



U.S. Food and Drug Administration
Protecting and Promoting Public Health



FDA Guidance Hot Topics: Pre-Submission Guidance Review

AMDM Focus Meeting

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Elizabeth Hillebrenner, MSE

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

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
Agreement Meeting	Yes	30 days or within time frame 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 filing of PMA)

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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).



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

<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.
 - 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.



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



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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



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If you have questions...

Elizabeth Hillebrenner

Policy Analyst

Office of In Vitro Diagnostics

& Radiological Health

301-796-6346

elizabeth.hillebrenner@fda.hhs.gov