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YOU HAVE MET WITH THE US FDA - NOW WHAT?

By Elisa D Harvey

Making a positive first impression with the FDA is vital

A previous article in the *Journal of Medical Device Regulation* addressed the issue of how to successfully interact with the US Food and Drug Administration (FDA)[1]. Getting your working relationship with the FDA team who will be reviewing your submissions off to the best start possible is critical because, good or bad, it can have a lasting influence on all subsequent interactions with the Agency. If your first interactions are difficult, acrimonious or ill-prepared, it can take a long time to overcome negative impressions and recover. On the other hand, if your first meeting is well-managed, smooth and mutually informative, you will have gone a very long way towards establishing a long-term, collaborative, efficient and productive working relationship. Needless to say, it only stands to reason that this latter kind of interaction is not only more pleasant, but has the practical advantage of having a higher chance of producing a faster and better result (i.e. getting your product cleared or approved for the US market) than the former.

This article focuses on what to do once you have had an initial interaction – such as a face-to-face meeting – with the Agency. Once you have already spent a lot of time preparing, doing your homework, producing a quality pre-IDE submission, planning and rehearsing a quality presentation and providing specific focused questions, and then finally actually had the meeting, what happens next? You have doubtless received a lot of information from the FDA team that attended the meeting that you now need to digest and determine how to respond. This article examines the various things that can or should occur during and especially after a meeting with the FDA, and how to react to ensure your project continues to move forward.

Documentation of the Meeting

Accurately recording the meeting minutes, in detail, is very important

The single most important 'deliverable' that comes from a pre-IDE meeting with the FDA is the written record of the meeting (i.e. the meeting minutes). Although pre-IDE meetings are not legally binding on either the FDA or the sponsor, and provide no guarantees or formal agreements on any aspect of the discussion, whatever occurs during the meeting and is captured in the ensuing minutes are nevertheless critical guides for how to proceed, and to how the FDA will react to your future submissions. Capturing this interaction accurately and in detail will be most useful as you move forward with pre-clinical bench, animal and clinical testing, as well as submission of marketing applications.

Typically, the Center for Devices and Radiological Health (CDRH) will request that the meeting minutes be taken by someone on behalf of the sponsor. This 'transcriber' can be anyone the sponsor

chooses (e.g. from the company itself or a consultant) but it should be someone who can listen carefully for the duration of the meeting and take copious notes of the entire discussion. It should not be someone who will be likely to be actively participating in or leading the discussion because it is too difficult to both participate and take complete notes.

The notes should include attributions for who said what, specific areas of consensus and/or disagreement, and specific action items and timeframes for both the FDA and the sponsor. Generally, tape recording the meeting is discouraged as it tends not to promote a free discussion and exchange of ideas, nor does a transcript necessarily produce a clearer picture of the overall meeting than a detailed summary of the meeting.

Action points and timeframes should be recorded for the FDA and the sponsor

The meeting minutes should be written as soon after the meeting as possible, ideally within about 72 hours. This draft version of the minutes should be reviewed by everyone on the team who attended the meeting to ensure accuracy and completeness. When these draft minutes are deemed adequate, they should then be sent electronically using a Word rather than Acrobat document to the lead reviewer at the FDA for the pre-IDE, with a request that they and their team review the minutes and provide any comments or edits back to the sponsor as soon as possible. The FDA team may provide a list of comments or they may edit the document using Track Changes. The FDA review can be expected to take 7-14 days. If you have not heard back from the reviewer within this timeframe, the reviewer should be contacted as to the status of the minutes. The obvious reason for timeliness in writing and having the sponsor and the FDA review the minutes is that the attendees have the meeting fresh in their minds. The longer it takes to get the minutes finalised, the more likely they will not completely or as accurately capture the interaction that took place.

FDA's review of the minutes may take 7-14 days to complete

Meeting minutes should be as detailed as possible in order to be useful when they might be referred to one or more years later, when everyone has forgotten what actually took place at the meeting, or the attendees (both the FDA and sponsor) might not even be a part of the team any longer. A one-hour meeting should produce meeting minutes that are around five, single-spaced, typed pages. Fewer than that may mean that there is insufficient detail for the minutes to clearly indicate what happened in case there are any questions later.

Once the FDA provides comments, one of two things usually occurs. The simplest is that the sponsor agrees with the comments and edits made by the FDA, quickly incorporates these changes, and then provides a final copy by email and in hard copy (as a supplement to the pre-IDE) to the FDA as well to their own internal records. The FDA will add these minutes to the official pre-IDE document where they will be able to be accessed and referred to in the future if and when any questions arise. It is important that the version the FDA has in their records matches exactly with the version held by the sponsor.

A final, hard copy of the minutes should be submitted as a supplement to the pre-IDE

Areas of disagreement ideally need to be resolved by the lead reviewer and sponsor

The other possibility is that the FDA provides comments or edits with which the sponsor does not agree. In this case, the lead reviewer and the sponsor (ideally one person from the company) need to begin communicating to address each area of disagreement until all of the issues have been resolved. Most of the time, a mutually acceptable version can be agreed upon. Any remaining disagreement should be addressed by noting it clearly in the minutes as well.

The meeting minutes then become the official record of what transpired at the meeting and should be relied upon as the point of reference for future interactions with the FDA. From experience, meeting minutes have often been invaluable to both the FDA and sponsors in refreshing their memory or clarifying the history of interactions and discussions to new FDA reviewers and new members of the sponsor's team.

Outstanding Questions

One of the other main purposes of a pre-IDE meeting with the FDA is to reduce the uncertainty around key aspects of the device development plan. The specific, focused questions posed to the FDA at the meeting should provide a sponsor with the best opportunity to get feedback from the FDA. During the course of the meeting, if there are any statements made by the FDA that are at all unclear, they should be clarified as soon as possible. Ideally anything that is unclear should be discussed immediately, at the meeting, so that there is a clear understanding of the FDA's position. Getting such issues resolved in the context of the meeting, when all the right people are at the table, is much easier than attempting to recreate the discussion after the event.

Areas requiring clarification are best addressed during rather than after the meeting

If there arise or remain areas of uncertainty that were not sufficiently addressed at the meeting, these should be brought forward as soon as possible after the meeting. Working through the FDA lead reviewer for the pre-IDE is the best way to address these issues. The lead reviewer will contact other members of the review team and management as necessary to be able to answer a sponsor's remaining questions. However, this will take additional time, and obviously it is preferable to avoid having to do this after the meeting by speaking up at the time of the meeting to be sure that all of FDA's statements and positions are unambiguous.

Post-Meeting Action Items

Most meetings will generate a set of action items to be addressed by both the FDA and the sponsor after the meeting. These should be clearly identified at the end of the meeting, and incorporated into the meeting minutes. The timetable and person(s) responsible for addressing any action items should also be explicit.

Sponsors should complete their action items on time

It is important for sponsors to follow through with timely completion of any stated action items for two reasons. First, it will obviously keep the project moving forward more efficiently. Second, it demonstrates to the FDA that as a company you are committed

to working collaboratively with the Agency, which will also help with preserving the project's momentum.

Likewise, a sponsor should also be sure that the FDA holds to the commitments it made during any interaction, whether this is scheduling a follow-up meeting or teleconference, or providing additional information to the sponsor. The CDRH now holds more meetings with sponsors than ever before (upwards of 600 per year) and has many other responsibilities and deadlines to meet other than your project. So the challenge for you as a company is to keep the attention of the FDA and your project as a relative priority without excessively contacting them.

Generally, the FDA is very good about adhering to its commitments and completing the action items with which it is tasked at a meeting with a sponsor. Nevertheless, it is prudent to keep in mind the increasing number of responsibilities (e.g. *Medical Device User Fee Modernization Act* (MDUFMA) review deadlines, guidance and standards development, stakeholder outreach, mentoring and professional development) that FDA reviewers and management have, and to be sensitive to the fact that your project is not the only one in which they are involved.

FDA staff are, in general, very good about meeting their commitments

Follow-Up Discussions

Frequently there will be a need for follow-up discussions on one or more topics after a pre-IDE meeting with the FDA. These discussions may involve any of a number of the members of the review team, including the lead reviewer, medical officer, various engineers (software, mechanical, biomedical), statisticians, or other areas of expertise. It is always highly preferable to work only through the lead reviewer for all such interactions.

Follow-up discussions should be organised through the lead reviewer...

Although you may have the direct contact information available for a specific reviewer (e.g. the medical officer, engineer or statistician), contacting them directly is inadvisable for at least three reasons. First, it is important that the lead reviewer be the steward of the entire project on the FDA side, and if other interactions are taking place with members of their own review team without their prior knowledge or involvement, then they may not be recognised as part of the official correspondence for the project. Second, if you do not involve the lead reviewer in all such discussions there may be a perception that you are not respecting the structure of the team or the role of the lead reviewer in managing the overall project. Third, a consulting reviewer may not see the 'big picture' that the lead reviewer does and, in the course of discussions with you, may provide information or opinions based on incomplete information or incorrect assumptions. It simply is not worth jeopardising a productive and collaborative working relationship, despite the fact that working through the lead reviewer sometimes adds an additional layer and possibly more time to getting such follow-up discussions accomplished.

...for three important reasons...

Sometimes, if specific and highly technical discussions are needed with a member of the FDA review team following a face-to-

face meeting, the lead reviewer may give their permission to contact the consulting team member directly, and only then would this approach be advisable.

Guidance

Many of the issues discussed at the time of, and after, the meeting will revolve around the acceptability of certain kinds of testing of the device. This can apply to bench testing, animal testing and clinical studies. There are a huge number of both horizontal (applicable to many medical areas) and vertical (applicable to all types of testing in a specific device area) guidance documents available for these general categories for many device areas. For a list of available guidance documents, see www.fda.gov/opacom/morechoices/industry/guidedc.htm.

Numerous horizontal and vertical guidance documents are available

Guidance documents issued by the FDA must undergo internal Agency scrutiny for conformance to what is termed Good Guidance Practices (GGPs). The main goal of GGPs is to ensure that guidance documents represent the FDA's current thinking on a topic. As every FDA guidance states in its introduction, they 'do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations'. In other words, guidance documents may not indicate what you must do, or require any particular test or approach, except for that which is already explicitly described in the *Federal Food, Drug and Cosmetic Act* or the Code of Federal Regulations (CFR). They are intended to provide a roadmap for what the FDA finds acceptable in a given area at the time that guidance document was published. To the extent that following this guidance means less uncertainty regarding the acceptability of a certain approach, it is advisable to follow FDA guidance whenever feasible. Likewise, to the extent that such guidance is not followed, the FDA is likely to ask more questions and need more information in order to be assured that any alternative approaches meet the same level of rigor as that recommended in the guidance document. Alternative approaches may actually end up taking more time and effort than a recommended 'conventional' approach, so these should be carefully considered before being undertaken.

Whilst guidance is not legally binding, it is advisable to follow FDA's recommendations whenever possible

It is also important to realise that guidance documents are never really 'final'. They are first issued in draft, in order to solicit comments from interested stakeholders (mainly the regulated industry and professional clinical societies). Once the public comment period is over and comments have been received and reviewed, the guidance document is eventually reissued, taking into account the outside feedback. Even after it has been reissued, guidance documents may be periodically revisited to be updated based on new information. Stakeholders may always provide comments to the CDRH on guidance documents even outside of the specified comment period, although it should be recognised that such feedback may not result in any change to the guidance at all, or may not

Final guidances are periodically updated to take account of new information

until that document is otherwise determined to need updating.

As guidance documents are not legally binding on either a sponsor or on the FDA, this provides the flexibility to explore and entertain alternative approaches. If you believe a particular test or approach that is advocated or recommended within a guidance document is not possible, or needed, you have the opportunity to explore alternative approaches with the Agency. The alternative approach, whether it is another test methodology, or a rationale for waiving a test, must still satisfy the Agency's concerns in that area. However, as science advances, knowledge changes over time and information in guidance documents may simply not be applicable to some devices. If you believe that an approach recommended in an FDA guidance document is not applicable to your device, or that you have a preferred test methodology over what is identified in a guidance document, you should bring this to the attention of the FDA review team at the earliest possible point. After a face-to-face meeting, it is advisable to let the lead reviewer know of your intentions in this regard, before such an alternative approach is included in either an Investigational Device Exemption (IDE) application or a marketing application. Without prior warning to the FDA that you are including an alternative approach from what the Agency would normally recommend, you risk significant delays or possible disapprovals because of the additional questions that are likely to arise. With the opportunity to informally let the review team know of your plan, you can gauge the likelihood of its success or find out what might be needed to ensure its acceptability.

Intended use of an alternative approach should be brought to FDA's attention as soon as possible

What to Do About Disagreements

Occasionally, there will remain disagreements about an approach that cannot be resolved at the time of the face-to-face meeting, or even after follow-up discussions with the review team. Determining the most appropriate course of action with respect to any disagreement obviously will depend on many factors, including:

- the cost of using your preferred approach versus the FDA recommended method;
- the level of risk posed by using your preferred approach versus the FDA's recommended method;
- the magnitude of the 'gap' between your and FDA's thinking;
- how many other disagreements you may have; *and*
- the priority of all of these individual issues.

Appropriate course of action will depend on...

It is important to choose your 'battles' carefully. Not every area of disagreement is necessarily worth arguing indefinitely about. By the time the several months that may be needed to 'win' your argument have passed, you may have been able to use the FDA's recommended approach for less time and money overall. In each case of disagreement a careful risk/benefit and cost/benefit analysis should be undertaken.

A risk/benefit and cost/benefit analysis should be performed

Once you determine that you want to pursue 'dispute resolution', the next step is to determine the most appropriate avenue

for that resolution. For resolving any dispute or disagreement with the FDA, it is *always* advisable to start with the most straightforward and simplest avenue possible. This usually means a request (by telephone or in writing, by mail, email or fax) for supervisory oversight by the next manager up in the chain of command. Typically this means an interaction with the Branch Chief or Deputy Division Director. It is almost never productive or helpful to go straight to the Center Director for a solution to every problem; in fact, this may be counterproductive in the long-term as it does not allow for the possibility of a solution by working directly with the review team. Often, if a sponsor contacts the Center Director for resolution of a problem, the Center Director will first 'down-delegate' the issue to the division or office anyway, before agreeing to meet with a sponsor.

First step in dispute resolution is supervisory oversight by Branch Chief or Deputy Division Director

If the disagreement is not resolved to your satisfaction after attempting to work with a Branch Chief or Deputy Division Director, there is the option of contacting the Division Director or Director of CDRH's Office of Device Evaluation (ODE). In this case you should be prepared to assemble a comprehensive, clear and concise written description of the situation, all of the steps taken to that point, why the current scenario remains unsatisfactory, and what you believe is a reasonable solution. You should also be prepared for this route to take a minimum of six to eight weeks of additional time. This, and the possibility that the supervisory chain of command may uphold any previous review team positions, should be factored in when determining how far to pursue any areas of disagreement with the FDA.

Referral to Division Director or ODE Director may take an extra six to eight weeks

There is also the option of contacting the CDRH Ombudsman to participate and facilitate any such interactions. More information about the CDRH Ombudsman is available on the FDA's website at www.fda.gov/cdrh/ombudsman. Sponsors can request that the Ombudsman participate in any meetings held to address the disagreement. There are also more formal procedures for addressing disputes. However, formal dispute resolution tends to be a much lengthier process and can involve public proceedings. Therefore, they should only be utilised when all other avenues for resolution of the dispute have been exhausted.

CDRH Ombudsman may also be requested to participate in meetings

Top 10 Tips for Maintaining Momentum After Meeting with the FDA

1. Complete comprehensive and accurate meeting minutes in a timely fashion and share them with the FDA so that there is a single, mutually agreed upon version of the meeting.
2. Complete all action items with which you have been tasked in the timeframe identified at the meeting.
3. Keep in contact with the lead reviewer to be sure that the FDA completes all of its stated action items.
4. Always be sure to work through the FDA lead reviewer for facilitating any follow-up interactions even if the primary person you need to communicate with is not the lead reviewer.

5. Do not expect to be able to have many follow-up discussions since the Agency is already working at its limits because of all the other meetings and follow-up discussions it is having with other sponsors.
6. Document every follow-up interaction (whether by phone, fax or email) as carefully as you would the original face-to-face meeting.
7. Remember that FDA guidance is just that – guidance - not law or regulation. Use it to your best advantage.
8. Choose your battles carefully. Not all areas of difference between a company and the FDA are worth pursuing indefinitely - evaluate the cost/benefit for every area of concern.
9. For resolving any disputes or disagreements with the FDA, start with the most straightforward and simplest avenue possible (i.e. request a review of the situation by the next manager up in the chain of command, which is usually the Branch Chief or Deputy Division Director). Do not go directly to the Center Director for a solution to every problem.
10. If you do determine that going to the Division or Office Director is necessary to resolve a dispute, you should be prepared to assemble a comprehensive, clear and concise written description of the situation, the steps taken to that point, why the current scenario remains unsatisfactory, and what you believe is a reasonable solution. Be prepared for this route to take a minimum of six to eight weeks of additional time.

Points to bear in mind...

A full, written report of the situation is required for Division or Office Director review

Summary

Having a meeting with the FDA to discuss your device development plan is only the beginning of what could potentially be a long working relationship with the Agency. There are many steps to take after the meeting that are just as important as the preparations leading up to the meeting and the meeting itself. To keep your device development plan on track, it is critical to take the right steps after a meeting to capitalise on the momentum achieved by this first interaction. It is important to make the most, not only of the meeting itself, but also the post-meeting activities and interactions.

It is important to capitalise on the momentum achieved by the initial meeting

Reference

1. *Journal of Medical Device Regulation*, 2007, **4**(2), 20 (May 2007).

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