The Pre-Submission How to Efficiently Communicate with FDA About Planned Applications

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Contents

- Q-Submission Program: Definition, Origin and Scope
- Pre-Submission: Applicability, Contents and Review Workflow
- FDA Written Feedback: Topics and Examples of Questions and Responses
- The Meeting: Before, During and After
- Benefits of Pre-Submission
- References and Contact

Q-Submission Program: Definition and Origin

- A structured process for managing and tracking interactions between manufacturers and FDA about future applications for approval or clearance, prior to their submission
- Emerged from pre-IDE program established in 1995
- Instituted as a structured process in the HHS Secretary's MDUFA III Commitment Letter to Congress in 2012

Q-Submission Program: Scope

- **Pre-Submissions (Pre-Sub)**
- Submission Issue Request (SI)
- Study Risk Determination (SRD)
- Informational Meeting
- PMA Day 100 Meeting
- Agreement and Determination Meeting
- Breakthrough Devices Program
- Accessory Classification Request

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What is a Pre-Submission

- Opportunity to obtain FDA feedback **prior** to an intended submission
- Voluntary
- Requires a formal written application
- FDA feedback is provided in the form of a written response
- Applicants may also request a face-to-face meeting or tele-conference

    - Meeting documented in meeting minutes

Pre-Sub is Applicable to

- **Investigational:** New Drug Applications (IND); Device Exemption (IDE); Humanitarian Device Exemption (HDE); Master Files; Special Protocol Assessments
- **Marketing:** New Drug Application (NDA); Premarket Approval (PMA); Biologics License Application (BLA); Premarket Notification (510(k)); Evaluation of Automatic Class III Designation (De Novo Request)
- **Other:** Accessory Classification Requests; Clinical Laboratory Improvement Amendments (CLIA); CLIA Waiver by Applications (CW); Dual: 510(k) and CLIA Waiver by Application

Pre-Sub is NOT Applicable to

- General FDA policies or procedures
- Simple review clarification questions that can be readily answered by FDA staff
- Discussion of issues identified **while** a submission is under active FDA review
- Appeal meetings

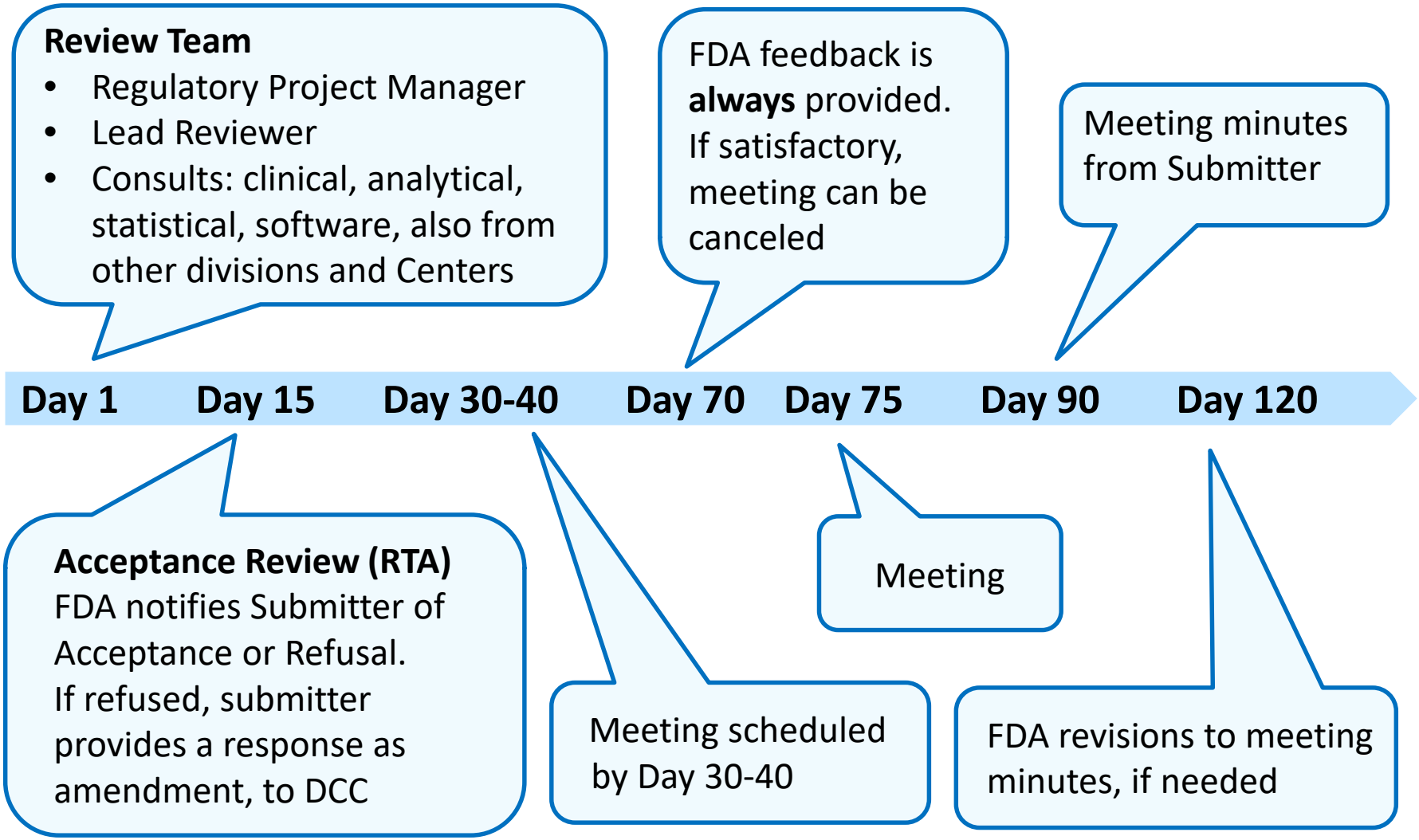
When to Submit a Pre-Submission

- When considering submitting investigational or marketing application to:
  - Apprise FDA review team on specifics of device
  - Gain insight into potential hurdles for approval or clearance
- When a new device does not clearly fall within an established regulatory pathway (new analyte, technology, etc.)
- When planning a study that will support future application

What to Include

- Cover Letter with:
    - Identification of communication type
    - Submitter information
    - Device name
    - Contact person information
- Premarket Review Submission Cover Sheet (Form 3514)
- Type of requested feedback
- Specific questions

Pre-Submission Review Workflow



Other Elements of a Pre-Submission

- **Amendments** BQxxxxxx/A01…A02 etc.

  Contain additional information about an existing request for feedback, for example:

  - Presentation Slides
  - Agenda updates
  - Meeting minutes
  - Meeting minutes disagreement

Other Elements of a Pre-Submission, cont.

- **Supplements** BQxxxxxx/S01...S02 etc.

  New requests for feedback on the same device or indication, for example:

  - Planned IU
  - Analytical plan
  - Clinical plan

- **New Q-Submission numbers**

  Assigned for subsequent requests for feedback if the device and/or indications for use have changed

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FDA Written Feedback

- Advice based on the information provided
- Feedback includes:
    - Responses to specific questions
    - Additional comments, if needed
- FDA recommendations are not obligatory for applicant
- The advice is binding on FDA, unless the circumstances change such that our advice is no longer applicable
- Pre-Sub does not guarantee approval, clearance, or licensure

Topics for Feedback from FDA

- Regulatory pathways: IND/IDE, PMA, 510(k), BLA
- Device classification questions
- Intended use:
    - Medical condition and population
    - Type (qualitative *vs* quantitative)
    - Screening *vs* diagnostic
    - Point of Care, home use
    - Matrix: whole blood *vs* plasma *vs* serum
    - Blood *vs* tissue donation
- Planned nonclinical studies: precision/reproducibility, stability, interference, carryover, cross-reactivity etc.

Topics for Feedback from FDA, cont.

- Planned clinical studies:
  - Population (adults, pediatric, pregnant etc.)
  - Inclusion/exclusion criteria
  - Sample size
  - Clinical sites
  - Clinical reproducibility, specificity/sensitivity
- Reference method and/or method comparison
- Statistical analyses
- Software/cybersecurity/risk management
- Labeling

Examples of Questions

- **Q1.** Has the attached protocol adequately outlined a plan for addressing the record-keeping (21 CFR 812.140(a)) and labeling (§812.5) requirements for investigational devices?
- **Background:** detailed protocol provided
- **FDA assessment**: information sufficient
- **FDA response:** The record-keeping plan provided in the protocol is acceptable.

Examples… cont

- **Q2.** The manufacturer of the investigational device is a foreign company, which requires the sponsor to import the device. In addition to FDA guidance are there specific requirements that the study sponsor must align with related to this importation?
- **Background**: necessary info provided
- **FDA assessment**: information sufficient
- **FDA response**: Please see the attached import compliance program document. You may direct any questions pertaining to the importation of CBER-regulated products to CBERImportinquiry@fda.hhs.gov.

Examples… cont.

Q3. Are the proposed internal verification studies, method comparison, anticoagulant, interfering substances, stability acceptable to support the proposed change?

Background: Detailed protocols provided

FDA assessment: The question is very broad. Due to the multiple studies listed in one question, we might not address specific issues a submitter is concerned about

FDA response: The proposed studies are acceptable

Examples… cont.

- **Q4.** Is the proposed stability protocol acceptable?
- **Background**: The only information provided was: "Stability testing will be performed on three conformance lots"
- **FDA Assessment:** Insufficient information
- **FDA response**: We are unable to comment on whether the proposed stability study is acceptable. In your future submission, please provide detailed information on the study protocol and a description of the stability program protocol you plan to follow after licensure.

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Before the Meeting: How to Prepare

- Provide several options for meeting dates
- Confirm meeting details with RPM:
  - Set up a phone line for tele-conference
  - Confirm attendees
  - Provide the foreign visitors forms
  - Provide the agenda
- Prepare presentation:
  - Identify meeting topics, questions based on the FDA feedback
  - Send to FDA at least three business days prior to meeting

At the Meeting: Dos and Don'ts

Do

- Limit the meeting to 1 hour unless requested in a Pre-Sub, justified and accepted
- Allow time for discussion
- Take detailed notes (bring a dedicated attendee)
- Ask for clarification if needed
- Summarize action items at the close of the meeting

At the Meeting: Dos and Don'ts

Don't

- Expect FDA to act as a consultant (we don't discuss data)
- Expect that we clear/approve/license a device at the meeting
- Send new questions or discussion topics at the last minute

After the Meeting: Document It

- Meeting minutes: summarize discussion, agreements and action items
- Amendment; within 15 calendar days
- FDA revisions via email within 30 days; become final after 15 days
- Disagreement? A tele-conference to resolve the issue
- Final disagreement minutes within 15 days: Issue resolved or a point of disagreement

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Benefits of Pre-Submission

- Improved quality of subsequent application
- Enhanced transparency of the review process
- Smoother review process
- Potentially shorter total review times
- No fee

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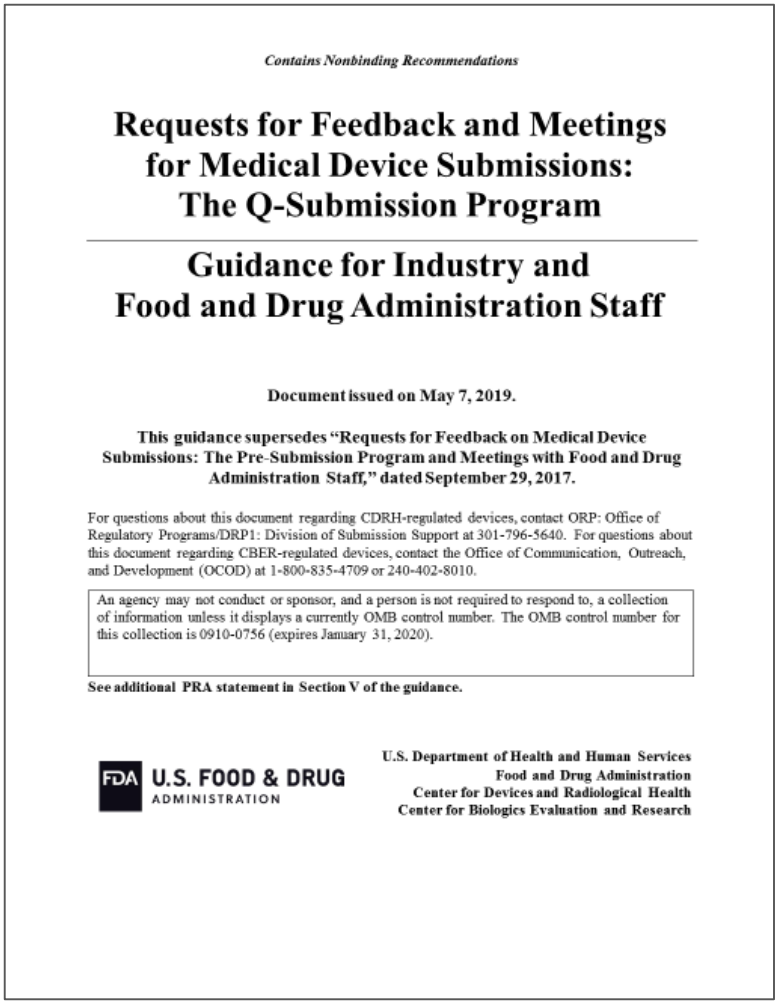
Q-Submission Guidance Updated and Finalized May 2019

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program OR at CBER webpage: (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm).



Contains Nonbinding Recommendations

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on May 7, 2019.

This guidance supersedes "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," dated September 29, 2017.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently OMB control number. The OMB control number for this collection is 0910-0756 (expires January 31, 2020).

See additional PRA statement in Section V of the guidance.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Thank you!

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