FDA Guidance Hot Topics: Pre-Submission Guidance Review
AMDM Focus Meeting
October 25, 2013

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OIR/CDRH/FDA
Updates to Guidance: Draft → Final

- Broaden scope to address all types of requests for FDA feedback that are tracked as Q-Submissions
- Explanation of Q-Sub tracking/logistics
- Additional clarification re when a Submission Issue Q-Sub is and is not appropriate
- Minor policy clarifications re meeting logistics
- Appendix with RTA checklist
# Q-Submission Types

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**21 days for urgent public health issues
Q-Submission Logistics

• Submit to DCC
  U.S. Food and Drug Administration
  Center for Devices and
  Radiological Health
  Document Control Center –
  WO66-G609
  10903 New Hampshire Avenue
  Silver Spring, MD  20993-0002

• eCopy and single hard copy required

• Cover Letter with:
  – Identification of Q-Sub type (ie, Pre-Sub, Submission Issue, etc)
  – Sponsor contact information
  – Device name
  – Information specific to the Q-Sub type, if applicable
Q-Submission Logistics

**Amendments** contain additional information about an existing request for feedback, for ex:
- Slides
- Agenda updates
- Meeting minutes
- Meeting minutes disagreements

**Supplements** contain NEW requests for feedback on the same device/indication, for ex:
- Original request for feedback on analytical plan
- S001 request for feedback on clinical plan

**New Q-Sub numbers** are assigned for subsequent requests for feedback if:
- The device and/or indications for use have changed significantly
- The type of Q-Submission has changed (i.e., informational, pre-submission, submission issue, etc)
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Definition of a Pre-Submission*

- A formal written request from an applicant for feedback from FDA provided in the form of:
  - a formal written response or
  - a meeting or teleconference in which the feedback is documented in meeting minutes
- When FDA’s feedback on specific questions is necessary to guide product development and/or application preparation (i.e., prior to intended submission of an IDE or marketing application)
- Request must include specific questions regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements).

*From the MDUFA III Commitment Letter
A Pre-Sub is:

- Intended to be specific to the questions posed
  - however, if other deficiencies or concerns are noted during review, they may be included in FDA’s feedback.
- Generally meant to be a one-time process per topic (i.e., not iterative)
  - but can be utilized at different times and/or for multiple topics for the same device (e.g., prior to IDE submission for bench testing and clinical protocols, then prior to PMA submission regarding data presentation).
  - If significant changes are made to sponsor’s proposal in response to initial FDA feedback, may be appropriate to engage in repeat interaction on the same topic.
A Pre-Sub is NOT:

- A mechanism for FDA to design nonclinical test or clinical study protocols for the sponsor
- Phone calls or emails regarding questions that can readily be answered by the reviewer (+/- routine involvement of the supervisor or mentor)
- Interactive review of an active submission
- An RFD, 513(g), or appeal
- A determination or agreement meeting
- A meeting that is informational only (i.e., no FDA feedback requested) or to discuss a request for additional information as part of submission review
When to submit a Pre-Sub?

General Considerations

- Voluntary, but encouraged
- Prior to initiating long term preclinical studies
- When planning a study that does not require an IDE
  - Studies that are outside the US, exempt, or NSR
- Before submission of an IDE to:
  - Discuss nonclinical data and clinical study design
- Before submission of a marketing application to:
  - Apprise FDA review team on specifics of device and clinical study if there have been changes since initiation of the IDE
  - Obtain feedback on preferred data presentation
  - Gain insight into potential hurdles for approval or clearance
- When preparing a submission for a new device that does not clearly fall within an established regulatory pathway
When to submit a Pre-Sub?
IVD-Specific Considerations

- Before conducting clinical, nonclinical, or analytical studies or submitting a marketing application for a new IVD that:
  - Is a multiplex device capable of simultaneously testing a large number of analytes
  - Contains a new technology
  - Has a new intended use
  - Includes a new analyte
  - Presents new clinical questions
  - Presents complex data/statistical questions
  - Uses a predicate or reference method that is unclear or uncertain
Overview of the Pre-Sub Process

1. Sponsor submits to DCC
2. FDA conducts acceptance review (14 days)
3. If Meeting/tcon requested:
   a. FDA works with sponsor to schedule the meeting/tcon (21 days)
   b. FDA provides preliminary feedback via email (at least 3 days prior to the meeting/tcon)
4. FDA provides feedback (75 -90 days)
5. If Meeting/tcon held:
   a. Sponsor provides draft minutes to DCC (15 days)
   b. FDA reviews/edits minutes (30 days)
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Informational Meetings

- Purpose: to share information with FDA
- May be appropriate to:
  - Provide an overview of ongoing device development when there are multiple submissions planned within the next 6-12 months, or
  - Familiarize the review team about new device(s) with significant differences in technology from currently available devices.
- NO expectation of feedback, although review team may ask questions or offer suggestions if appropriate
- Granted as resources allow
- If granted, should be scheduled within 90 days
- Meeting package should contain sufficient background information to allow FDA to identify appropriate attendees
- Follow meeting minutes procedure for Pre-Subs (although minutes may be much briefer)
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Study Risk Determinations

- FDA is available to help sponsors of clinical investigations and/or IRBs in making a risk determination (significant vs. nonsignificant risk)
- Policy unchanged; reference existing Information Sheet Guidance
- Administrative procedures new as of Oct 2012
  - Sponsor submits Q-Sub with written request
  - FDA will respond with a formal letter
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Formal Early Collaboration Meetings

• FDAMA provides for two types of early collaboration meetings:
  – Determination Meetings
  – Agreement Meetings

• Policy unchanged; reference existing Guidance
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

• Administrative procedures new as of Oct 2012
  – Sponsor submits Q-Sub with written request
  – FDA/sponsor agree to a meeting date w/in ~30 days
  – Minutes tracked as amendment to Q-Sub
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Submission Issue Meetings

• **Appropriate** for sponsor requests for:
  – an *in-person meeting* to discuss a planned approach to responding to deficiencies;
  – a *teleconference with management participation* to discuss a planned approach to responding to deficiencies; or
  – *feedback* on a planned approach to responding to deficiencies *that requires in-depth preparation by the review team and management* due to the nature of the questions.

  • Eg, Sponsor requests for feedback on plans to submit a justification for not providing information requested in one or more deficiencies will likely require submission of a Q-Sub, as this type of question typically requires input from FDA management.
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<td>brief clarification questions that can be readily addressed by the lead reviewer</td>
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<td>teleconferences for which the sponsor has not requested the participation of a manager</td>
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<td>feedback on a proposed protocol prior to conducting a major (clinical or animal) study to address a deficiency</td>
<td>To allow the review team adequate time to review the proposed protocol, the sponsor should instead submit the protocol and focused questions for FDA feedback in a Pre-Submission</td>
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<tr>
<td>pre-review of planned responses</td>
<td>This information should be reviewed only within a formal response to the deficiency letter, submitted to the DCC</td>
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<td>interactive review</td>
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PMA Day 100 Meetings

- Purpose: to discuss status of PMA review
- Tracked as a Q-Sub and linked to the PMA in FDA’s database
  - If request in Original PMA, FDA will automatically log in Q-Sub
  - If request comes later, sponsor must send request to DCC as a Q-Sub
- FDA will provide outstanding PMA deficiencies to sponsor (i.e., substantive interaction) 10 days in advance of meeting
- Sponsor should work with lead reviewer to develop agenda
  - General discussion of identified issues and remedial actions
  - Discussion of an action plan with estimated dates of completion
  - Discussion of FDA estimated timetables for review completion
  - Identification of need for panel involvement
  - Discussion of possible premarket versus postmarket requirements
- Meeting minutes tracked as amendment to Q-Sub
Tips for Successful Meetings with FDA
Best Practices for Meetings with FDA

- Follow the suggested logistics in the guidance document
  - Provide several options for dates to remain flexible
  - FDA will contact you within 7 days of acceptance to schedule
- Think carefully about what you want to get out of a meeting
  - Submit focused questions in advance
  - Develop the agenda based on these questions
  - Bring the right experts to execute your objectives
- Do not expect FDA to:
  - Make guarantees or binding commitments
  - Hold to informal feedback provided years ago
  - Approve a study or clear/approve a device at the meeting
  - Act as a consultant
  - Have iterative meetings on the same topic – make the most of each meeting
Best Practices for Meetings with FDA

- FDA will prepare to ensure that the meeting is productive, make sure you are prepared as well
  - Do not send new questions/discussion topics at the last minute or during the meeting; FDA needs time to prepare
- Suggest limiting presentation of the information in the pre-meeting materials to 1/3 of the allotted time to allow for discussion
- Bring a dedicated attendee to take detailed notes
- Summarize action items at the close of the meeting and ask for clarification if needed
Meeting Minutes

- Sponsor must submit draft minutes to DCC within 15 days
  - May also submit courtesy copy to lead reviewer via email
  - Please submit on time, while the discussion is still fresh in minds
- Minutes should reflect a summary of the discussion during the meeting; should not include:
  - A transcript
  - Responses to FDA’s feedback provided during the meeting (should be addressed in future submission)
  - Follow-up requests for feedback (should be submitted as a Q-Sub Supplement)
Meeting Minutes

- FDA review team reviews and edits, if necessary, within 30 days of receipt
- If edits needed, FDA sends revisions to sponsor via email
- After 15 days, FDA-edited version becomes final, unless:
  - Sponsor submits a “minutes disagreement amendment” to DCC identifying substantive issues with FDA’s edits
    - minutes disagreement should refer to disagreement regarding what was said/agreed upon during the meeting; not disagreement with the substance of FDA’s feedback
  - FDA will arrange a teleconference to discuss minutes
  - At conclusion of teleconference, FDA will revise minutes to reflect resolution OR note that the parties agree to disagree
  - Minutes (as revised by FDA based on tcon) considered final
If you have questions…

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