FDA 483 Responses—Suggestions for Industry

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“Global Regulatory Viewpoint” addresses various regulatory and compliance topics including newly published regulations from a global perspective. The content in this column is intended to be useful to those who deal with pharmaceutical development, development of CMC dossier sections, and guidelines for manufacturing, validation, and CGMPs. The objective of this column: Useful information.

Reader comments, questions, and suggestions are requested to help us fulfill our objective for this column. Readers are invited to submit manuscripts for publication in this column. Please contact column coordinator Richard Poska at richard.poska@abbott.com or journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are discussed in this article:

• Anita Richardson, of the US Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), discussed topics associated with writing an effective Form 483 response during a January 2009 meeting in Las Vegas, Nevada
• The FDA 483 is the official recording of FDA investigator observations from an FDA inspection
• Responses to FDA 483 are not legally required; however, responses are strongly recommended
• Responses may mitigate an FDA compliance decision for further action
• Responses demonstrate understanding and acknowledgment of the observations
• Responses demonstrate a commitment to correct or voluntarily comply with corrective actions
• Responses establish credibility with FDA
• Failure to respond, inadequate responses, or failure to adhere to promised corrective actions make a firm susceptible to aggressive regulatory or legal actions by FDA such as product seizure, legal injunction, and other actions
• After an inspection, an action plan should be quickly developed to address each observation
• Effective responses should include a commitment statement from senior leadership, address each observation separately, provide corrective action accomplished or planned, be specific, complete, realistic, and deliver on commitments
• Effective responses must be timely, include time-frames for correction, verification methods, and monitoring of corrections
• Effective responses should include science-based supporting documentation
• The Enforcement Story, Fiscal Year 2008 summarizes FDA compliance activities during 2008 and provides useful statistics
• Firms should be familiar with their incoming materials and product supply chain
• Firms should fully understand the interactions of the processes and systems that impact quality, safety, and effectiveness of their products.

INTRODUCTION
A January 2009 presentation by Anita Richardson of the US Food and Drug Administration’s Center for Biologics Evaluation and Research (CBER) (1) discussed topics associated with writing an effective Form 483 response. These included the regulatory framework...
for FDA policies for writing an FDA 483; reasons for submitting well-reasoned, complete, and timely 483 responses; suggestions for activities following an FDA inspection and 483 observations; and suggestions for an effective 483 response. The fact that FDA specifically addressed this topic suggests that a significant part of the industry has not been successful in basic current good manufacturing practice (CGMP) compliance and subsequent responses. FDA 483 observations remain at a high level; responses to 483 observations are not technically sound; and, deficiencies are often not adequately corrected resulting in subsequent regulatory action. The issuance of 483 observations and subsequent warning letters undermine FDA confidence that a firm can consistently manufacture safe and effective products.

**FDA 483 DEFINITION**
The FDA Form 483 (or “483”) is the official recording of FDA investigator observations from an FDA inspection. It is presented to the organization being audited at the conclusion of an inspection. The FDA 483 is the starting point for this discussion. The observations of the investigator should be the clear focus of the 483 response.

**FDA AUDIT PRIORITIZATION**
Prioritizing sites for inspection has been a long-standing challenge for FDA managers. In the past, FDA district offices have identified specific sites in their geographical areas for inspection each year. These decisions were made based on a variety of informally applied factors, including, for example, a district manager’s knowledge of the inspectional history and corporate culture of the district as well as the perceived risk to the public health of manufacturing errors. Even before the CGMP initiative, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) prioritized the use of inspectional resources. Three categories of facilities were identified as high priority for inspections: Sterile drug product manufacturers, manufacturers of other (non-gas) prescription drugs, and new registrants that have not been previously inspected. A more complete discussion of the FDA risk-based approach to inspections is referenced (2).

**WHY SUBMIT A 483 RESPONSE?**
If your firm has been audited and the FDA investigators have presented management with a 483, what should be done? The first consideration is whether or not to develop a response to the 483 and submit this response to the agency. Ms. Richardson’s presentation clearly stated that responses to FDA 483 are not legally required. However, her presentation indicated that responses are strongly recommended. Responses are recommended for the following reasons:

- Responses may mitigate an FDA compliance decision for further action, such as an untitled letter or a Warning Letter. As a general rule, a warning letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the letter have been corrected (2).
- Responses demonstrate to FDA and other stakeholders an understanding and acknowledgment of the observations
- Responses demonstrate to FDA and other stakeholders a commitment to correct or voluntarily comply with corrective actions
- Responses establish credibility with FDA.

An FDA 483 contains the investigator’s observation and is not the final agency decision on the “observation.” It is thus imperative that a written response be submitted to the agency in a timely manner and prior to the agency’s final decisions on the merits of the observations. Failure to provide a response to an FDA 483 leaves you at the mercy of the investigator’s observations and demonstrates an inept attitude toward compliance. Firms that fail to respond to an FDA 483, submit an adequate response, or fail to promise corrective actions are placed on an aggressive inspection schedule—with low tolerance for non-compliance. Failure to respond, inadequate response(s), or failure to adhere to promised corrective actions place a firm on a collision course for aggressive regulatory or legal actions by FDA.

Although not required, responding to 483 observations is the best way to prevent escalation of actions that FDA can take against a company. These actions can include seizure of product, legal injunctions, not able to execute government contracts, failure to be issued export certifications, approvals of other of the firm’s pending new drug applications (NDAs), license suspension, refusals for export, and increased regulatory inspection frequency. A company should also consider the unpredictable intangible effects of bad press, such as was seen with the KV Pharmaceutical regulatory actions (4) that resulted in a significant financial loss to the St. Louis-based company in late November 2008.
WHAT TO DO FOLLOWING AN INSPECTION

A firm has many options as how to respond to a 483 that is issued following an inspection. The following are some suggestions based on Ms. Richardson’s presentation:

• Develop an action plan to achieve immediate, short-term and long-term correction and to prevent recurrence (i.e., corrective and preventative action [CAPA])
• Know when to seek outside assistance
• Assess each observation
• Focus on specifics
• Focus on system-wide implications
• Focus on global implications
• Consider affected products
• Consider root-cause analysis
• Focus on the regulatory requirements associated with the observation.

Some other considerations include assembling appropriate data to form the basis for all actions. There should be a scientific and technical basis for actions whenever possible. The applications of observations to similar products produced in the same facility should be considered. Voluntary removal of suspect product(s) from consumer channels should be considered, as well as the voluntary shutdown of operations if deficiencies warrant such action.

After the FDA inspector has left the company premise, one of the best actions a company can take is to immediately assemble a team, including management and legal counsel (if concerns are severe), to evaluate and confirm a full understanding of the concerns that the inspector has noted in the 483. Once there is internal consensus on the issues, the actions can be broken into those needed to specifically write the 483 response (short-term correction) as well as the long-term correction, which should include steps to prevent the recurrence of the issue. In the case where the company truly believes that the observation is not warranted, it is best to tactfully voice the concern during the closing meeting and when preparing a thorough, scientifically-based, and thoughtful reply.

ADDRESSING 483 OBSERVATIONS

Ms. Richardson’s presentation (1) provided eight suggestions for effectively responding to a 483. These include the following:

• Include a commitment statement from senior leadership
• Address each observation separately
• Note whether you agree or disagree with observation
• Provide corrective action accomplished or planned; tell FDA the plan. Firms should be specific (observation by observation), complete, realistic, able to deliver what is promised, and should address affected products.
• Provide timeframes for correction
• Provide method of verification and/or monitoring of corrections
• Consider submitting documentation of correction when reasonable and feasible
• Be timely.

A well-written and carefully prepared FDA 483 response, founded in science, provides the agency with a documented record of a firm’s commitment to compliance. Further, the firm demonstrates seriousness in responsibility and its desire to manufacture safe and effective products under the agency’s jurisdiction. It is important to not over-promise and fail to deliver—by doing so; a firm’s credibility can be seriously tarnished.

Of course, it is always best to avoid receiving 483 observations during an inspection. Common sense “soft skills” such as being respectful to the investigator and acknowledging an understanding of the inspector’s concerns can influence the final action of the investigator. It is always a good idea to confirm at the end of each day what concerns that the inspector may have so as to minimize surprise observations. However, if a 483 is issued, then it is important to consider assembling a multi-functional team to consider the strategy for addressing the concerns as well as a timetable for corrections. It is in the company’s best interest to treat the 483 responses with high priority.

INDUSTRY PERFORMANCE

FDA issued The Enforcement Story, Fiscal Year 2008 (5) in March 2009. This document provides a good overview of industry compliance performance during 2008. For example, the most frequently cited categories of FDA observations during 2008 are presented in Table I.

FDA WARNING LETTER REVIEW

A total of 104 warning letters have been posted on the FDA website (www.fda.org) associated with CGMP violations during 2008 (6) and were issued to drug product manufacturers, active pharmaceutical ingredi-
Global Regulatory Viewpoint.

**Table I:** Most frequently cited categories of FDA observations.

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>21CFR Reference</th>
<th>Deficiency</th>
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<tbody>
<tr>
<td>887</td>
<td>211.22(d)</td>
<td>OCU responsibilities</td>
</tr>
<tr>
<td>709</td>
<td>211.100(b)</td>
<td>Adherence to production procedures</td>
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<tr>
<td>618</td>
<td>211.110(a)</td>
<td>Production procedures (validation)</td>
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<tr>
<td>553</td>
<td>211.100(b)</td>
<td>Laboratory controls</td>
</tr>
<tr>
<td>518</td>
<td>211.100(a)</td>
<td>Written procedures for production</td>
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<td>506</td>
<td>211.192</td>
<td>Investigations</td>
</tr>
<tr>
<td>478</td>
<td>211.165(a)</td>
<td>Testing and release</td>
</tr>
<tr>
<td>456</td>
<td>211.25(a)</td>
<td>Personnel qualification and training</td>
</tr>
<tr>
<td>449</td>
<td>211.188</td>
<td>Batch record preparation and review</td>
</tr>
<tr>
<td>397</td>
<td>211.67(b)</td>
<td>Equipment cleaning and maintenance</td>
</tr>
</tbody>
</table>

The FDA considered the response dated March 26, 2008, addressing the deviations from the inspection observations as inadequate because the firm failed to provide sufficient information to fully assess the adequacy of the proposed corrective actions. Furthermore, the information submitted to address many of the inspectional observations only indicated that the observations will be corrected; however, a specific timeframe for implementing the proposed corrective actions was not indicated.

Table II lists randomly selected warning letters issued to major companies in 2008 available on the FDA website. It all cases, the warning letter specifically stated deficiencies in the firms’ responses to the FDA 483. Again, this indicates the need for industry to improve their responses to FDA 483 observations.

**OTHER FDA ACTIONS**

The FDA Enforcement Story (5) also provides examples of other FDA actions following and much beyond an FDA warning letter. These demonstrate the breadth of enforcement tools used by FDA to enforce drug CGMPs. The following incidents may have begun with issuance of an FDA 483.

**Example One**

The following example is cited in the FDA Enforcement Story (5):

“At the request of the FDA, on October 31, 2007, US marshals seized more than $300,000 worth of product, including an antifungal product and other drugs for human and animal use, dietary supplements, and ingredients to make those products. These products were seized because some lacked FDA approval and all were maintained under grossly unsanitary conditions. All of the finished products and raw materials were deemed adulterated. The FDA considered NC Solution to be a drug because it was intended for use in the diagnosis, cure, or treatment of disease in people or animals. NC Solution was also a new drug because it was not generally recognized as safe and effective for its intended uses.

“This action was the culmination of concerted efforts by FDA to get the firm to follow the law when it comes to manufacturing safe products for consumers. In August and September, FDA inspectors found that the company was still
manufacturing drugs and dietary supplements under unsanitary conditions, including findings of insects and rodent filth on and around manufacturing equipment despite warning by FDA of similar serious violation in 1999. Following the 1999 inspection, a company official told the FDA in January 2000 that the firm would stop manufacturing drugs.

“The FDA’s action against the company was consistent with the Agency’s initiative on unapproved drugs, which pose potentially harmful risks to consumers.”

Example Two
The following example is cited in the FDA Enforcement Story (5):

“On May 27, 2008, FDA requested that a pharmaceutical firm of Miami, Florida recall all Xiadafil VIP Tabs sold in eight tablet bottles (lot #6K029) or blister cards of two tablets (lot #6K029-SE1) because the products contained a potentially harmful, undeclared ingredient that may dangerously affect a person’s blood pressure and can cause other life-threatening side effects. Although labeled as a dietary supplement and touted as “all-natural,” Xiadafil VIP Tabs were an illegally marketed drug that contained a potentially harmful, undeclared ingredient. FDA chemical analysis revealed that Xiadafil VIP Tabs contained hydroxyhomosildenafil, which is an analog of sildenafil, the active ingredient in Viagra, an FDA-approved prescription drug for erectile dysfunction (ED). The undeclared ingredient may interact with nitrates found in some prescription drugs (such as nitroglycerin) and can lower blood pressure to life-threatening levels. Consumers with diabetes, high blood pressure, high cholesterol, or heart disease often take nitrates. ED is a common problem in men with these medical conditions.

“The safety and effectiveness of Xiadafil VIP Tabs is unknown. The product was promoted, sold over the Internet, given away as free samples at trade shows, and sold in health food store nationwide. On May 13, 2008, Florida officials issued a “stop sale” action at a distribution facility. This action required the firm to hold, intact, violative Xiadafil VIP Tabs found on-hand at the facility. The State of Florida’s action to control the supply of the product, coupled with the formal requires by FDA to recall this product from the marketplace, further reduced the likelihood that unsuspecting consumers would use this potentially dangerous product.

“Alternative products like Xiadafil VIP Tabs were often sought out because they were marketed as “all natural” or as not containing the active ingredients in approved, prescribed ED drugs.

“Because the manufacturing source of the active ingredients in many of these alternative products is unknown, consumers should also be aware that the FDA has not verified the safety, efficacy, and purity of these ingredients.

“On July 24, 2008, US federal marshals seized nearly $74,000 worth of Xiadafil VIP tablets. The seizure action protected the public from dietary supplements containing prescription drug ingredients that are potentially harmful.”

Table II: Randomly selected warning letters presented to major companies.

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<th>#</th>
<th>API</th>
<th>Drug product</th>
<th>Country</th>
<th>Procedures/records</th>
<th>Scientific approach</th>
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CONCLUSIONS
The January 2009 presentation by Anita Richardson provides useful suggestions for a framework for responses to observations. Companies should focus on problems based on risk analysis. Review of warning letters indicates ongoing problems with basic GMP requirements. Review of warning letters further indicates widespread problems with responses. Following Ms. Richardson’s suggestions should help improve quality and comprehensiveness of responses. Recent FDA and International Conference on Harmonisation initiatives, including quality by design, indicate the need for better technical understanding of products and processes. This understanding should be the basis for responses to observations when appropriate.

Not only should a company focus on problems based on risk analysis, but it should also be familiar with the product supply chain. This includes the API, excipients, and container/closure systems in an effort to fully understand the interactions of the processes and systems that impact quality, safety, and effectiveness of their products. Firms with complete understanding of these parameters, along with a thorough understanding of product parameters and associated quality attributes, will be in a better position to avoid potential FDA 483 observations. In addition, having this kind of substantial product knowledge will be beneficial in a company being able to write clear, valid procedures to manufacture their products within the scope and intent of CGMPs. The considerations must be monitored throughout the product lifecycle (i.e., beginning with development and including clinical manufacturing and continuing throughout the entire commercial life of the product).

REFERENCES
5. FDA, The Enforcement Story, Fiscal Year 2008, Published March 2009.

ARTICLE ACRONYM LISTING
CAPA Corrective Action and Preventive Action
CBER Center for Biologics Evaluation and Research
CDER Center for Drug Evaluation and Research
CGMP Current Good Manufacturing Practice
FDA US Food and Drug Administration
NDAs New Drug Applications
ORA Office of Regulatory Affairs
QCU Quality Control Unit