Path to Approval: Why the FDA Q-Submission Program Is a Key Regulatory Strategy Component

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Wanda Carpinella, VP Regulatory Affairs
Mack Rubley, Executive Director, Business Development

The path to premarket approval (PMA), 510(k) clearance, and other medical device submissions is filled with uncertainty. To help medical device manufacturers resolve some of those uncertainties and smooth the submission process, the FDA developed the Pre-Submission (aka Q-Submission or Q-Sub) program. Because early communication with the FDA is invaluable in improving the medical device development process, Q-Sub is an integral component of regulatory strategy.

What Is Q-Sub?

Q-Sub is a voluntary opportunity — available at no cost — to obtain FDA feedback before a premarket submission.[1] Interacting with the FDA early, and incorporating the agency's recommendations, may help improve submission quality and smooth the path to submission and clearance/approval.

The Q-Sub program applies to the following[2]:

- 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 (501(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

The Q-Sub process starts with a formal written application to request the FDA's written, non-binding feedback to specific questions posed by the sponsor. The sponsor may also request to meet with the FDA review team either in person or by teleconference.

The FDA provides advice based on information provided by the sponsor. Feedback may include responses to specific questions and additional comments as necessary. Pre-Submission recommendations are not obligatory, nor is the FDA feedback binding.

What the Q-Sub Is Not

While the information given by the FDA during the Q-Sub process can help sponsors address issues that may delay or prevent approval, it does not guarantee approval, clearance, or licensure.

Sponsors must ***not*** use the Q-Sub program to:

- Seek guidance or ask questions related to general FDA policies or procedures
- Ask simple review clarification questions that can be readily answered by FDA staff
- Facilitate a discussion of issues while a submission is under active FDA review
- Appeal outcomes of prior appeal meetings

Why Is It Called Q-Sub?
The FDA tracks Q-Submissions with a "Q" number, which is how Q-Sub got its name.

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Benefits of Q-Sub

While moving through the Q-Sub process adds about 60-75 days to a timeline, as well as additional costs around preparing a submission, the benefits to lowering risk of rejection more than compensate. The benefits of Q-Sub include:[3]

- Improved quality of subsequent application
- An opportunity for the sponsor to obtain FDA's buy-in on testing plans before initiating long-term, expensive testing
- Insight into the review process and the items of concern for the FDA review team
- A smoother review process with the FDA and potentially shorter total review times

The Q-Sub Timeline

The Q-Sub timeline varies depending on whether the sponsor seeks Pre-Submission feedback, advice on an approach to marketing submission (submission issue request), a study risk determination, or an early informational meeting.[4] A typical Pre-Submission process takes three to four months. The timeline typically follows the following format:

Q-Sub Timeline
• Upon receipt of the submission by the FDA, a review team is assigned that includes a regulatory project manager, a lead reviewer, and appropriate consults
• By Day 15 the Acceptance Review is completed, and the FDA notifies the submitter of acceptance or refusal
• The FDA begins coordinating the meeting about two weeks after the submission is logged with the FDA
• FDA aims to schedule a meeting within 60 to 75 days from submission date, depending on the FDA's schedule and availability
• The FDA aims to provide written feedback five calendar days before the meeting; if the feedback alone is satisfactory the sponsor can cancel the meeting
• If the meeting takes place, the sponsor submits meeting minutes to the FDA within 15 days of the meeting

Appropriate Q-Sub Topics

- Device classification questions
- Intended use clarifications
- Planned nonclinical or preclinical studies
- Planned clinical studies:
  - Population
  - Inclusion/exclusion criteria
  - Sample size
  - Clinical sites
  - Specificity/sensitivity
- Method of comparison
- Planned statistical analyses
- Software or cybersecurity
- Risk management
- Labeling

Q-Sub Program Tips for Success

- Participate in the Q-Sub process. Don't avoid it for fear of going to the FDA too soon.
- Request an in-person meeting when possible. A face-to-face meeting is most effective and provides an opportunity to have a meaningful interaction with the FDA. Teleconference is a suitable alternative when a face-to-face meeting is not possible.
- Review the FDA Guidance — limit the feedback request to three or four substantial and appropriate topics that the FDA can address in a one-hour meeting.
- Avoid modifications of your Q-Sub before the meeting. Be sensitive to the reviewers' timeline and multiple demands. The FDA will not review new information outside of what was submitted in the Q-Sub. If new information arises, the FDA will ask you to submit the new information in a Pre-Submission supplement and the clock re-starts.
- Ask specific questions. For example, does the FDA agree with the study design or endpoints, preclinical test plan, number of test samples, etc.? Why or why not?
- Confirm meeting details, logistics, and attendees, and complete foreign visitor forms for in-person meetings, all at least two weeks before the meeting.
- Prepare an agenda and PowerPoint presentation to guide the discussion. Focus on key discussion points rather than areas the FDA agrees with.
- Clear your team's schedule for the five days before the meeting. Sponsors will need "all hands on deck" to properly respond to the FDA's feedback and prepare the meeting presentation.
- Practice, Practice, Practice. Make sure every attendee knows when to speak and what to say, including the key opinion leader (KOL) or medical expert. The meeting will be limited to one hour unless requested and accepted otherwise. Allow time for introductions and discussion. Assign an experienced scribe to take detailed notes.
- Ask for clarification when needed and close any open topics.
- Summarize action items at the close of the meeting.
- Do not expect the FDA to act as a consultant. They will not discuss data at the meeting.
- Do not raise new questions or discussion topics at the last minute.
- Summarize your discussion, agreements, and action items in a set of minutes. Submit minutes to the FDA within 15 calendar days.

Case Studies of Successful FDA Q-Sub Meetings

Cost Savings on Biocompatibility: Avania recently supported a client with a Pre-Submission focused on preclinical biocompatibility testing. A third-party testing lab proposed two series of biocompatibility studies: one for each implant to be performed in parallel.

Upon further discussion, the client was concerned about timeline and cost. We revised the strategy and prepared a Q-Sub. We proposed the biocompatibility test plan to test the two different implants in a single series of biocompatibility testing. The FDA agreed with the combined biocompatibility study, which saved Avania's client considerable money and time during development.

Reduced Data Burden for 510(k) Submission: Avania worked with a client to develop a thorough regulatory and clinical strategy. The clinical strategy took a phased approach for gaining clearance for the ultimate indications and claims sought. The first phase leveraged clinical data for one subset of the population. The second phase involved a pivotal trial to expand the patient population. During Pre-Sub, the FDA agreed with this approach but asked for a small confirmatory clinical study of a subset of the intended population to support the first 510(k) clearance.

Even though the FDA asked for a small confirmatory study for the first patient population subset, the Pre-Submission process still identified a least-burdensome approach that involved significantly fewer study patients compared to the number of patients studied by the predicate to achieve commercial clearance of the same patient population. The client saved significant time and financial resources.

Conclusion

It's common for sponsors to have dozens of questions related to regulatory submissions. Take full advantage of opportunities to communicate with the FDA early in the process to increase odds of success. The Q-Submission program is one way to identify and resolve issues that may hinder regulatory clearance or approval.

If you have a medical device in development, Avania will support you through the entire FDA pre-submission process.

Let's Talk

References

[1, 2.] Fijalkowska, Iwona, Ph.D. The Pre-Submission: How to Efficiently Communicate with FDA About Planned Applications. FDA, July 15, 2019.

[3, 4.] Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program. FDA Guidance Document, January 2021.