FDA Test Drives Its Draft Refuse to Accept Policy for 510(k) Notices

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Introduction

Following the August 2012 publication of its draft refuse to accept ("RTA") policy for 510(k) premarket notifications ("510(k) notice"), {NOTE: insert footnote 1} and just after the closing of the comment period in October, the Food and Drug Administration ("FDA" or "the agency") began "informally" implementing the draft policy. Since November, the agency has refused to accept 510(k) submissions for a variety of reasons based on the draft RTA checklists contained in the draft guidance. This "informal" implementation of the draft guidance has highlighted the need for additional clarity surrounding checklist items, as well as greater uniformity in reviewer interpretation and application of the checklists between the various branches and divisions within the Center for Devices

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and Radiological Health ("CDRH"). While test driving the draft policy may allow FDA to work out the kinks before going live, the review clock for many 510(k) submissions filed after November has been affected.

The purpose of the agency's updated RTA policy with regard to 510(k) notices is to "assess whether a 510(k) notice meets a minimum threshold of acceptability and should be accepted by FDA for substantive review." The draft guidance states that FDA's review resources should be focused on complete submissions as this will provide a more efficient approach to ensuring that safe and effective medical devices reach patients as quickly as possible. More telling, perhaps, is the reference to the enactment of the Medical Device User Fee Amendments of 2012 ("MDUFA III") wherein FDA agreed to performance goals based on the timeliness of submission reviews. This is an important reference as the draft guidance explains that the agency's review clock for purposes of MDUFA goals will not begin until FDA determines that the submission is administratively complete and accepted by FDA for substantive review.

Proposed Policy and Procedures

In summary, FDA has modified the agency's RTA policy to include an early review against specific acceptance criteria and to inform the submitter within 15 calendar days after receipt of a 510(k) notice submission if the submission is administratively complete, and if not, to identify missing required elements of the submission.[1]

In order to provide some consistency in the agency's review of 510(k) notices for purposes of being administratively complete, the draft guidance includes detailed checklists for traditional, special and abbreviated 510(k) notices. The provided checklists are based largely on the regulatory requirements for 510(k) notices as outlined in 21 C.F.R. § 807.87 to § 807.100. The draft guidance instructs submitters to provide a rationale/justification for not including a particular item typically required in 510(k) notices. For example, if a submitter does not believe that biocompatibility testing is required for a device that is the subject of a 510(k) notice, the submitter will need to include an explanation as to why such testing is not necessary, in order to prevent FDA from refusing to accept the submission. If one or more items noted as RTA items on the agency's applicable checklist are not present in a submission, FDA staff conducting the acceptance review is instructed to obtain management concurrence and notify the designated contact person in writing that the submission has not been accepted. FDA intends to provide an explanation to describe the missing elements of a submission when notifying the submitter of a RTA decision.

Once notified of a RTA decision, the submitter may respond by providing the missing information. The guidance states that submitters should submit the missing information under the originally assigned 510(k) number. There is no need to re-file the entire submission or pay a new user fee. Following receipt of the missing information, FDA has another 15 days to perform an acceptance review. The guidance also states that if FDA fails to complete the acceptance review within 15 days, the submission should be considered accepted. However, it is important to note that "FDA may ask for any information during the substantive review that may have been unintentionally overlooked during the acceptance review."

RTA Principles

The draft guidance document outlines certain principles that reviewers and submitters should follow in making a determination as to whether a 510(k) notice is complete. Specifically, the guidance document lists the following basic principles that should be considered in making a RTA decision: (1) acceptance should not be based on a substantive review of the information provided in the 510(k) notice; (2) FDA staff should consider the submitter's justifications for any alternative approaches and/or rationales provided by the submitter as to why certain information is not included in a submission; and (3) the submitter should review device-specific and cross-cutting guidance documents, applicable recognized standards, and applicable regulations.

The Checklist: Preliminary Questions

In addition to the basic principles outlined above, the draft guidance document discusses the five initial questions listed on each of the acceptance checklists for traditional, special and abbreviated 510(k) notices. The five initial questions on each checklist are as follows:

1. Is the product a device (per section 201(h) of the FDC Act) or a combination product (per 21 C.F.R.§ 3.2(e)) with a device constituent part?
2. Is the application with the appropriate Center?
3. Is a 510(k) the appropriate regulatory submission?
4. Is there a pending PMA for the same device with the same indications for use?

5. If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy?

While the majority of these questions seem simple enough to answer based on a preliminary, non-substantive review of a 510(k) notice, the question as to whether a 510(k) notice is the appropriate regulatory submission may well involve an agency reviewer to substantively review a submission to appropriately answer this question.

Special 510(k) Notices

In addition to the general review principles discussed above for preliminarily reviewing 510(k) notices administratively to determine acceptability for substantive review by the agency, FDA specifically included within the draft guidance a new standard for Special 510(k) notices. FDA states at the end of the guidance document that "if a 510(k) designated as a Special 510(k) qualifies as a Special 510(k) but the submission includes performance data, FDA should offer the submitter two options: (1) the data can be removed from the 510(k) and staff will proceed with the Special 510(k) checklist, or (2) the 510(k) can be converted to a traditional 510(k) and the submitter will provide any other missing information needed for a traditional 510(k) in order to be accepted for substantive review.

Noteworthy Elements of the Draft Guidance

There are various elements included in the proposed RTA policy draft guidance proposed by the agency that industry should take note of for future submissions.

First, the draft guidance document does not appear to limit the number of 15-day acceptance reviews that can be performed by FDA. While the document clearly discusses at least two rounds of acceptance reviews, it is unclear if there will be a limit to these reviews. If there is no limit to such reviews, it could result in numerous rounds of acceptance reviews prior to the agency accepting a submission for substantive review wherein the agency review clock starts to run. The option for multiple acceptance reviews essentially allows FDA to have a head start in reviewing the document prior to FDA's 90-day review clock starting for traditional and abbreviated 510(k) notices or the agency's 30-day review clock starting for Special 510(k) notices. Accordingly, one would hope that FDA would not invoke this policy simply as a method for improving agency review times, but would instead only refuse to file a submission that is truly deficient.

Next, as indicated above, while the majority of preliminary questions included on each of the draft checklists seem simple enough to answer based on a preliminary, non-substantive review of a 510(k) notice, the question as to whether a 510(k) notice is the appropriate regulatory submission may well involve an agency reviewer to substantively review a submission, particularly the substantial equivalence analysis, to appropriately answer this question. The inclusion of this question clearly blurs the lines between an administrative versus substantive review of a 510(k) prior to FDA's acceptance of the submission. AdvaMed recently commented on this draft guidance and stated that "[i]t is critical that FDA limit its acceptance review to prescreening of 510(k) submissions, that is, determining whether an element is present and not whether it is substantively acceptable."[2] AdvaMed points to specific questions included in the draft checklists regarding labeling requirements and shelf life information as blurring the lines between an appropriate acceptance review and a substantive review of a 510(k) submission. AdvaMed states that "[t]he acceptance review should determine that the required elements of a 510(k) are present, that they are legible and provided in English. It should verify that the submission is organized in a manner that allows efficient substantive review."

Lastly, the draft guidance document has clearly added a new standard to the review of Special 510(k) notices not previously followed by FDA by stating that a Special 510(k) that includes performance data either needs to be converted to a traditional 510(k) notice or have the performance data removed to be reviewed as a Special 510(k) notice. The agency has previously indicated in a recent draft guidance document that Special 510(k) notices requiring either animal or clinical data to support a substantial equivalence determination are not appropriate for the Special 510(k) pathway[3]; however, the agency has not previously indicated that no performance data is appropriate for inclusion in a Special 510(k).

Experiences to Date Based on "Informal" Implementation of the Draft Guidance

While the subject draft guidance is intended to be made final in January 2013,(insert footnote 5) FDA began implementing the draft guidance in November 2012 on an informal basis. In sum, the agency is currently using the draft checklists provided in the RTA guidance document for 510(k) notices to determine whether the 510(k) notice is administratively

complete. If an agency reviewer determines that items on the checklist are missing from a submission, the reviewer is e-mailing the checklist with the missing items to the company, with a request that the missing items be provided to FDA by a specified date, after which the submission will be placed on hold. Accordingly, while FDA claims that the checklists are being review is affecting the review clock for submissions now, before the draft guidance document has been made final.

To date, we have seen FDA identify the following items as reasons for refusing to accepting a 510(k) submission for substantive review: (1) inclusion of limited performance data in a Special 510(k) notice (insert footnote 6) ; (2) minor administrative omissions such as a failure to explicitly state in the cover letter that the device has not been the subject of prior filings with the agency, lack of bates numbering, etc. In addition, it has become clear that not every FDA reviewer is interpreting or implementing the draft RTA checklists in the same manner. Specifically, some FDA reviewers are clearly blurring the lines between an administrative versus substantive review of recently submitted 510(k) notices. For example, reviewers have recently requested "more details" in certain sections of recent submissions that give rise to substantive questions of device testing, etc., as well as requests for clinical data to support a filing. In sum, the draft RTA policy for 510(k) notices was put into practice shortly after the notice and comment period for the draft guidance document closed, without much warning to industry. In light of current practices, if you intend to file a 510(k) in the near term, it would be wise to closely review your submission against the draft RTA checklists before filing, and plan on some amount of delay in the starting of your review clock based on the RTA policy.

1. When final, the guidance document will supersede the following agency guidance documents, which are outdated and have rarely been adhered to by FDA: (1) Center for Devices and Radiological Health's premarket Notification (510(k)) Refuse to Accept Policy (June 30, 1993), and (2) 510(k) Refuse to Accept Procedures (K94-1) Blue Book Memo (May 20, 2994).
2. It is important to note that the draft guidance that is the subject of this update is applicable only to original 510(k) notices and responses to RTA letters. It is not applicable to supplements or amendments submitted in response to agency requests for additional information after a submission has been accepted.
3. Advanced Medical Technology Association. Comments Re: Docket No. FDA-2012-D-0523; Draft Guidance for Industry and Food and Drug Administration Staff: Refuse to Accept Policy for 510(k)s (September 27, 2012).
4. See Draft Guidance for Industry and Food and Drug Administration Staff: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (December 27, 2011).
5. See FDA'S website for a list of priority guidance documents to be finalized in 2013 at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAIII/ucm321367.htm. Also, in a November 27, 2012, FOI Services Teleconference entitled FDA Device Program Staff Explain the Revised Refuse to Accept/File Guidance Documents, FDA explained that the subject draft guidance would be made final in January 2013.
6. Note: FDA has communicated informally that a Special 510(k) notice with more than a summary paragraph or two of performance data will not be accepted for review. As outlined in the draft guidance document, the sponsor will have the option of removing the performance data from the submission or converting the file to a traditional 510(k) notice. With respect to this policy and software performance documentation, based on recent communications with 510(k) staff, FDA has informally instructed companies that the agency's software guidance documents will trump the RTA guidance. Thus, the submission of the necessary documentation to support a software modification in a Special 510(k), which may include performance testing, should theoretically not result in a refuse to accept determination.