Responding to an FDA Form 483
A Five-Step Approach

by Taylor Burtis

When the US Food and Drug Administration (FDA) inspects your company’s biomanufacturing facility, investigators use the FDA Form 483 to record observations and findings (1). Such inspections typically review all good manufacturing practices and good laboratory practices (GxP) quality systems documents. If those investigators find compliance issues, they deliver a summary of their observations and findings using a Form 483, a copy of which will be provided to your company at the end of the inspection visit.

How to Respond

An FDA Form 483 is issued to a firm’s management at the conclusion of an inspection when investigators have observed conditions that in their judgment may constitute violations of the US Food, Drug, and Cosmetic (FD&C) Act and related acts. FDA investigators are trained to ensure that each observation noted on a Form 483 is clear, specific, and significant. The form’s language states each observation without a great deal of additional information. You will have to wait for a targeted establishment inspection report (EIR) to be sent to your company 30 days after the inspection for details related to those observations (2).

Receipt of a Form 483 should be viewed as an opportunity. It represents a key test of your inspection readiness procedures and processes. This event can serve as a chance for you as a regulatory compliance executive to correct a few issues your company has not yet addressed or problems that have stalled. A Form 483 has the effect of generating a certain degree of focus that should be channeled constructively. We use the following five-step approach to guide our clients through the Form 483 response process.

Five Step Approach

Step 1: As an experienced regulatory compliance executive, use the closing meeting with FDA investigators to clarify findings outlined in a Form 483. You need to fully understand the basis for each finding and gather as much specific information as possible while investigators are on site.

Remember, the investigators’ findings reflect their observations at the time of the inspection, so it is important to gain clarity. Investigators are making observations based on limited information and perceptions developed within a very short span of time. The closing meeting is where such open, nonconfrontational discussions should take place.

Step 2: Assemble a response team comprising representatives from the departments or areas where findings were identified in the 483. Review the Form 483 findings as a team and make sure that everyone is interpreting the observations in the same way. This is why each observation needs to be clarified at the closing meeting of the inspection visit.

As the regulatory expert on the team, identify the regulation/directive or guidance to which each observation is linked. That will help in writing and focusing your response.

Assign a subject matter expert (SME) lead and author to each observation. As quickly as possible, those SMEs will need to collect as much background information and data as they can about each observation. You need to determine quickly whether new data, equipment, or personnel will be needed to support your company’s response. Focus on identifying the root cause of each observation. Depending on the citation, that may take some careful detective work.

Remember, based on the FDA’s 2015 Investigation Operations Manual...
Be REALISTIC when describing the timeline requirements for remedial actions. Do not overpromise and underdeliver.

Investigators are human and could have misinterpreted what they observed. If investigators came to a misperception based on what was presented during their inspection, state why an observation is incorrect and present data supporting the correct perception. Send your response to the FDA following the instructions given to you by the investigators at the close of the inspection.

Step 5: As a regulatory compliance SME, you must consider and discuss with your team whether you need to request a meeting with your assigned FDA review division. Perception is extremely important: You want the agency to understand that your company takes the Form 483 observations seriously and has robust quality systems in place to meet GxP compliance requirements.

A formal dispute resolution process is outlined in a 2013 draft guidance (3). In addition, a 2015 guidance provides a mechanism for requesting a meeting with the agency (4).

Final Dos and Don’ts

As a regulatory SME, do not allow your company to become complacent if you did not get a Form 483 at the end of an inspection visit. That does not necessarily mean everything is GxP compliant. It simply means that on the day of inspection, investigators observed no noncompliance issues. Conversely, if your company is issued a Form 483, do not allow your colleagues to underinterpret (e.g., that the observations are the only noncompliance issues) or overinterpret (e.g., because there were observations, GxP processes are broken). An FDA inspection — whether or not a Form 483 is issued — provides an opportunity for you to refocus attention on the adequacy of your existing quality systems and look for improvement opportunities. Finally, use the Form 483 experience as a learning tool, and consider it to be an audit report that you did not have to pay for directly.

References


Taylor Burtis is a senior consultant of BioProcess Technology Consultants’ advanceONE Division and has over 30 years of regulatory and senior management experience. She can be reached at 12 Gill Street, Suite 5450, Woburn, MA 01801-1728, 1-781-281-2701; info@bptc.com.

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