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Medical Device Update: FDA Releases Final Pre-Submission Guidance

Background

As we noted in our recent Medical Device Update,[1] on February 18, the U.S. Food and Drug Administration (FDA or the Agency) issued a final guidance titled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (Guidance).[2] This Guidance contains substantive changes from the pre-submission (Pre-Sub) draft guidance released by the Agency on July 13, 2012, and it replaces and supersedes FDA's 1999 guidance "Pre-IDE Program and Meetings with Food and Administration Staff: Issues and Answers." The new guidance includes requirements on the type, timing, format, and content of requests for feedback meetings and telephone conferences with FDA. Therefore, it will be important for the medical device industry to be aware of these requirements in planning their device development activities and timelines.

Q-Sub Organizational Structure

One significant difference between the draft and final guidance documents is that the Agency introduced the concept of the "Q-Submission" (Q-Sub) organizational structure in the final guidance. Q-Subs encompass various types of requests for feedback, including Pre-Submissions, Informational Meetings, Study Risk Determinations, Formal Early Collaboration Meetings (i.e., Agreement and Determination Meetings), Submission Issue Meetings, and Premarket Approval (PMA) Day 100 Meetings. The Agency will refer to these requests for feedback collectively as "Q-Subs," and the goal for the Q-Sub program is to provide a convenient and effective way to track such requests.

When to Submit a Q-Sub

Q-Subs can be invaluable for early feedback on specific questions during submission preparation, such as in the following circumstances:

- Before conducting clinical, nonclinical, or analytical studies or submitting an investigational device exemption (IDE) or marketing application when:
  - The new device involves novel technology, and it may be helpful to familiarize the FDA review team with the technology in advance of the submission.
  - A company is proposing a "first of a kind" indication or a new indication for an existing device.
  - The new device does not clearly fall within an established regulatory pathway, and the company desires informal input on a proposed regulatory strategy.
  - The new device is a multiplex device capable of simultaneously testing a large number of analytes.
  - The new device is an in vitro diagnostic (IVD) device that contains a new technology, a new intended use, a new analyte, new clinical questions, complex data/statistical questions, and/or where the predicate of or the reference method is unclear or uncertain.
  - FDA guidance is desired on specific issues related to nonclinical study protocols and/or animal study protocols before initiating a study.
  - FDA input is desired on specific issues related to a planned clinical study, especially if it involves complex or novel statistical approaches.
  - FDA input is desired on the extent that existing data may be leveraged in preparing a PMA submission for a device in accordance with section 520(h)(4) of the Federal Food, Drug, and Cosmetic Act.

1. View our March 2014 Medical Device Update at http://www.morganlewis.com/pubs/MedicalDeviceUpdate-4Mar2014.
2. View the Guidance at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

  - FDA input is desired on a clinical protocol before conducting a clinical study that does not require FDA review of an IDE, such as for a nonsignificant risk device or a study that will be conducted entirely outside the United States (OUS).
- Before submitting a marketing application in order to:
  - Apprise the FDA review team on the particulars of the device and the clinical study (if there have been changes since the initiation of the IDE).
  - Obtain FDA feedback on the use of data collected from an OUS study to support clearance or approval.
  - Obtain FDA feedback on its preferred data presentation and to ensure clarity with respect to expectations regarding the elements to be included in the marketing application.
  - Gain insight into potential hurdles for approval or clearance (e.g., numerous protocol deviations, missing data, or a failed study endpoint), some of which could require additional data or analyses.

However, Q-Subs are **not** appropriate for any of the following:

- General questions on FDA policy or procedure
- Questions that can be readily answered by an FDA reviewer based on his or her experience and knowledge and that do not require the involvement of a broader number of FDA staff
- Requests for clarification on technical guidance documents

Manufacturers may request more than one Q-Sub meeting/teleconference for a device submission. However, the Agency will not grant more than one meeting/teleconference covering the same or similar issues. Thus, it would be appropriate to request a meeting on preclinical studies and, subsequently, a meeting on a clinical study, but it would not be appropriate to request multiple meetings on the iterative versions of the same clinical study.

Q-Subs for Combination Products

FDA's guidance acknowledges that manufacturers often seek input on issues relating to the device component of a combination product, for example, on devices such as pumps that deliver a drug. Combination product manufacturers should be aware that the new guidance recommends that the Center for Devices and Radiological Health (CDRH) staff notify the lead center for the combination product whenever it receives a Q-Sub and that review staff from the other center(s) be involved to ensure that the entire review team is aware of the questions raised and the responses provided.

Reliability of Agency Feedback

FDA intends that its feedback in response to a Q-Sub will not change, provided that the information submitted in support of the Q-Sub remains accurate. The Agency intends to limit modifications to its feedback to those situations where the initial feedback does not address important new issues relevant to a determination of safety or effectiveness that emerge after the Q-Sub is submitted. However, FDA recommends that sponsors contact the review branch to confirm the feedback guidance if more than one year has passed since the last feedback on key clinical trial design elements. An additional Q-Sub is not required to obtain such confirmation; the confirmation may be obtained through a phone call with the review branch.

Timeframes for Requested Feedback

FDA has established new procedures and timelines for Q-Subs that could significantly impact a device company's timelines for bringing a device to market. For example, many device stakeholders have found that it is increasingly important to obtain FDA feedback prior to conducting a clinical study on a novel device or a novel modification to an existing device. Because the costs of designing and conducting a clinical study have increased substantially in recent years, companies often seek to avoid the risk of undertaking a study that FDA might later determine is not adequate to support the proposed intended use or marketing claims. Now, for those companies that wish to avoid such risk by obtaining FDA feedback prior to conducting a clinical study, it will be necessary to build into the development plan adequate time to request and obtain such feedback.

In the Guidance, the Agency specifically addresses the timeframes within which FDA intends to provide the requested feedback. **Significantly, however, the timeframes provided in the Guidance do not begin until the**

Q-Sub is deemed "accepted." In a process similar to that adopted for 510(k) and PMA submissions, during the first 14 days after a request is submitted to FDA, Agency staff will review the submission to determine whether it (1) includes a valid eCopy, (2) meets the definition of the identified Q-Sub type, and (3) is administratively complete. If the submission is not complete, FDA will inform the applicant that it is not accepted and will identify the reasons for not accepting it. The following chart, provided by the Agency in the Guidance, sets forth the timeframes for meetings/teleconferences for each Q-Sub type and indicates whether a meeting is available as an avenue of receiving feedback from FDA.

Q-Sub Type	Meeting as Method of Feedback?	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission*	Upon request	75–90 days**
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within timeframe agreed to with sponsor
Determination Meeting	Yes	Date for meeting agreed upon within 30 days of request
Submission Issue Meeting	Yes	21 days
PMA Day 100 Meeting	Yes	100 days (from PMA filing date)
*As defined in MDUFA III Commitment Letter **21 days for urgent public health issues		

We recommend that companies use the Acceptance Checklist in Appendix 2 of the Guidance prior to submission to ensure all of the required criteria are explicitly addressed.

Contacts

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