Pre-Submissions and Q-Subs

AMDM

510(k) Submissions Workshop, April 9, 2019

Pre-Submissions Workshop, April 10, 2019

Majda Haznadar, PhD

Immunology and Flow Cytometry Branch (IMFB)

Division of Immunology and Hematology Devices (DIHD)

Office of In Vitro Diagnostics and Radiological Health (OIR)

Center for Devices and Radiological Health (CDRH)

Our Path Today

- Q-Sub Types
- Pre-submissions (Pre-Subs)
  - Applicability
  - Managing Risk and Uncertainty
  - Important Elements of a Pre-Sub
  - Specific Questions
- PMA Day 100 Meetings
- Submission Issue Meetings
- Designation Requests for Breakthrough Devices
- Tips

Q-Subs cover many different submitter requests

- Informational Meetings (Info)
- Study Risk Determinations (SRDs)
- Pre-Submissions (Pre-Subs)
- Submission Issue Meetings (SIMs)
- PMA Day 100 Meetings (PMA 100)
- Breakthrough Device Designation Requests

Pre-Subs

Pre-Subs are one type of Q-Sub

- Pre-submissions (Pre-Subs)
  - Questions related to a future submission
  - Can be
    - written feedback and a face to face meeting
    - written feedback and a teleconference (easier to schedule)
    - purely written feedback

Pre-Subs are one type of Q-Sub

- Pre-submissions (Pre-Subs)
- **Study Risk Determinations**
  - Is the proposed study a significant risk or non-significant risk or exempt?
  - Will determine if Investigational Device Exemption (IDE) is needed.

Pre-Subs are one type of Q-Sub

- Pre-submissions (Pre-Subs)
- Study Risk Determinations
- **Submission Issue meetings**
  - Issues related to a hold letter or an IDE letter

Pre-Subs are one type of Q-Sub

- Pre-submissions (Pre-Subs)
- Study Risk Determinations
- Submission Issue meetings
- **Informational Meetings**
  - When you want to let FDA know about a novel device or indication and don't need feedback

Pre-Subs have Broad Applicability

- Future submission can be a PMA, 510(k), De Novo, CLIA Waiver, or IDE

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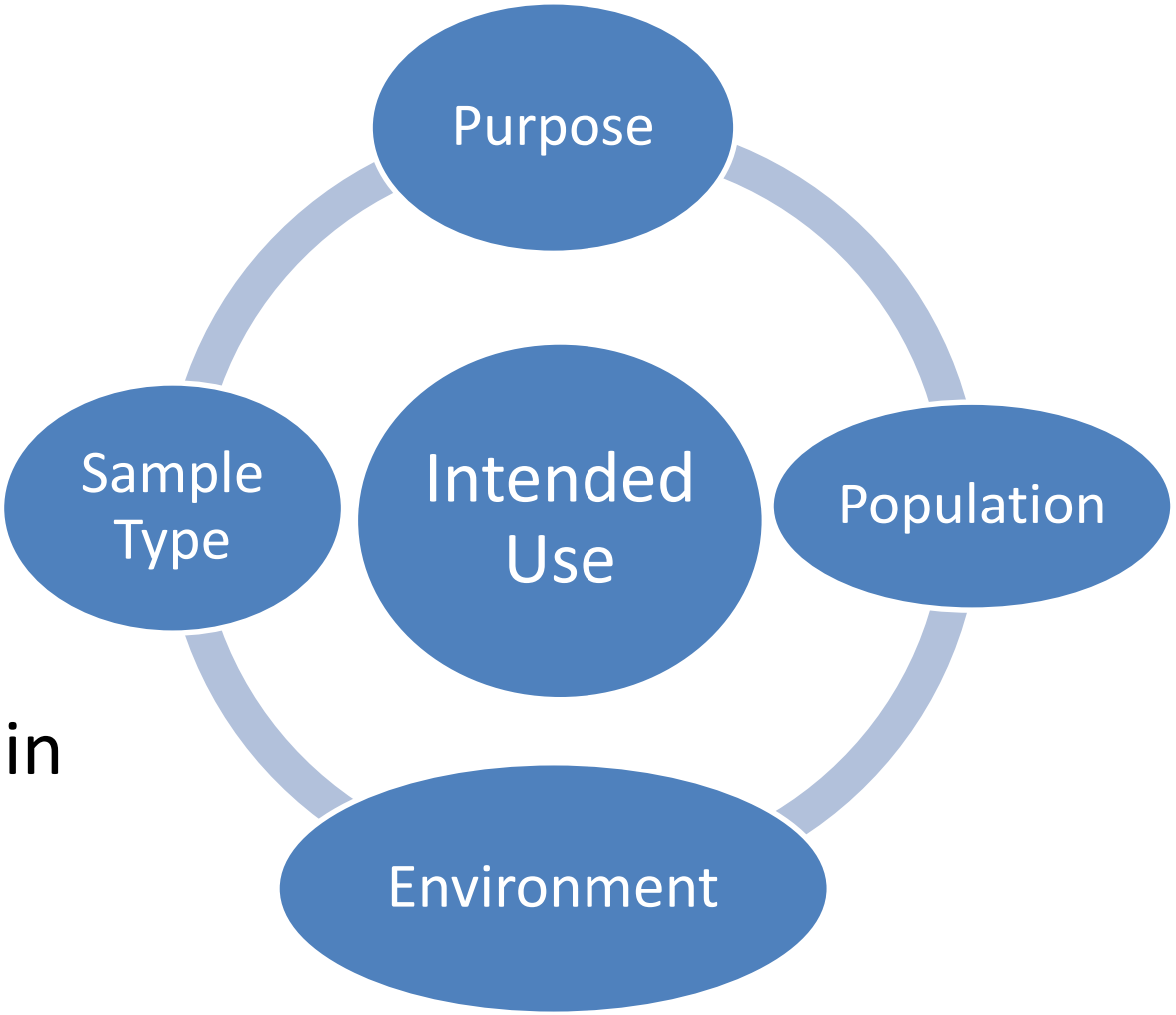
- Can address many types of questions, the more specific the better (more on this later)
- **Can be useful at different stages of product development**

Uncertainty is Best Addressed Early

- Course corrections are less expensive when made early
- More opportunity to work towards win-win approaches

Describe Your Device in Detail

- How does it work?
- How is the device used in clinical practice?



Critical Element of a Pre-Sub: Intended Use (IU)

- The most important part of any pre-sub
- Analytical and clinical validation studies should support the IU of the proposed device
- Clinical study should be conducted in the IU population
- May be amended/modified over time

IU Elements

- Assay name
- Technology
- Instrument name
- Sample matrices (serum, plasma)
- Quantitative or qualitative
- Clinical use – disease /condition
- The clinical purpose (diagnosis, prognosis, monitoring)
- The target population for whom the test is intended
- Setting (clinical laboratory, point-of-care, etc.)

IU Example (DEN170019)

Matrix

Instrument

Analyte(s)

The Vitamin D 200M Assay for the Topaz System is intended for in vitro diagnostic use in the quantitative determination of total 25-hydroxyvitamin D (25-OH-D) through the measurement of 25-hydroxyvitamin D3 (25-OH-D3) and 25-hydroxyvitamin D2 (25-OH-D2) in human serum using LC-MS/MS technology by a trained laboratory professional in a clinical laboratory. The Assay is intended for use with the Topaz System. The Vitamin D 200M Assay for the Topaz System is intended to be used in conjunction with other clinical or laboratory data to assist the clinician in making individual patient management decisions in an adult population in the assessment of vitamin D sufficiency.

Intended Population

Condition

Analytical Performance Characteristics

- Precision
- Linearity/assay reportable range
- Limit of Detection
- Cross reactivity/ Interfering substances
- Method comparison (to the predicate or reference method)
- Matrix comparison
- Traceability, Stability
- Controls and calibrators
- Reference range (in normal population)

Clinical and Laboratory Standards Institute (recognized by FDA)

Clinical Performance Characteristics

- Examples of parameters in clinical studies: Sensitivity/Specificity, Negative Predictive Value (NPV)/Positive Predictive Value (PPV) based on comparison to a gold standard (i.e., American College of Rheumatology (ACR) classification criteria, biopsy, etc.)
- Inclusion/Exclusion criteria should be well defined
- Specimens: where possible, the set of subjects and specimens to be tested include:
  - Specimens across the entire range of disease state to reflect the target population for the device (e.g. stage, grade)
  - Differential diagnosis specimens (normal samples are not appropriate for determining specificity)

Pre-Sub Meeting Milestones

Timeline	Action
Day 15	Acceptance after receipt in Document Control Center (DCC) If accepted, email states whether meeting agreed to or provides 2 alternative dates
Day 30	Meeting date agreed to or escalation to management
5 days Before Meeting (or Day 70 if earlier)	Written Feedback
Meeting	Meet unless you cancelled Q-Sub Closed
Meeting plus 15 Days	Your deadline for submitting meeting minutes

Do ask Specific Questions

- Our goal is to meet your current need
- If your question is specific, we can address it
- If your question is vague or too broad, we'll do our best, but may miss your real need

Which Questions are a Good Fit for a Pre-Sub or Submission Issue Mtng?

1. Does FDA agree with the proposal for use of contrived samples in analytical studies described in Section X?
2. Is this sufficient for a 510(k)?
3. We have provided a response to FDA's question about clinical study sample size, along with a justification based on a power analysis. Is this plan acceptable? If not please provide further guidance.
4. Does FDA agree with all of our analytical performance studies?
5. …

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Address our Answers

- When you submit your next submission…
- If you didn’t follow our advice, say why

In Summary, submit a Pre-Sub when…

- A new intended use
- Contains new technology or analytes
- Clinical Implications Unclear
- Presents complex data/statistical questions
- Presents a significantly new approach to analytical or clinical study designs or analyses
- Uses a predicate or reference method that is unclear or uncertain

PMA Day 100 Meeting

PMA Day 100 Meetings May not be Your Best Choice

- Day 100 meetings should happen by day 100
  - Guidance Issued prior to MDUFMA

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- **Day 90 – MDUFA goal for Major Deficiencies**
  - Leaves < 10 days for you to review deficiencies prior to meeting

PMA Day 100 Meetings May not be Your Best Choice

- Day 100 meetings should happen by day 100
  - Guidance Issued prior to MDUFMA
- Day 90 – MDUFA goal for Major Deficiencies
  - Leaves < 10 days for you to review deficiencies prior to meeting
- **Submission Issue Meeting may be a better option**

Submission Issue Meetings

Submission Issue Meetings are for Hold Letters and IDE Letters

- When:
  - Your marketing application or CLIA Waiver has received a deficiency letter
  - Or you have an IDE letter

Submission Issue Meetings are for Hold Letters and IDE Letters

- Hold letter or IDE
- **You want to review your planned approach to the deficiencies with FDA**

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  - Call or email the Lead Reviewer

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  - Call or email the Lead Reviewer
- **Not a 'pre-review' of your response**
  - Intent is to chart a path
  - Not to review the entire response

Submission Issue Meetings can be Quick

- Our goal is to turn these around in 21 days
- New protocols or other complex proposals will take longer
- The sooner you submit your Submission Issue Meeting request, the more likely you are to receive prompt feedback

Submission Issue Meetings – be clear about what you want

- In your submission, we suggest that you:
  - State your objectives for the meeting
  - Include specific questions or specific deficiencies you want to discuss
  - Provide an agenda for the above with estimated times for each
  - Indicate specific expertise

Designation Requests for Breakthrough Devices

Breakthrough Devices

- Voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions

- The goal of the program is to provide patients and health care providers with timely access to these medical devices by speeding up their development, assessment, and review

- See Breakthrough Devices Program Web page: https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/ucm441467.htm

- Our Breakthrough Devices Program Guidance was issued on December 18, 2018

Breakthrough Devices – Designation Requests

Which pre-market submissions can be granted a designation request?

- Devices subject to premarket approval applications (PMAs), premarket notification (510[k]) or requests for De Novo designation are eligible for Breakthrough designation if certain criteria are met

Breakthrough Devices – Criteria

1) Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; **AND**
2) The device meets at least one of the following criteria:
   a. Represent breakthrough technologies;
   b. No approved or cleared alternatives exist;
   c. Offer clinically meaningful advantages over existing approved or cleared alternatives including the potential, when compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
   d. The availability of which is in the best interest of patients.

Tips

Write a Clear Cover Letter

- What type of Q-Sub do you want?
- If Pre-Sub
  - Do you want written feedback only or do you want a meeting?
  - If a meeting, propose three specific meeting dates
- Ongoing Q-Sub?
  - Same device and intended use
- With whom should we correspond?

Q-Submission Nomenclature – Amendments and Supplements

- ***Amendments*** contain additional information about an existing request for feedback, for example:
  - Slides
  - Agenda updates
  - Meeting minutes
  - Meeting minutes disagreements
  - Change of Submitter/Correspondent

- ***Supplements*** contain new requests for feedback on the same device/indication
  - Can be any kind of Q-Sub

Successful Meetings take Planning and Focus

- Focus the meeting on what you want to get out of it
  - Do ***not*** spend 10-15 minutes on a company history or its management
  - Allow 2/3 of the time for discussion
  - Limit background review to 1/3
- Dedicate someone to take minutes
- Should not ask questions based on new information provided during the meeting – we may not be able to answer them

Be Clear at Close of Meeting

- Summarize action items
- Ask for clarification if needed
- When FDA can expect meeting minutes

Top Ideas I Hope You Take Away…

- **Pre-Subs are available to help you mitigate risk**
  - Risk reduction is most effective when done early
  - Please talk to us if you are unsure, and be willing to listen to what we say

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- **Have focused questions for the meeting**

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  - Risk reduction is most effective when done early
  - Please talk to us if you are unsure, and be willing to listen to what we say
- Have focused questions for the meeting
- **Write clear cover letters**

Q-Sub Resources

- **The Q-Submission Guidance**
  - *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff*
    - Updated issued September 29, 2017
    - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- **eCopy Program**
  - The page contains links to Guidance, video, FAQ, and tools, including a validation module https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370879.htm
- **Optional form 3514**
  - Be clear about what you're submitting, who you are, and whom we should contact – optional because a good cover letter can have all this
  - https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf

U.S. FOOD & DRUG ADMINISTRATION

Thank You

Majda Haznadar
Majda.Haznadar@fda.hhs.gov


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