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

An Introduction to Pre-Submissions:
The What, Why, When, Where & How's

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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)

*As defined in MDUFA III Commitment Letter.

**21 days for urgent public health issues

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Outline

- *What is a Pre-Submission (Pre-Sub)?*
- *Why should you submit a Pre-Sub?*
- *When to submit a Pre-Sub?*
- *How and Where to submit your Pre-Sub?*
- *What happens to the pre-sub at FDA?*
- *What to include in your Pre-Sub?*
- *How to gain the most from your Pre-Sub?*
- *What outcomes you should expect?*
- *Q & A*

What is a Pre-Sub?

- A mechanism to obtain FDA feedback on future submissions: 510(k), PMA, HDE, IDE
- A voluntary, formal request from an applicant for feedback
- Free, confidential advice on regulatory process and feedback on proposed studies
- Allows for informal discussion of complicated questions.
- An opportunity to ask **specific** questions and conduct discussions **prior to** initiating studies for the intended future submissions.
- Non-binding - not an agreement meeting
- Interactive and Flexible

A Pre-Sub is NOT:

- Not a mechanism for FDA to design study protocols for the sponsor
- Not a preliminary data review
- Not intended for studies already performed
- Not interactive review of an active submission
- Not an Request for Designation (RFD), 513(g), or appeal
- Not a determination or agreement meeting
- Not a meeting that is informational only (i.e., no FDA feedback expected)

Why should you submit a Pre-Sub?

IVD-Specific Considerations

- New indications for use
- Novel devices (new technologies or new analytes)
- Guidance on product development
- Discussion of analytical and clinical study protocols
- CLIA waiver studies (January 2008 guidance)
- PMA or De Novo anticipated

Why should you submit a Pre-Sub?
IVD-Specific Considerations

- Multiplex devices detecting multiple analytes
- Multivariate assays with composite score (IVDMIAs)
- Drug-device companion diagnostics
- Complex statistical data analyses
- Provide supplemental information in response to the Agency's feedback
- This is your first submission

Goals of a Pre-Sub

- Well prepared submission
- Mutual education
- Focused validation studies
- Familiarize FDA with new technology
- Define possible regulatory pathways
- Shortened Review Times

When to submit a Pre-Sub?

- ***Early*** in your IVD development process
  - You have a defined intended use/indications for use.
  - You have a defined patient population
  - You are ready to discuss protocols and regulatory pathway.
- Before conducting clinical, nonclinical, analytical studies
- Before submission of an IDE
- Before submission of a marketing application
- When preparing a submission for a new device that does not clearly fall within an established regulatory pathway
- When you have specific questions for the FDA regarding your study protocols

Pre-Sub Process Timeline

- FDA review timeline: 75 – 90 days total
  - Sponsor submits to DCC (day 0)
  - FDA conducts acceptance review (by day *14*)
  - FDA provides written feedback (day *75 – 90*)
  - If Meeting/Tcon requested and held:
    - FDA and sponsor schedule the meeting/tcon date (by day *21*)
    - FDA provides preliminary feedback via email (*at least 3 days prior to the meeting/tcon*)
    - Sponsor provides draft minutes to DCC (*±15 days post meeting*)
    - FDA reviews/edits minutes (*±30 days receipt of draft minutes*)
- No user fee
- Interactive and flexible process

How do I get the process started?

- Pre-Submissions are not mandatory but are encouraged
- Submit a request and materials directly to the Document Control Center (DCC)*
- Format of interaction can be:
  - Written comments
  - Meetings:
    - Teleconference, in-person
- Pre-subs related to the same device should be tracked as supplements to the original submission

*** Where =** U.S. Food and Drug Administration, Center for Devices and Radiological Heath
Document Control Center – WO66-G609
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002

I sent my Pre-Sub to DCC, now what?

- DCC logs submission in as received (day 0)
  - Electronic copy (eCopy) uploaded
- Submission arrives at appropriate office (~ days 1 – 5)
  - Logged into Division
  - Lead reviewer assigned
- Acceptance checklist (RTA) completed (by day *14*)
- Lead Reviewer requests appropriate consults (after completion of RTA; ~ day 14-20)
  - Expert analytical consult, Statistical consult, Clinical consult, Software consult, Intra/Inter-Center consult
  - Recommended consult review time is a minimum of ~ 30 from date assigned

I sent my Pre-Sub to DCC, now what?

- Interactive review between lead reviewer and sponsor, as needed (days 15 – written feedback sent)
  - Requested meeting/Tcon scheduled (by day 21)
- Lead reviewer holds internal meeting(s) with review team (~ day 45 – 75)
- FDA provides written feedback (by day *75 – 90*)
  - Review team signs off on final memo
- Meeting/Tcon held if requested (by day 75 – 90)

What to include in your Pre-Sub?

- Cover letter containing:
  - Sponsor Contact information
  - Device name
  - Desired communication format
  - Reference prior communications (if applicable)
- Device description/ test principle
- Clearly stated intended use
- Content depends on the questions you're asking:
  - Regulatory questions
  - Analytical study design
  - Clinical study design
  - Statistical analyses plan
- *Specific Questions*

Device Description

- Components
- Technology
- Scientific principle
- Result generation and interpretation
- Related instrumentation
- Related software
- Calibrators and Controls

Intended Use

- Should describe how the device is to be used and for what/for whom the device is to be used.
- Should address the following:
  - Measurand (e.g. analyte, organism, cell, protein that is measured, identified or detected)
  - Type of test (e.g. quantitative, semi-quantitative, qualitative)
  - Specimen type/testing matrix (e.g. serum, Na-Heparin)
  - Target population (e.g. pediatric)
  - Condition(s) or disease(s) to be screened, monitored, treated or diagnosed
  - Adjunctive or stand alone test
- Intended Use will guide FDA feedback!

Analytical Validation

- Objective:
  - Establish analytical performance characteristics of the test (e.g., accuracy, reproducibility, etc.)

- Describe:
  - Studies to be performed
  - Detailed proposed study design
  - Samples (nature, number) to be tested
  - Statistical Plan
  - Acceptance criteria

Recommended Analytical References

- CLSI Guidelines:
  - EP05-A2 – Establishing precision
  - EP06-A – Establishing linearity
  - EP07-A2 – Interference studies
  - EP09-A3 – Systemic Differences
  - EP12-A2 – Qualitative tests
  - EP17-A2 – LoB, LoD, and LoQ
  - EP21-A – Total error
  - EP25-A – Reagent stability
  - C28-A3 – Reference ranges
- Statistical Guidance for Reporting Diagnostic Tests
  - *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071287.pdf*
- Published Decision Summaries
  - Predicate device
  - Related product codes
    - *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm*

Clinical Validation

- Objective:
  - To support the proposed intended use
  - To establish clinical performance of the device compared to clinical truth.
  - To establish the assay performance characteristics in "real world" conditions when no predicate exists

- Describe:
  - Study protocol
  - Patients/samples & sites
  - Define "clinical truth"
  - Statistical analyses plan
  - Acceptance criteria

Making the Most of your Pre-Sub

- Know your Intended Use
- Justify your proposed regulatory pathway
- Justify and support your proposed studies
- Statistical analysis plan
  - Sample size justification
  - Statistical methodology
- Ask specific questions
- Prior to submitting, review for content clarity and errors
- Test your eCopy format
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

Examples of Good Pre-Sub Questions

- Given our power calculations, does FDA agree that our proposed study size is reasonable?
- Given the intended use of the subject device, does FDA agree with the proposed comparator method for evaluation of the clinical performance?
- Does FDA agree that the existing medical and scientific literature referenced in the pre-submission have established the clinical utility of *X* testing, and therefore [*this sponsor*] will not be required to perform a separate clinical study for the approval of the test?
- Is a “moderate level of concern” the appropriate level of concern for my software?

Examples of not so good Pre-Sub Questions

- No specific questions asked.
  - Refuse to Accept as of 3/31/14
- Does FDA agree with all the proposed analytically performance study designs?
- Is the sample size of 500 subjects adequate?
  - without providing a statistical analysis proposal
- Given the IU, does FDA agree that our device qualifies for de novo approval?
  - no details provided on related regulations, predicate

FDA Feedback on a Pre-Sub

- Most current thinking and advice on your proposal.
- Contains non-binding recommendations.
- Closes the pre-submission officially, except in the case of a meeting request which formally closes the pre-Sub.

Day of the meeting Pre-Sub Meeting

- Most meetings one hour
- Submit any slides to lead reviewer by email
  - Saved as part of Q-sub package
  - Back-up if needed
- Names of Sponsor participants should have been submitted to FDA in advance of meeting
  - Foreign visitors min of 10 days prior for clearance
- Pre-Designate a meeting minutes recorder
- Have a clear agenda
- Meeting should focus on content of Pre-Sub and FDA's written feedback
  - Discuss written feedback both FDA responses and possible additional questions raised by FDA in memo
  - Discuss regulatory pathway options
  - Should not raise new issues and expect agreement/resolution during meeting
- Allow extra time!
  - Parking, security, computer set-up

What about Pre-Sub Meeting Minutes?

- Sponsor should have a designated meeting recorder.
- Sponsor must submit draft minutes ***to DCC*** within 15 days
  - o May submit courtesy copy to lead reviewer via email
  - o Submit any slides if not previously sent to reviewer
- Minutes should reflect a summary of the discussion during the meeting, include Action Items
- Meeting minutes should not include:
  - o A transcript
  - o Responses to FDA's feedback provided during the meeting
  - o Raise new issues
  - o Follow-up questions
- Any subsequent new questions or new issues raised during the meeting should be addressed in a supplement

What Outcome Should you expect from the Pre-Sub process?

- FDA's most current thinking and advice on your proposal
- An opportunity to clarify FDA's expectations pertaining to your future submission
- Often leads to a better submission and faster regulatory decision
- No assurance of a positive regulatory decision!

Pre-Sub process Summary

- Free premarket proposal feedback
- FDA's most current thinking and advice on your proposal
- Flexible
- Not binding on the FDA or the Sponsor
- What you make of it!

Questions?

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