Resolving Scientific Disputes with FDA: Regulatory Processes and Practical Tips

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The US Food and Drug Administration (FDA) is a science-based organization that makes decisions based primarily upon thorough and transparent review of the scientific information provided by applicants, existing regulations and previous decisions on similar cases. However, at times, questions have been raised about FDA's conservative approach in review of new and existing products, the differences in FDA's review of a given product compared to that of other regulatory agencies, FDA's disagreements with recommendations of its own independent Advisory Committees, and the influence of political policy on FDA's decisions.

Since these and other factors may influence the opinions and decisions of FDA reviewers, it is not surprising that occasional disagreements between the applicant and the reviewers occur. A negative decision by the agency can impact product development and carry heavy commercial and logistical consequences for the applicant. Equally important, the applicant might feel it has been treated unfairly or that the agency's decision is without scientific merit.

Recognizing that the ability to appeal a decision plays an important role in increasing confidence in its decisions by applicants and the general public, FDA has established well-defined policies and formal processes to address conflicts of opinion both among review team members and between reviewers and applicants. This article discusses processes by which the aggrieved party can initiate an appeal and escalate the dispute, and provides some practical tips about dealing effectively with FDA in a dispute.

Processes for Appeal of Decisions Internally at FDA Emphasize Transparency and Fairness

Under 21 CFR Part 10.70, Administrative Practices and Procedures,[1] FDA employees responsible for handling a matter are responsible for ensuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings and other pertinent written documents. The file must also contain recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter and reveal significant controversies or differences of opinion and their resolution. An employee who has worked on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file.

It further states that the written document must relate to the factual, scientific, legal or related issues under consideration; be dated and signed by the author; avoid defamatory language, intemperate remarks, undocumented charges, or irrelevant matters (e.g., personnel complaints); once completed not be altered or removed; and all involved personnel provided copies of the document. Any other documents related to the matter but not in the administrative file are not considered to have any status or effect on subsequent reviews in case of disputes.

The Staff Manual Guide (SMG) 9010.1, Scientific Dispute Resolution at FDA,[2] provides guidance to agency personnel about the appropriate resolution of internal disputes. The process uses the management chain to escalate the matter step-by-step, all the way to the FDA commissioner. Each FDA center is required to have a scientific dispute resolution (SDR) standard operating procedure (SOP).

FDA expects scientific disputes to be resolved at the working level within the organization whenever possible, after full and frank discussion among interested parties. When resolution is not possible, the manual sets forth the process for appealing the decision by submitting the case for review by the Office of Accountability and Integrity and a final decision from the commissioner. The appeals process must be completed within 90 calendar days and may be accelerated at the discretion of the commissioner.

At all times, staff that initiate or engage in disputes are protected from retaliation by their supervisors, peers, senior leaders and anyone else. The SMG does not supersede the fundamental protections of the *Whistleblower Protection Act* of 1989, the *Federal Employee Antidiscrimination and Retaliation (No FEAR) Act* of 2002 and all applicable federal laws, regulations and Executive Orders that afford protection under the law.

Based on 21 CFR 10.70 and SMG 9010.1, each center has developed formal policies and practices specific to the activities at the respective center to address resolution of disputes. For example, Center for Drug Evaluation and Research (CDER) Manual of Policies and Practices (MAPP) 4151.1, 4151.2, 4151.8 and 4150.1 address the various elements of CDER-wide practices[3-6] for dispute resolution. These MAPPs go into much greater detail than the SMG, providing better insight into the processes followed by agency reviewers in case of a scientific disagreement. Similarly, Center for Biologics Evaluation and Research's (CBER's) Standard Operating Procedures and Policies (SOPPs) 8005, Major Dispute Resolution Process,[7] describes the processes followed at CBER. Similar SOPs exist for Center for Devices and Radiological Health (CDRH) as well.[8]

Processes for External Dispute Resolution are Well-Defined

While primarily focused on internal dispute resolution, the SMG and the MAPPs include provisions for a sponsor to request review of a decision by the FDA division or center director. In addition, each center provides processes that an applicant can use to formally appeal a

decision by FDA reviewers, ranging from contacting the ombudsman at the individual center to requesting independent review by an outside panel, advisory committee or the Office of the FDA Commissioner.[9-11] Based on the request and supporting materials, the center either grants the appeal and initiates a reevaluation of the decision internally or denies the request and provides an explanation to the sponsor.

In the end, if all measures to resolve the matter via the above processes are exhausted or deemed unproductive, the sponsor has the right to take legal action against FDA.

Tips for Nonconfrontational and Scientific Discussions

These formal processes for dispute resolution should be the last resort, and should be preceded by informal communications with the review team such as emails, written responses to review comments and additional information submissions to try to resolve scientific dispute. A nonconfrontational, scientific, peer-to-peer discussion whereby each side attempts to convince the other using logic and reason can go a long way in finding an amicable solution to a given situation.

I suggest the following ground rules for dispute resolutions with the agency.

1. *Regulatory history of a given product is cumulative.* All prior discussions with the agency and information provided by a sponsor for a given product are considered by the reviewers in making their decisions. So, it is very important for the sponsor to carefully plan all interactions with the agency, knowing they will be evaluated during the review. Agreements made at a meeting with FDA usually need to be kept. Any changes to the agreed-upon plan should be carefully considered and, if possible, an update agreement with the agency should be obtained before implementation. Making major changes to the agreed-upon plan without providing sufficient rationale to the reviewers not only creates confusion but also gives the perception of incomplete disclosure of information. This can raise the reviewers' suspicions.
2. *All data available for a given product is relevant to FDA's scientific review.* All data for a given product submitted by a manufacturer plays a role in FDA's final decision about that product. Hence, complete reports of all studies conducted are expected. Incomplete reports or partial disclosure could be

perceived as the sponsor trying to hide critical information about its product and should be avoided. It is important to be straightforward and open with the reviewers, as the same group most likely will continue to review the product throughout its lifecycle.

3. *Timely completion of project deliverables is important.* Regulatory has often been called a "moving target" where policies, review guidelines, criteria for review, etc. change over time as new products come for review to FDA. Hence, any clinical program that takes more than a reasonable time post first FDA submission could lead to a perception of incompetent teams, concerns by investigators or Independent Review Boards regarding the clinical trials, recruitment issues, etc. All these could lead to concerns with the reviewers. In case of longer than usual delays, the agency should be kept in the loop regarding the developments in the project, reasons for delay with request for changes and adaptation to the plan as needed.
4. *Periodic discussions with FDA are a must for all programs.* Perhaps the best way to avoid conflict is to have good communication with the reviewers. Addressing FDA concerns in a timely manner could exponentially increase the chance of a positive decision. FDA meetings are perhaps one of the most valuable tools available to a manufacturer to increase the likelihood of securing approval for a given product.[12] Regulatory strategy should always be confirmed directly with the agency before or early on during implementation.
5. *Conflict resolution should be systematic.* FDA's suggested processes for conflict resolution should be followed appropriately. The best strategy is to try to work with the reviewers to address their concerns about validity of the data by providing additional information. Aggressive approaches using legal threats and coercion seldom work. If the data are being challenged based on a scientific basis, there are two ways to resolve the challenge: a scientific peer-to-peer discussion between your subject matter experts and FDA reviewers to understand the concerns and provide an explanation; and to identify the missing data and fill those gaps with newly generated data from additional clinical trials or other methods.
6. *FDA is neutral about your product.* A common misconception by applicants is misunderstanding FDA's negative feedback as misdirected criticism. Most accusations of unfair treatment arise from the applicants feeling that the FDA reviewers are biased against their product. FDA is mandated with protecting patients and consumers in the US. It is FDA's job to make sure that all products available to patients have adequate justification for safe and effective use. FDA reviews are neutral with regard to the commercial success or failure of a given product. So, when FDA reviewers have comments about your product, the manufacturers are served better by listening and trying to resolve the scientific issues.

Scientific disputes, like all other disputes in life, are multi-dimensional. Usually the best solutions are the simplest and involve thinking with a cool head and honestly considering the other party's opinion. The key is to avoid defamatory language, intemperate remarks, undocumented charges or irrelevant matters (e.g., personnel complaints). Since the sponsor has far more to lose than the review team in case of a negative outcome, it bears the burden of making the effort to make sure a dispute does not devolve into non-scientific arguments.

References

1. FDA Administrative Practices Regulations, 21 CFR 10.70 and 10.75 and the FDA-NTEU Collective Bargaining Agreement (CBA)
2. FDA Staff Manual Guide 9010.1, Scientific Dispute Resolution at FDA.
3. CDER MAPP 4151.1 Revision 1. Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain.
4. CDER MAPP 4151.2 Revision 1. Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.
5. CDER MAPP 4151.8 Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions.
6. CDER MAPP 4150.1, Role and Procedures of the CDER Ombudsman.
7. CBER SOPP 8005, Major Dispute Resolution Process.
8. CDRH SOP for Resolution of Internal Difference of Opinion in Regulatory Decision Making. FDA website. http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOmbudsman/ucm183860.htm. Accessed, 6 Feb 2011.
9. Resolution of Difference of Opinion. FDA website. http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOmbudsman/ucm113713.htm. Accessed, 6 Feb 2011.
10. Formal Dispute Resolution: Appeals Above the Division Level. FDA website. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf. Accessed, 6 Feb 2011.
11. Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMPs. FDA website. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052502.pdf. Accessed, 6 Feb 2011.
12. Meeting with the FDA Can Increase the Probability of Product Approval, *Regulatory Focus*, Oct 2010, Pages 22-27.

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