

Effective Responses to Avoid Warning Letters

The following sentence fragments represent but a very small sample of trumpet calls heralding that a firm may have fumbled an opportunity to avoid a Warning Letter after receiving an FDA-483:

- “We have reviewed your response and have concluded that it is not adequate because...”
- “The adequacy of the response cannot be determined because the response did not include...”
- “Your response does not address...”
- “We have reviewed your firm’s response and note that it lacks sufficient corrective actions regarding...”
- “We have reviewed your firm’s responses; however we continue to have concerns related to your firm’s compliance...”
- “The adequacy of your firm’s response cannot be determined at this time...”
- “Your response is inadequate because...”

We say this because of the following: while a response to an FDA-483 is not mandatory and does not represent a final Agency determination regarding firm’s compliance, a firm’s voluntary response often does impact the Agency’s conclusion of the need for follow-up actions, one of which may be the much feared and dreaded Warning Letter. How so, you ask? Here is how....

As the FDA indicates in section 5.2.7 of the *Investigations Operations Manual*, “If FDA receives an *adequate response* to the FDA-483 within 15 business days of the end of inspection [emphasis added]”, FDA will conduct a detailed review of the response before determining whether to issue a Warning Letter. Alternatively, responding late negates any chance that the FDA will consider the firm’s responses in its resolution regarding whether a Warning Letter is warranted and not responding at all, of course, has the same outcome as responding late.

This brings us to the quality of the response itself. In this context, the higher the “quality” of the response, the more likely the FDA will consider the response as “adequate” and, as a result, may not issue a Warning Letter. Since the firm’s management controls the quality and timeliness of everything that goes on, we suggest that the following guidelines be used to craft the response to the FDA-483 to increase the firm’s chances of avoiding the Warning Letter:

- Train the individuals involved in the FDA-483 response effort regarding what information should be included in the response and the format chosen to present the response.
- Assign someone to review recent FDA Warning Letters to identify those items where the FDA indicates that the response to the respective FDA-483 was not adequate and include these items in the training to ensure that known mistakes/failures are not repeated.
- Focus on evaluating the extent of the observation in terms of whether the issue could have potentially impacted data integrity, and, if so, whether the issue is systemic (e.g., how many studies, batches, sites, etc. could be possibly affected). This is the most important point to address in terms negating the observation or softening the impact of the observation. If an observation points to actual data integrity issues, these issues need to be brought to the attention of the respective sponsors, where applicable, and responses to the FDA should be discussed with them first.

- Establish the true root cause of the observation. In doing so, look for the operational gap (e.g., inefficient project management oversight) that resulted in the regulatory deficiency (e.g., lack of timely document reviews and/or approvals) so that it can be fixed properly and permanently.
- Provide specifics regarding any corrective actions taken or proposed. It is not adequate to state that the problem was or will be corrected. Details regarding 1) what was/will be corrected (e.g., development of a remediation plan), 2) when it was/will be completed and 3) if applicable, the timeframe for training (e.g., as in case of a revised procedure) should be provided.
- Describe preventive actions that will minimize or eliminate the chance of recurrence of the problem in the future.
- Provide supporting documentation for every claim made.
- Show commitment regarding implementing all of the proposed activities by 1) specifying activities to be taken and target dates for their completion, 2) assigning accountability for the actions, 3) ensuring proper completion of each respective activity through internal audits.

The quality of the response to the FDA-483 is also important for another reason: groups like FOI Services request the Establishment Investigation Reports (EIR) and FDA-483s through the FOIA, so this information eventually winds up in the public domain. The firm can request that its FDA-483 response be published along with the FDA-483 itself, in which case the response should be such that it gives confidence not only to the FDA but also, where applicable, to existing and potential clients, that non-conformities have not and do not impact data integrity.

The bottom line is this: Do not ever get yourself in trouble with the FDA. But if you do, avoid unforced errors by 1) taking the time and making the effort to respond to the FDA-483, if you get one, in a timely fashion, 2) using the guidelines above in doing so, or 3) calling Emma Barsky and Len Grunbaum, the partners of The Practical Solutions Group, LLC (www.practicalsolutionsnj.com) for further assistance.