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## FDA Will See You Now!

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A new guidance document outlines the process for meeting with FDA about medical devices.

Earlier this year, FDA released the important new final guidance document Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff. This guidance is essential for Class II and III manufacturers wondering how to seek clarifications from U.S. regulators before or after applications are sent to FDA for new or modified medical devices (including IVDs, mobile medical apps, accessories, etc.). Included is how to receive written feedback from FDA, as well as setting up teleconference and in-person meetings to exchange information in real-time and receive verbal feedback. Recent practical experience with one such meeting will be discussed.

### Background

Because of differences between EU and US regulatory processes, manufacturers in Europe have various reasons for seeking direct feedback from FDA – and at different times in the product application process. The new FDA guidance outlines the steps and timing that apply to this feedback process, as well as several specific examples of situations, including but not limited to:

- When the company has received questions or deficiencies from FDA during the device application process, including 510(k), de novo, PMA, etc.
- When the company has questions about proper test methods (clinical, animal, biocompatibility, human factors, bench, etc.), statistical data analysis, etc. for an upcoming submission
- When the company is seeking FDA review of a submission containing a new medical indication, technical innovation, etc.
- When the company is planning to sponsor a clinical study in Europe under the Investigational Device Exemption (IDE) rules, and needs to know whether FDA would consider the risk level to be Significant Risk (SR) or Non-Significant Risk (NSR).
- Both industry and regulators hope that standardizing the FDA feedback process will decrease the problems sometimes encountered in bringing new technologies to the US market. FDA published a draft guidance document on this topic last year. The new guidance discussed in this article now supersedes both the draft guidance document and the previous FDA guidance document on this subject Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, published in 1999.

### “Q-Sub”

FDA requires that a formal set of written materials be supplied from the company when seeking feedback on a device issue, including the situations noted above. FDA has created the term “Q-Sub” (Q-Submission) to identify this formal documentation package, in these feedback circumstances. When received at FDA, the materials will be assigned a unique identification number beginning with the letter “Q” followed by two digits representing the current calendar year followed by four digits representing the number of Q-Subs received in that year. For example, the twelfth Q-Sub submitted in 2014 would be assigned the number Q150012. Please understand that the Q-Sub process is entirely voluntary, but may be advantageous in certain circumstances, like when feedback may clarify important points early in the development process – in order to avoid headaches later in the device submission process.

The new guidance lists many situations for which the Q-Sub is not the appropriate method for receiving feedback from FDA. The following are some examples where other feedback methods (explained in the guidance document) would apply:

- Guidance document clarification
- FDA policy and procedure questions
- Regulatory classification requests for new devices that should be conducted instead per section 513(g) of the Federal Food, Drug, and Cosmetic Act
- Appeals of FDA device application decisions

### Feedback Method

Within the Q-Sub contents, the medical device company requests the method for the FDA feedback from the following choices: in-person meeting at FDA headquarters, teleconference, Fax or email. However, FDA makes the final decision about what feedback method will be used. Three different preferred dates and times can be suggested to FDA for holding the meeting, if an in-person or teleconference meeting is requested as the feedback method.

### Preparations

Like any other FDA submission, the Q-Sub working language is English, as stated in the new guidance document: “Please be advised that your Q-Sub should be written in the English language. Any material in a foreign language should be accompanied by an accurate and complete English translation.”

An “eCopy” (electronic copy) must also be sent to FDA for each Q-Sub. Separate FDA guidance exists on this subject that explains the eCopy standards, quantity, logistics, and so on.

If an in-person meeting is requested by a company from Europe, for example, each non-US Resident coming to the FDA meeting must complete the “Foreign Visitor Data Request Form” located on the FDA website. These forms must be provided to the FDA at least 10 days before the scheduled meeting. Companies can also request consultants, US subsidiary staff, technical specialists and others to attend the meeting to represent the company’s interests.

### Appropriate Q-Sub Questions

The FDA guidance document gives numerous examples of appropriate (and also examples of inappropriate) questions to ask FDA in Q-Sub materials provided to FDA. Examples of appropriate questions are:

- Are the primary and/or secondary clinical study endpoints appropriate for the proposed indication for use?
- Are the proposed clinical trial design and selected control group appropriate?
- Are the proposed clinical trial sample size calculation method and related elements of the statistical analysis plan appropriate for the proposed clinical study?
- In addition to the biocompatibility testing recommended for the type and duration of tissue contact defined by FDA's G95-1 Bluebook Guidance and ISO 10993-1, what other device-specific biocompatibility testing may be necessary?
- Does the FDA concur with the use of the proposed alternative test method, which is different than the normally recognized standard?
- Is the animal testing method proposed appropriate for testing the new device?
- Is a "moderate level of concern" the appropriate level of concern for my software?
- Is the planned approach to human factors assessment appropriate for the intended use of my device?
- Does FDA have any concerns with the proposed predicate device, which is planned to be used to compare with the new device in the upcoming 510(k) application?

#### During Device Application Review

The new guidance also allows the Q-Sub system to be used for a "Submission Issue Meeting" after the company has sent FDA a device application, but before FDA has completed the review of the submission. Keeping in mind that numerous submission issues can be resolved working directly with the reviewer during the review process, FDA has limited the Q-Sub "Submission Issue Meeting" to the following situations where FDA management is required to participate:

- In-person meeting with review team (or teleconference meeting including FDA management participation) to discuss the approach currently planned by the company to answer FDA concerns/questions/deficiencies about the device
- Feedback requested from FDA that will require detailed preparation by the FDA review team who is evaluating the new device (because feedback will likely require FDA management input)

#### Recent Q-Sub Experience

An overseas manufacturer recently requested Ken Block Consulting to create the Q-Sub documentation package and coordinate the entire effort, for a teleconference with FDA regarding a unique new diagnostic device. The eventual device would include at least two product codes from two different FDA review branches. Following is a list of significant events, in chronological order, where everything sent by FDA was via email:

- Day 1: FDA received physical Q-Sub package
- Day 9: FDA sent "Acceptance Review Notification" including name of lead reviewer who will eventually be assigned the future submission, as well as other statements including: "We have determined that your submission includes sufficient information to enable feedback in the manner you have requested (written feedback or in a meeting or teleconference)."
- Day 10: FDA lead reviewer sent initial introduction note
- Day 16: FDA proposed three specific dates and times for teleconference (of which client then chose one)
- Days 24 & 27: FDA sent clarification questions about Q-Sub documentation contents (which were promptly answered)
- Day 64: FDA sent initial list of planned attendees for teleconference:
  - o 2 branch chiefs (responsible for the subject product codes)
  - o 2 reviewers (one from each of the two review branches)
  - o 1 director (overseeing the two branches involved)
  - o 1 statistician
  - o 1 medical director
- Day 70: FDA sends PDF document titled "Pre-Submission Memorandum" including written FDA feedback to the initial Q-Sub documentation package (addressing issues such as predicate devices, product codes, clinical study population/methods/criteria/statistics, Indications for Use statement, and labeling including user manual), along with several statements including:
 

"This is an informal communication that represents the best judgment of the [specific FDA division] staff and consultants who reviewed the pre-submission. It does not constitute an advisory opinion and does not bind or otherwise obligate or commit the Agency to the views expressed, as per 21 CFR 10.85(k)."
- Day 71: Teleconference agenda and PowerPoint presentation sent to FDA, with content based upon the "Pre-Submission Memorandum" received from FDA
- Day 72: Both FDA and client finalize the attendees for the upcoming teleconference
- Day 73: Q-Sub teleconference held with FDA

The written feedback from FDA in the "Pre-Submission Memorandum" included resolution of numerous items for our client, and therefore allowed us to focus the PowerPoint materials on the items that were yet unresolved. Our company teleconference service was used as the method for holding the multi-party event. The teleconference was held on the date and time agreed, starting with an introduction of each participant (FDA, client, consultant). The agenda was followed, and during the teleconference, several FDA staff muted their lines for a brief discussion amongst themselves about a few key points. Because only one hour is allocated for such an event, it was necessary to keep the discussion proceeding on topic and on schedule to maximize the benefit for the manufacturer.

This approach essentially allowed for two different types of valuable FDA feedback for the manufacturer: the first feedback in written form regarding the initial documentation package, and the second feedback verbally and interactively, to focus on and clarify the fewer remaining issues. After the teleconference, we drafted the meeting minutes which were first sent to our client for review and then to FDA for agreement and finalization. Although not "binding" this feedback provided our client with clear answers to numerous issues, prior to investing significant time and resources into clinical testing for a new device.

#### Summary

Some simple device application issues can be handled directly (email, telephone) with the FDA group that would review a future submission or the submission already under review. However, in those important times when FDA feedback could reduce some substantial "risk of the unknown" then the Q-Sub process can be used to resolve those more significant issues. FDA continues to standardize the methods for its activities, and these new rules for FDA interaction are important to understand and conduct correctly. Doing so can help get your company's new device through the FDA and onto the US market.

By Ken Block:

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