# Pre-Submissions and Meetings with FDA Staff

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# Introduction

- *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff*
  - Draft guidance issued July 13, 2012
  - Final guidance issued February 18, 2014

- Supersedes *Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, dated March 25, 1999*

# 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 for when a Submission Issue Q-Sub is and is not appropriate
- Minor policy clarifications for meeting logistics
- Appendix with RTA checklist

# Q-Submission Types

| Q-Submission Type | Meeting | 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 |
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**21 days for urgent public health issues

# Q-Submission Types

- Qsubs NOT applicable to:
  - industry trade organization,
  - consumer or patient advocacy organizations,
  - other government agencies, or
  - other stakeholders that are not planning a medical device submission to FDA

# Q-Submission Logistics

- Submit to Document Control Center (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

- 1 eCopy and 1 hard copy required
- Cover Letter with:
  - Identification of Q-Sub type (i.e., 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 example:
  - Slides
  - Agenda updates
  - Meeting minutes
  - Meeting minutes disagreements
- ***Supplements*** contain NEW requests for feedback on the same device/indication, for example:
  - Original request for feedback on planned bench testing
  - 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)

# Acceptance Review (RTA)

- Automatically accepted if Qsub type is:
  - Agreement Meeting
  - Determination Meetings
  - PMA Day 100 Meeting
  - Study Risk Determination
- For all other Qsub types, RTA review conducted within 14 days to determine:
  - If the request qualifies as a Pre-Submission, Submission Issue Meeting, or Informational Meeting
  - If the submission is complete enough to proceed with review and meeting planning, if meeting is requested

# Acceptance Review (RTA)

- Acceptance checklist included in Appendix 2 of guidance
- FDA will notify the sponsor of:
  - Acceptance: auto-generated email notification of acceptance and name of lead reviewer
  - Rejection: email notification that request was incomplete, including the information needed to make it complete and name of lead reviewer
- Sponsor response to RTA
  - should be submitted as amendment to DCC
  - Review clock begins on date of receipt of accepted submission or amendment

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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).

*http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf

# 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*)

# FDA Feedback on a Pre-Sub

- Feedback represents FDA's best advice based on the information provided
- FDA intends to stand behind our feedback unless:
  - Information in subsequent submission is not consistent with Pre-Sub (e.g., change in proposed indication for use or device design)
  - Data in the subsequent submission raise important new issues related to safety and effectiveness (e.g., a study is conducted as recommended by FDA, but results raise new safety concerns)
  - Feedback given previously does not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the Pre-Sub (e.g., new alternative therapies/diagnostics have emerged since discussion of the clinical protocol making the previously recommended study design unethical)

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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
- Policy unchanged; reference existing Information Sheet Guidance: *Significant Risk and Nonsignificant Risk Medical Device Studies*

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf
- 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.
    - For example, 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.

# Submission Issue Meetings

| Generally NOT Appropriate For: | Appropriate Mechanism: |
|---|---|
| brief clarification questions that can be readily addressed by the lead reviewer | documented in the review record associated with the parent submission |
| teleconferences for which the sponsor has not requested the participation of a manager | documented in the review record associated with the parent submission |
| feedback on a proposed protocol prior to conducting a major (clinical or animal) study to address a deficiency | 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 |
| pre-review of planned responses | This information should be reviewed only within a formal response to the deficiency letter, submitted to the DCC |
| interactive review | documented in the review record associated with the parent submission |

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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…

**CDRH:** Division of Small Manufacturers, International and Consumer Assistance (DSMICA)

1-800-638-2041; 301-796-7100

dsmica@fda.hhs.gov

**CBER:** Office of Communication, Outreach and Development (OCOD)

1-800-835-4709; 301-827-1800

ocod@fda.hhs.gov