDA's procedures for acceptance review of De Novo requests, as well as when the agency's review clock begins for Medical Device User Fee Amendments (MDUFA) purposes. Of note, the criteria for making Refuse to Accept (RTA) decisions appear to be more extensive than those included in FDA's current RTA checklist for De Novo requests. For example, the proposed rule would require the requester to provide a "complete response" to all deficiencies identified by FDA in any prior submissions for the same device. Failure to do so, without including a rationale for the non-response, would result in an RTA decision. While addressing prior deficiencies is likely common practice for many applicants, the proposed rule would make this a requirement.

The De Novo proposed rule also

- includes procedures and criteria for the submission and withdrawal of a De Novo request;
- incorporates confidentiality provisions that appear to mirror those for other types of FDA marketing submissions (e.g., if submitter has previously publicly disclosed the material or fact of the application, these can be shared by FDA);
- proposes that FDA can inspect relevant facilities prior to granting or declining a De Novo request—while not precluded under current law, this has been done very rarely and could increase in frequency if the proposed rule is enacted;
- indicates FDA's intention to substantively review and grant/decline the request within 120 days in alignment with the statute. Although, notably, the current user fee agreement for FDA permits longer review times for a certain percentage of requests. Of interest, the median total review time for De Novo requests granted in 2017 was 253 days, as shown in the figure below; and
- provides that the De Novo will be granted if none of the specified grounds for denial are met (e.g., false statement of material fact, device already classified, etc.). In case of denial, an order declining the De Novo request will inform the sponsor of each applicable ground for the denial.

Total number of review days by calendar year for granted De Novo requests



*Incomplete data set

In addition, the new rule briefly touches on an FDA policy for using the De Novo process to create new exemptions from the 510(k) clearance requirement for class II devices. The proposed rule would require a De Novo applicant to follow a two-step process to seek clearance and exemption from future 510(k) notices for products of the same type. Going forward, applicants would need to obtain De Novo clearance and also follow the procedures for class II device exemptions under Section 510(m)(2) of the FDCA.

Perspectives on significance of the proposed rule

In a 4 December 2018 statement, FDA Commissioner Scott Gottlieb declared FDA's goal of making "the De Novo pathway significantly more efficient and transparent by clarifying the requirements for submission and our processes for review. As a result, we expect to see more developers take advantage of the De Novo pathway for novel devices." Since the De Novo program began, 237 medical devices have been granted marketing authorization through the pathway. In the early years of the program, typically less than five De Novo requests were cleared per year, whereas in recent years, more than 20 clearances per year have been granted. For 2018, we anticipate that more than 60 De Novo requests will be filed and others will remain under review from prior years. The De Novo proposed rule is designed to facilitate and accelerate the growing use of this process.

Based on our collective experience with dozens of De Novo requests since the inception of the pathway in 1997, our view is that the primary challenges to greater and more efficient use of this mechanism remain uncertainty regarding application of the benefit/risk standard to De Novo requests and uncertainty regarding review timing. While there is some evidence of improvement

in timeliness of review, there are still significant outliers in terms of time from submission to clearance. Although statistics on the rate of unsuccessful De Novo requests have not been published, review of sequential submission numbering suggests a higher proportion of De Novo requests are ultimately unsuccessful compared to other premarket review mechanisms. This may relate to varying interpretation of both the eligibility of products for the De Novo process and application of the risk/benefit standard. The amount of clinical data required to support De Novo clearance, for example, has varied widely by application. Finally, given the relatively infrequent use of De Novo requests by each branch within FDA (for example, only one orthopedic De Novo request has been granted in the past 21 years), a uniform standard of acceptable risk/benefit information to support De Novo clearance has yet to emerge.

To truly leverage the potential of this regulatory mechanism, further development of regulatory policy to facilitate consistent decision-making and improved certainty of review timing will be needed, with further input from stakeholders. Comments on the De Novo proposed rule may be submitted to FDA through Docket No. FDA-2019-N-0236 through 7 March 2019.

Contacts

Janice M. Hogan
Partner, Philadelphia
T +1 267 675 4611
janice.hogan@hoganlovells.com

Randy J. Prebula
Partner, Washington, D.C.
T +1 202 637 6548
randy.prebula@hoganlovells.com

Yarmela Pavlovic
Partner, San Francisco
T +1 415 374 2336
yarmela.pavlovic@hoganlovells.com

Lina R. Kontos
Counsel, Washington, D.C.
T +1 202 637 5713
lina.kontos@hoganlovells.com

Danielle C. Humphrey
Counsel, Washington, D.C.
T +1 202 637 8853
danielle.humphrey@hoganlovells.com

Kristin Zielinski Duggan
Counsel, Washington, D.C.
T +1 202 637 8894
kristin.duggan@hoganlovells.com

Suzanne Levy Friedman
Associate, Washington, D.C.
T +1 202 637 5532
suzanne.friedman@hoganlovells.com

Wil Henderson
Associate, Denver
T +1 303 899 7354
wil.henderson@hoganlovells.com

www.hoganlovells.com