Arnall Golden Gregory LLP
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AGG Webinar

FDA Formal Dispute Resolution Above the Division Level: I Fight Authority, Authority Always Wins (or Does it?)

Presented by Alan Minsk

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I Fought the Law

- Part of the Food and Drug Administration Modernization Act of 1997 – now section 562 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360bbb-1)
- Also 21 C.F.R. § 10.75
  - a sponsor, applicant or manufacturer of a drug or device may request review of a scientific controversy by an appropriate advisory committee
- For clarity, we will start out with disputes regarding drugs and biologics and then medical devices

It's Only You and Me and We Just Disagree

- Draft guidance – Formal Dispute Resolution: Appeals Above the Division Level (March 2013)

  www.fda.gov/downloads/drugs/guidancecompliancereg ulatoryinformation/guidances/ucm343101.pdf

- Attempt to resolve scientific and procedural disputes that cannot be resolved at the division level review

Here I Am, Stuck in the Middle with You

- What can be appealed:
  - Scientific and procedural matters, such as:
    - refusal to approve
    - clinical hold
    - refusal to enter into a Special Protocol Assessment
    - trial design requirements
    - applicability of statistical principles

Meet the New Boss, Same as the Old Boss

- FDA strongly recommends that the sponsor should try to resolve differences at the division level
- Consider a post-action meeting with the division or asking the division for reconsideration
- **Important** – *Because all FDA decisions on any dispute must be based on information already in the relevant administrative file, no new information should be submitted as part of a request for reconsideration appeal*
  - *if the sponsor has new information that may affect the original decision, any appeal should be deferred until the new information has been submitted to the administrative file and reviewed by the division*
  - *new analyses of data previously reviewed should be considered new information and, therefore, should be submitted to the division for review before being submitted as support for an appeal*

It's a Hard Knock Life

- FDA is clear that it will not grant an appeal for formal dispute resolution if a meeting with the revision division is planned, or if new information is presented that has not been reviewed by the division
- Can also request a Type A meeting as part of the appeal
- Can request that a scientific dispute be reviewed by an appropriate advisory committee

Fight the Good Fight

- How to Submit
  - written request with background package
  - nice touch is to tell CDER or CBER an appeal request is coming
  - slight variation on formalities between CDER (amendment and CDER Formal Dispute Resolution Project Manager), and CBER (work through CBER Ombudsman)

Turn the Page

Supporting Background Information

- Identification of the submission as FORMAL DISPUTE RESOLUTION REQUEST in bold, uppercase letters
- The application number (e.g., IND, NDA, BLA, ANDA), if applicable
- The proprietary and/or generic name and established name for drug products; proper name and trade name for biological products
- The division or office where the application is filed

Turn the Other Page

- The proposed indication(s), if applicable
- A brief, but *comprehensive* statement of each issue to be resolved, including:
  - a description of the issue to be resolved
  - identification of the issue as scientific, procedural, or both
  - a statement of the steps that have been taken to resolve the issue, including any previous informal and formal dispute resolutions
  - identification of possible solutions, including, for scientific issues, whether an advisory committee review is requested
  - a statement of whether a Type A meeting is requested
  - a statement of the proposed outcome

Are You With Me So Far

Supporting Background Information (cont'd)

- A statement identifying the division and/or office that issued the *original* decision on the matter and, if applicable, the last management level and official who attempted to formally resolve the matter
- A list of documents previously submitted to FDA that are deemed necessary for resolution of the issue, with reference to submission dates, so the documents can be readily located
- A statement that the previous management level has received and had the opportunity to review all of the material relied on for dispute resolution
- The name, title and contact information (i.e., mailing address, email address, telephone number, fax number) for the sponsor contact for the appeal

The Waiting is the Hardest Part

FDA Action

- Written decision with a response to all components of the appeal
  - grant an appeal
  - deny an appeal
  - agree with some
  - suggest an alternative resolution
- Possible interim response if needed for clarifying information or meeting request with the sponsor

Under Pressure

Timelines (focusing on PDUFA products)

- FDA should complete the review and provide a decision on the appeal within 30 calendar days from receipt of the appeal
  - FDA should respond to the sponsor within the 30-day window in writing or by telephone (i.e., *30-day response*)
- If a sponsor requests a meeting as part of its appeal, the meeting request should be treated as a Type A meeting
  - under the PDUFA meeting goals, FDA should either grant or deny the meeting request within 14 calendar days of receipt of the appeal
  - if the meeting is granted, FDA has 30 calendar days after the meeting date to provide a decision on the appeal
- There may be instances where the FDA needs additional clarifying information or input from the other persons knowledgeable in the matter to reach a decision
  - if the meeting is granted, FDA has 30 calendar days after the meeting date to provide a decision on the appeal

Time Passages

- Where FDA needs additional clarifying information from the sponsor, a request for this information should be sent within 30 calendar days from receipt of the appeal
  - FDA should make a decision on the appeal within 30 calendar days from receipt of the information to the administrative file
- Where FDA decides a meeting with the sponsor is needed before a response can be issued, a meeting request should be sent within 30 calendar days from receipt of the appeal
  - after the meeting is held, FDA should make a decision on the appeal within 30 calendar days from the meeting date

Time Passages *(cont'd)*

- When FDA requires limited discussion with one or more members of an advisory committee or internal or external experts, FDA should inform the sponsor of this plan within 30 calendar days from receipt of the appeal
  - after this limited discussion is held, the agency should make a decision on the appeal within 30 calendar days from the date of the discussion
- Where FDA requests an advisory committee review, and the drug is a human drug application covered by PDUFA, FDA should inform the sponsor of this plan within 30 calendar days from receipt of the appeal
  - FDA should make a decision on the appeal within 30 calendar days after the date of the advisory committee meeting

Don't You Cry

Advisory Committee Review

- If a sponsor seeking resolution of a scientific dispute requests advisory committee review of the matter, FDA should determine whether such review is appropriate
- If the request for review by an advisory committee is granted, the matter should be brought to the next scheduled advisory committee meeting, where there is time available on the agenda for adequate discussion of the issue
- After receiving the advice of the appropriate advisory committee, FDA should notify the sponsor of its determination on the matter within 30 calendar days
- If FDA does not grant the request for advisory committee review, it should notify the sponsor in writing of such decision, including the reason for the denial and any steps the sponsor may take to persuade the agency to reverse its decision

It's a Heartache, Nothing But a Heartache

- If a sponsor's appeal is denied at one management level, the sponsor can appeal the same issue to the next higher management level in the chain of command in the center
- After exhausting the center's management levels, a sponsor can request review of the center's decision by the FDA Commissioner
  - requests for such review should be submitted to the FDA's Ombudsman

Some Examples
The Winner Takes It All, The Loser Has to Fall

- Combination of two approved drugs
- Complete Response Letter issued by Division, requiring data from large clinical outcomes trial to rule out specific safety risk
- End-of-Review meeting required "unprecedented," "not feasible," study design
- Formal Dispute Resolution Response provided reasonable and feasible study design criteria and said approval possible on interim data
- Post-appeal-SPA engagement with Division on study design

Another Example

- Background
  - previously approved drug
- Pre-appeal Discussions
- FDRR
  - Dispute Appeal Denied
    - agreement with Review Division
  - "Dispute Appeal Denied on next level
    - **But** – recommended submission of new analyses to Review Division and consideration by Advisory Committee
- Post-Appeal
  - Resubmission and Advisory Committee, which voted to approve
  - Ultimate Approval

And Now for Something Completely Different… Medical Devices

In the Beginning

Center for Devices and Radiological Health Appeals Processes - Guidance for Industry and Food and Drug Administration Staff
(May 2013)
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm284651.htm

Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A - Guidance for Industry and Food and Drug Administration Staff
(July 30, 2014)
www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm352248.htm

Even it Up

- Dispute resolution and review of adverse decisions for medical devices typically takes the form of "supervisory review"
  - supervisor of CDRH employee will, at the request of an interested or aggrieved party, review decision of employee
- Direct requests for supervisory review go to the next level above the level at which decision was made
  - Branch → Division → Office → Center → Commissioner
- Supervisor decision likely will take one of the following forms:
  - overturning decision of employee
  - upholding employee decision
  - referring matter back to employee for reconsideration

In the Long Run

- Request for supervisory review of a "significant decision" must be submitted no later than 30 days after initial decision
  - guidance refers to phrase as "517A decision" including the following:
    - 510(k) : NSE, SE
    - PMA/HDE: Not Approvable; Approvable; Approval; Denial
    - IDE: Disapproval; Approval
    - Failure to reach agreement on a Protocol
    - Clinical Hold Determinations
  - no provision for extensions or waivers
  - more flexibility for non-significant decisions (appx. 60 days)

It's Alright to Cry

- Format: No required/specified format, but generally:
  - executive summary with documents attached, executive summary may include:
    - statement that review is being requested [with level of review]
      - e.g. review is being requested with the Director of ODE
    - request for in-person or teleconference
    - request for review authority to convene a meeting of relevant advisory panel
    - clear statement of issue and discussion of why relief should be granted
    - Mark as "Appeal"
- Scheduling: Mandatory vs. Discretionary
  - significant decisions: generally must schedule to occur within 30 days of request
  - non-significant: up to review authority whether or not to grant

Talk a Walk on the Wild Side

- Telescoped and Parallel Review
  - Telescoped: Supervisor performing review may reach out to individuals at a higher organizational level
    - especially if regulatory/policy/complex question
  - Parallel: Company with a request for review pending with Center may wish to engage in a discussion with review team in order to resolve issues under dispute before review process is complete
    - strongly discouraged by the FDA
- Conclusion: inssuance of decision letter, which describes:
  1. Basis for the request for review
  2. Decision of review
  3. Basis for decision
  - usually contains recommendations for further actions to resolve matters in dispute and options for the review/appeal

Go Your Own Way

- Medical Devices Dispute Resolution Panel
  - provides independent review of scientific controversy or dispute between a stakeholder and FDA
- Petitions
  - petitions may be filed to request that FDA take or refrain from taking an action, to reconsider a decision, or to place in abeyance an action pending further consideration
  - citizens petitions can be filed by any person to challenge FDA action or decision
- Hearings
  - availability depends upon specific circumstance of the case
  - generally more time-sensitive than other forms of dispute resolutions
- Judicial Review
  - if petitioner brings judicial action relating to a matter subject to a pending review, FDA Commissioner may request the court refer the matter back to the agency

Lawyers, Guns and Money

AGG Observations

- Is it worth it?
  - time, expense, and relationship with FDA to consider
  - have you truly exhausted options with the Review Division
  - do you have a good case
    - basis for overturning or modifying previous decision
    - alternative suggestion or proposal to get FDA out of box
- Be patient and focused
  - keep your eye on the prize and try to keep emotion out of it

Lawyers, Guns and Money *(cont'd)*

- Be realistic
  - this is an FDA process → the tie typically goes to FDA
    - have you heard about the lonesome loser
  - might need to go higher up in the chain to more senior FDA levels to achieve real benefit
  - expectations → think possible compromise, and not necessarily a complete win, although winning completely is possible
    - a nod is as good as a wink
  - might move things forward and lead to some resolution, even if not a complete win
    - and a win is not necessarily an approval of a product application; it is merely a review of the initial decision

Lawyers, Guns and Money *(cont'd)*

- Be a healthy skeptic
  - know the weakness in your arguments
  - be weary of the Beautiful Baby Syndrome
  - soon as I find myself a crystal ball
    - think of FDA's concerns

If you can't handle me randomly blurting out song lyrics that relate to what you just said, we can't be friends.

"All in favor of ditching the suits and forming a rock band, say 'aye'."

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not if, but how.®