The Pre-Submission
How to Efficiently Communicate with FDA
About Planned Applications
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Iwona Fijalkowska, Ph.D.
Division of Emerging and Transfusion Transmitted Diseases
Office of Blood Research and Review
CBER
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
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• 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

**Review Team**
- Regulatory Project Manager
- Lead Reviewer
- Consults: clinical, analytical, statistical, software, also from other divisions and Centers

**Acceptance Review (RTA)**
FDA notifies Submitter of Acceptance or Refusal. If refused, submitter provides a response as amendment, to DCC

**FDA feedback is always provided.** If satisfactory, meeting can be canceled

Meeting scheduled by Day 30-40

Meeting minutes provided by Day 30-40

FDA revisions to meeting minutes, if needed
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

OR at CBER webpage:
(http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm).
Thank you!

Iwona Fijalkowska
Iwona.Fijalkowska@fda.hhs.gov