FDA Pre-Submission or Q-Sub Program

Erika Huffman, MSBME, RAC, Principal Medical Research Manager, NAMSA
Prior to submitting an investigational device exemption (IDE) application or other premarket submission, the US Food and Drug Administration (FDA) recommends using the Pre-Submission (Pre-Sub) program to obtain feedback on the submission. This process can be useful for novel devices and device sponsors who are new to premarket submissions.

The pre-IDE program was first established in 1995 to provide feedback on IDE submissions and has become the most commonly used method of obtaining FDA feedback prior to a premarket device submission. This process eventually grew and now includes other premarket submissions such as:

- Premarket Approval (PMA) applications
- Humanitarian Device Exemption (HDE) applications
- Evaluation of Automatic Class III Designations (de novo petitions)
- Premarket Notification (510(k)) Submissions
- Investigational New Drug Applications (INDs)
- Biologics License Applications (BLAs)

These requests for feedback, which may be provided by formal written response, in-person meeting, or teleconference, are now collectively referred to as “Q-Submissions” or “Q-Subs.” FDA published a guidance document on the Pre-Sub (Q-Sub) program in February 2014 (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf). The guidance clarifies the process for requesting and obtaining FDA feedback by defining the objectives of the process, types of requests, and timelines. Medical device sponsors can use the Q-Sub program to seek advice for clinical testing and device development, to request a determination of IDE study risk, or to request Informational Meetings to educate the FDA about their device development or planned submissions, among other things.

**Q-Submissions**

Descriptions of the various types of Q-Subs and when to use them, along with associated FDA response times, are summarized in Table 1 and are discussed in more detail following the table.
<table>
<thead>
<tr>
<th>Q-SUB TYPE</th>
<th>DESCRIPTION</th>
<th>WHEN TO REQUEST</th>
<th>TIME FRAME FOR MEETING</th>
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</thead>
<tbody>
<tr>
<td>PRE-SUBMISSION</td>
<td>Feedback in the form of a written response or a meeting or teleconference</td>
<td>Useful for early feedback on specific questions during submission preparation or prior to initiating long-term preclinical studies</td>
<td>75-90 days (21 days for urgent public health issues)</td>
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<tr>
<td>INFORMATIONAL MEETING</td>
<td>Meeting to inform or educate FDA about ongoing device development or planned submissions without a specific request for feedback</td>
<td>When multiple submissions are planned within the next 6-12 months or to familiarize FDA review team with new device and differences from currently available devices</td>
<td>90 days (as resources allow)</td>
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<tr>
<td>STUDY RISK DETERMINATION</td>
<td>FDA determination of risk classification for planned clinical trials (significant risk or nonsignificant risk)</td>
<td>When sponsor is unsure of how to classify risk of device studies</td>
<td>Not applicable</td>
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<tr>
<td>AGREEMENT MEETING</td>
<td>Meeting to reach an agreement on investigational plan, including a clinical protocol</td>
<td>When planning to investigate safety or effectiveness</td>
<td>Within 30 days or within timeframe agreed to with sponsor</td>
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<tr>
<td>DETERMINATION MEETING</td>
<td>Meeting to discuss clinical trial design</td>
<td>When anticipating PMA submission and to provide FDA’s determination of type of evidence necessary to demonstrate device effectiveness for intended use</td>
<td>Meeting date agreed upon within 30 days of request</td>
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<tr>
<td>SUBMISSION ISSUE MEETING</td>
<td>Meeting to discuss deficiencies identified during premarket review</td>
<td>When sponsor requires significant clarification of deficiencies and/or to discuss sponsor’s approach to responding, or when sponsor requests feedback that requires in-depth preparation by FDA review team</td>
<td>21 days</td>
</tr>
<tr>
<td>PMA DAY 100 MEETING</td>
<td>Meeting to discuss the review status of PMA application</td>
<td>With the original PMA or within 70 days after the PMA filing date</td>
<td>Within 100 days (from PMA filing date)</td>
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IDE = Investigational Device Exemption.
**Pre-Submission**

A Pre-Submission is a formal written request from an applicant or sponsor for feedback from the FDA. The main purpose of the Pre-Sub program remains the same as the previously established pre-IDE program: to provide the opportunity for a sponsor to obtain FDA feedback prior to an intended submission of an IDE or marketing application. This type of Q-Sub is appropriate when FDA feedback is required for specific questions to guide product development and/or application preparation. This is an entirely voluntary process and is not required prior to submission of an IDE or any premarket application, but it is encouraged when specific questions arise that are not addressed by an existing guidance.

In the FDA Pre-Sub guidance, FDA outlines the format and content of a Pre-Sub package and provides examples of scenarios when early feedback may be useful, such as:

- The new device involves novel technology;
- Proposing a “first of a kind” indication or a new indication for an existing device;
- The new device does not fall in an established regulatory pathway;
- The sponsor desires guidance on specific issues related to nonclinical and/or preclinical study protocols, before initiating the studies;
- The sponsor desires guidance on specific issues related to clinical study protocols, using existing data, or using data from studies conducted outside the US (especially if they involve novel or complex statistical approaches);
- Changes have been made to the device or clinical study since the initiation of the IDE or IND; or
- The sponsor desires feedback on preferred data presentation, to ensure clarity of FDA expectations, and to gain insight into potential hurdles for approval or clearance.

**Informational Meeting**

Informational Meetings are intended to share information with FDA without the expectation of feedback. These are appropriate to apprise FDA of multiple submissions planned in the next 6-12 months, or to familiarize the FDA review team with a new device that has significantly different technology from currently available devices. FDA will accept the request as resources allow. If appropriate, the review team may ask questions or offer suggestions, although feedback should not be expected. Recommended information to include in the request is outlined in the guidance.

**Study Risk Determination**

There are three types of device studies: significant risk (SR), non-significant risk (NSR), and exempt studies per the IDE regulations (21 CFR Part 812). Studies that are not exempt require the sponsor to make the initial risk determination, SR or NSR. Study Risk Determinations are requests for FDA to assist a sponsor, clinical investigator, or Institutional Review Board (IRB) with classifying the study risk. FDA is the final arbiter as to the risk determination and makes the determination when an IDE is submitted to FDA if not consulted prior via a Study Risk Determination request.
Formal Early Collaboration Meetings
Two early collaboration meetings are provided by FDA: Agreement Meetings and Determination Meetings. Agreement Meetings are open to anyone planning to investigate the safety or effectiveness of a Class III medical device or any implant (including 510(k)-eligible devices) and are meant to reach agreement on key parameters of the investigational plan, including the clinical protocol. Determination Meetings are available to anyone planning a PMA submission or product development protocol (PDP) and are meant to provide the applicant with FDA's determination of the type of evidence required to demonstrate device effectiveness for the intended use. Determinations or agreements as a result of these meetings are binding, barring any significant changes.

Submission Issue Meeting
Submission Issue Meetings are used to discuss deficiencies identified by FDA during premarket review of a submission and are intended to provide clarification of FDA's questions and/or to discuss an approach to responding to complex issues. This type of meeting should be used when the sponsor desires an in-person meeting or teleconference to discuss their planned approach to responding to deficiencies, or when requests for feedback require in-depth preparation by the FDA review team and FDA management input. These meetings are generally not needed for brief clarification questions or when participation of FDA management is not necessary, and are not appropriate for pre-review of planned deficiency responses.

Day 100 Meeting for PMA Applications
Day 100 Meetings are a subset of Submission Issue meetings and are used to discuss the review status of a PMA application. FDA will meet with an applicant no later than 100 days after receipt of a PMA and will inform the applicant in writing of any identified deficiencies 10 days in advance of the meeting.

- General discussion of identified issues and remediation
- Discussion of an action plan with estimated dates of completion
- Discussion of FDA estimated timetables for review
- Identification of the need for panel involvement
- Discussion of possible premarket versus postmarket requirements

Additional information regarding the Day 100 meeting process can be found in “Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies” issued in February 1998 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080191.pdf).
Requests are automatically accepted by FDA if the Q-Sub is for an Agreement Meeting, Determination Meeting, PMA Day 100 Meeting, or Study Risk Meeting. For all other Q-Sub types, the timeline until acceptance will vary. Figure 1 depicts a general timeline for the process.

Figure 1. Timeline for Q-Sub Meeting Request

For all Q-Sub meetings, the sponsor must submit draft minutes within 15 days of the meeting that provide a summary of the discussion. This should not be a transcript of the meeting, include responses to FDA feedback, or include requests for additional feedback. If follow-up requests are needed, they should be submitted as a Q-Sub Supplement. The FDA review team will review and edit the minutes as needed within 30 days. The sponsor will have the opportunity to submit a “minutes disagreement amendment” or, if there is no disagreement, the FDA-edited version will become final.

RTA= refuse to accept.
Best Practices for Pre-Sub Meetings
To ensure that the Pre-Sub meetings go as smoothly as possible, it is best to follow the suggested steps provided in the FDA guidance document. You should provide several possible dates for the meeting and remain flexible. Your requests should be specific and it helps to provide focused questions and an agenda in advance. You should also bring the appropriate experts required to address your objectives and a dedicated attendee to take notes. Do not introduce new questions or topics immediately prior to or during the meeting. Also, allow at least two-thirds of the allotted meeting time for discussion.

RESOURCES

“Everything we do must be in our clients’ best interests.”
Ted Gorski, NAMSA Founder

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