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RESOLVING DISPUTES WITH YOUR US FDA REVIEW TEAM

By Elisa D Harvey

FDA's dispute resolution process is more flexible than the term may imply

Dispute resolution is a very formal term for the mechanisms available to sponsors when they have been unable to resolve a difference of opinion with their Food and Drug Administration (FDA) counterparts on a specific submission. However, this is really a much more flexible and customised process than the term might imply. This article is intended to provide helpful information for sponsors on how to go about solving the problem of a difference of opinion with an FDA review team.

Guidance Documents

It is important to be aware of the guidance that is available from the Center for Devices and Radiological Health (CDRH). There are three documents listed below that are most relevant and with which sponsors should be familiar. There are two additional guidances available regarding disputes that may also be of interest: one from the CDRH on the resolution of disputes regarding user fees[1] and a second from the FDA's Office of Combination Products on disputes regarding timeliness of combination product premarket reviews[2]. However, this article will focus on disputes relating to scientific issues. The most important guidances in this respect are the following:

Three main guidance documents relating to scientific disputes...

- *Resolving Scientific Disputes Concerning the Regulation of Medical Devices, A Guide to Use of the Medical Devices Dispute Resolution Panel; Final Guidance for Industry and FDA*, dated 2001 (www.fda.gov/cdrh/resolvingdisputes/1121.html);
- *Medical Device Appeals and Complaints*, dated 1998 (www.fda.gov/cdrh/modact/dispresl.pdf); *and*
- *Guidance for Industry: A Suggested Approach to Resolving Least Burdensome Issues*, dated 2001 (www.fda.gov/cdrh/ode/guidance/1188.html).

A fourth document of which sponsors should be aware is the Agency-wide regulation describing how to request a regulatory hearing (Regulatory Hearing; Code of Federal Regulations (CFR): Part 16 (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=16)). This regulation is often referred to in regulatory submission disapproval letters to sponsors.

FDA regulatory hearings usually have lead times of several months

However, an FDA regulatory hearing is a very formal process with a very long lead time (months at a minimum) and, for the vast majority of disputes, it is an extremely heavy-handed and excessive approach. Likewise, the step of going to a CDRH dispute resolution panel meeting should really be the last resort. Before getting to the point of requiring either of these options, there are much more

'friendly' and effective methods of reaching a mutually-acceptable solution to whatever problem has arisen in the review process.

This article is not intended to 'recreate' all of the information available in the above guidances. Rather it is intended to provide helpful ideas for maximising the success of your dispute resolution efforts. Of course, the ultimate dispute resolution is to avoid getting to that point in the first place, through effective communication and planning with the Agency[3,4]. However, if you find yourself with a dispute, there are several important things to keep in mind.

CDRH Ombudsman

Position of CDRH Ombudsman was created in 1998

There is a CDRH Ombudsman just as there is for the rest of the FDA. The position was created in 1998 to provide a clear point of contact for sponsors with a complaint. No one is obliged to contact the Ombudsman with any complaint but the Ombudsman is available should a sponsor wish to have him involved in addition to the involvement of the review team and any other FDA staff. There is a website link available which provides information on the Ombudsman's office and how to contact it: www.fda.gov/cdrh/ombudsman/index.html.

It is important to keep lines of communication as open as possible

In general, the best approach for resolving disputes is to speak directly with the review team involved. In other words, it is best to keep the lines of communication as open as possible with the lead reviewer, their review team and the branch chief. Even if you choose to ultimately involve other parties such as the Ombudsman or supervisory staff (e.g. the Division, Office or Center directors), you will eventually need to go back to working with the review team to implement the decisions made during the dispute resolution process. It will not further the process to circumvent the review team by contacting the Commissioner of the FDA to complain about the problem. The complaint will simply be down-delegated to the level that is most familiar with the issues involved. It is always preferable, both in the short-term interest of solving the immediate issue and longer-term interest of keeping a good working relationship between the review team and sponsor, to deal as directly with the FDA team as possible.

Speed of Resolution

Areas of dispute should always be resolved rather than ignored

Likewise, the sooner you realise there is a dispute to be solved, the sooner the resolution can happen. This may seem self-evident but sponsors have often tried to ignore a problem in the short term in the hope that the problem will somehow go away because the FDA will 'forget' about it or not bring it up again. For instance, waiting to bring up an issue that arises during the review of an Investigational Device Exemption (IDE) until the Premarket Approval application (PMA) is submitted will only delay the PMA. Years may have passed since the initial issue was raised. By this time, everyone will need to re-familiarise themselves with the problem, and valuable time will be wasted that could have been spent more productively at the time the issue was first raised.

Building a Case

Before deciding to move forward with an official complaint, regardless of the mechanism you choose, it is critical to research everything possible about which resolution method will work best for your individual circumstances, how that process will work for you, and what scientific literature and regulatory precedents exist that will both help and hinder your case. If there is clear precedent against your position, you can be sure the Agency will bring it up. It may not be advisable to 'swim upstream' in this way if the Agency has already clearly stated its position on the issue and this position is not in your favour. Either way, you need to be aware of all relevant information before proceeding. Being unaware of such information may cost valuable time and effort by causing a sponsor to move forward with a dispute when there may be no chance of success in resolving it satisfactorily.

Be aware of any regulatory precedents that may exist

Working with the Agency

Although disagreements and disputes are, by nature, frustrating experiences, there is nothing to be gained by uncivil or hostile behaviour. In fact, it is likely to significantly impede the resolution process. Also, although working systematically through channels can be frustrating for a sponsor when they have a dispute they want solved immediately, it is important to recognise the organisational structure, the FDA individual's and review team's jobs, and the mission of the Agency. Staff at the FDA take their jobs just as seriously as you, the sponsor. Maintaining an atmosphere of respect and cooperation will speed up the process and improve the likelihood of a favourable outcome that both the Agency and the sponsor can live with. Lack of respect will break the dispute resolution process down faster than anything else, which will then only add to the time and resources necessary to reach a resolution.

Follow the appropriate channels and respect the Agency's organisational structure

As with any interaction with the FDA, it is absolutely essential to keep detailed written documentation of each and every communication to and from the Agency. This includes emails, faxes, telephone discussions and face-to-face meetings. You should also keep a running log of all these different communications. In addition, there should be only one designated point of contact for the sponsor to deal with the Agency. The more individuals that are communicating back and forth, the higher the potential for confusion and miscommunication. This will only result in prolongation of the dispute resolution process.

A sponsor should have a designated point of contact with the FDA

Once you have gone down the path of dispute resolution because there is a conflict with the Agency that has not been able to be worked out to your satisfaction, this is the most important time to do everything you can to achieve the highest quality communications possible with the Agency. This means making the FDA's job easy in understanding your dispute, presenting your case as clearly as possible, providing as much support for your position as you can, and offering a cooperative environment in which to resolve the dispute. All communications should be clearly and

concisely written (and proofread by multiple people for content, grammar and tone). All presentations to the Agency should be carefully constructed and rehearsed to document your position clearly. Anything you as a sponsor can do to make the Agency's job easier in evaluating the merits of your case will ultimately make the dispute resolution process go more smoothly and quickly.

In your interactions with the Agency, it is critical to have the right people involved. More is not necessarily always better. In other words, you want to have the right people engaged: decision-makers, those individuals most familiar with the specific details of the situation, and those who can most clearly articulate the sponsor's position. This means not automatically bringing the most prominent clinical advisor or consultant you can find, or the highest ranking person in a company who is not intimately familiar with the specific details of the issue. The perception created by this sort of approach, whether intended or not, may be that intimidation is being attempted, which is obviously counterproductive to resolution of the issues.

Care should be taken when selecting the people to be involved in the resolution process

What is the Best Course of Action?

Thorough and comprehensive analysis of the issue is the very first step in deciding whether and how to move forward with a dispute. You may be certain that your position is correct and scientifically defensible, and in fact that may be true, but you should realise that even if you are correct and the Agency ultimately agrees with you, there may be a significant cost in terms of time and resources to get to that point. Sometimes the shortest distance from point A to point B is to acquiesce to the Agency's position, even if you disagree. Every case is unique, and a careful analysis of the pros and cons of disputing versus acquiescing needs to take place before taking any action. There should not be an automatic reaction to move forward with every dispute. The smarter approach is to evaluate the business and scientific implications of pursuing a dispute before going down that road.

Pros and cons of disputing versus acquiescing should be carefully evaluated

Least Burdensome Principles

In addition, especially with respect to dispute resolution, there continues to exist much misunderstanding in the regulated industry of what the Agency's 'least burdensome' regulatory provisions mean. The CDRH's 2002 guidance document on this provision, *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry* (www.fda.gov/cdrh/ode/guidance/1332.html), is the definitive source of information on what 'least burdensome' actually means. This article will not provide a detailed analysis of the concept of least burdensome, but suffice to say the following: the FDA defines the term 'least burdensome' as a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort and resources on the part of industry and the FDA. It should not be thought of as a rationale for circumventing a regulatory pathway or necessary testing.

'Least burdensome' is defined as...

Time and Resources

If dispute resolution is using up too much time and resources, it may be better to accept the Agency's viewpoint

Finally, every sponsor should realise from the outset that dispute resolution takes significant time and resources. If you find you are not making the desired progress with the Agency in making your case and having them agree with your position, at a certain point it may be advisable to cut your losses. The alternative is continuing to pursue a course that will consume valuable time and resources that might be better spent on the path the Agency is recommending. It is not necessary to continue to pursue the dispute resolution process to its last possible point for its own sake, and there should be proactive thinking at every point as to whether it is better to accept the decision or continue to take the dispute resolution process to the next level.

Top 10 Tips for Resolving Disputes

Listed below are 10 main ways of increasing your chances of a successful outcome when working through a dispute with the CDRH:

1. **Keep it local**. In other words, keep the resolution of the dispute as close to the review team or individual(s) as possible rather than going straight to the Commissioner with a complaint about how a reviewer is handling your submission.

Delaying the start of the resolution process may hamper the chances of a satisfactory outcome

2. **Keep it recent**. The sooner disputes are resolved, the better the resolution. The more time that passes between the event causing the dispute and beginning the process of resolution, the less likely you are to have a satisfactory outcome.
3. **Stay respectful**. Although the process of dispute resolution, regardless of the mechanism you use, is inherently frustrating, all parties must remain respectful of individuals, the Agency and the Center's organisation, and the process. Lack of respect will break down the process faster than anything else.
4. **Do your homework**. Understand the mechanisms for dispute resolution, the organisational hierarchy, and any regulatory precedents that may help you make your case.

Maintain a detailed log of all communications with the Agency

5. **Document your efforts**. Once you feel you have a dispute, document and keep a detailed log of every interaction, including emails, faxes, teleconferences and face-to-face meetings.
6. **Make the FDA's job easy**. Do whatever you can to make the FDA's job easier in coming to your conclusion. Write clearly and present clearly.
7. **Involve the right people**. In the process of getting your dispute resolved, engage the people on your behalf who can speak most clearly on the issues, not necessarily the highest ranking person you can find.
8. **Be smart**. Make a careful analysis of whether you want to dispute a decision in the first place. Even if you are right, there are costs in terms of time and resources. Be sure that following the course of dispute resolution is the right one from a business perspective as well as a scientific perspective.

9. **Understand the 'least burdensome' principles**. As the Agency will point out to you, these principles are not a way of avoiding addressing issues but finding the least burdensome method for addressing those issues.
10. **At a certain point, cut your losses**. If at the end of the day the Agency still disagrees with you, it will be necessary to decide whether it is better to accept the decision or take the dispute resolution process to the next level.

Least burdensome principles are not a way of avoiding addressing issues

References

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