FDA 483 Responses—Compliance Considerations

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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 guidances 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:

- US Food and Drug Administration current good manufacturing practices (CGMPs) provide fundamental requirements for pharmaceutical manufacturing
- The FDA 483 is the official recording of FDA investigator observations from an FDA inspection
- An inadequate inspection response is the primary reason for warning letters being issued in 2008
- FDA's Anita Richardson (Center for Biologics Evaluation and Research) discussed topics associated with writing an effective Form 483 response at the 5th Annual *FDA and the Changing Paradigm for HCT/P Regulation* conference in January 2009
- Responses to FDA 483s are not legally required; however, responses are strongly recommended
- Responses may mitigate an FDA compliance decision for further action
- Responses demonstrate understanding and acknowledgement 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, should address each observation separately, should provide corrective action accomplished planned, and should be specific, complete, realistic, and deliver on commitments
- Effective responses must be timely, include timeframes for correction, verification methods, monitoring of corrections, and supporting documentation
- FDA has implemented a Warning Letter Close-out Program
- *The Enforcement Story, Fiscal Year 2008* summarizes FDA compliance activities during 2008 and provides useful statistics
- Firms should be very 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
- As part of responding to FDA 483 observations, firms should also assess their general internal compliance programs—Why were 483 deficiencies not detected internally?
- FDA 483 observations may be caused or intensified by inadequate audit management (i.e., logistics, timelines of responses, documentation retrieval, etc.) as well as soft "people" skills.

INTRODUCTION

The United States Congress enacted requirements that all drugs must be produced in accordance with current good manufacturing practices (CGMPs) more than 40 years ago. These requirements were intended to address significant concerns about substandard drug manufacturing practices by applying quality assurance and control principles to drug manufacturing. The last comprehensive revisions to the regulations implementing CGMP requirements occurred more than 25 years ago. In addition, pre-market approval requirements, pertaining to chemistry and manufacturing controls, have also been in effect for many years to ensure quality manufacturing of approved drugs. The CGMP and pre-approval programs have been extremely successful, and pharmaceuticals produced for American consumers are recognized as the world's gold standard for safety and effectiveness.

To ensure the quality of drug products, the US Food and Drug Administration has made an increasing number of commitments to programs, systems and initiatives to carefully monitor drug manufacturers' compliance with CGMP regulations. For many years, FDA has enforced CGMP as part of its overall drug quality assurance program. The approval process for drug marketing applications (i.e., original and abbreviated new drug applications and antibiotic) includes a review of the manufacturer's compliance with CGMPs. More recently, FDA has assumed additional roles in the area of assurance of drug quality involving good manufacturing practice through such programs as the Government-Wide Quality Assurance Programs for drug purchase contracts by the Department of Defense and the Veterans Administration, and the Maximum Allowable Cost (MAC) program of the Department of Health and Human Services (HHS). Decisions regarding compliance with CGMP regulations are based upon inspection of the facilities, sample analyses, and compliance history of the firm. These data are summarized in profiles that represent several years of history of the firms. In consideration of the growing number of programs dependent upon CGMP assessment, agency policy must be consolidated in regard to approval or disapproval of drug marketing applications, government purchasing contracts, etc., and the relation of such determinations to regulatory action.

CGMP deficiencies supporting a regulatory action also support decisions regarding non-approval of drug marketing applications, government purchasing contracts, candidates for MAC, etc. Therefore, the issuance of a warning letter or initiation of other regulatory action based upon CGMP deficiencies must be accompanied by disapproval of any pending drug marketing application, or government contract for a product produced under the same deficiencies. Similarly, disapproval of any drug marketing application, government contract, etc., based upon CGMP deficiencies must be accompanied by regulatory and/or administrative action against any other product produced under the same conditions.

An analysis by Hogan & Hartson cites inadequate inspection responses as the top reason for warning letters

to be issued by FDA (1). This emphasizes the timeliness of a presentation by FDA's Anita Richardson of the Center for Biologics Evaluation and Research (CBER) that discussed topics associated with writing an effective Form 483 response (2). 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 this topic has been specifically addressed by FDA suggests that a significant part of the industry has not been successful in basic 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.

Although a firm's response to a FDA 483 represents an internal group effort, the quality organization of a pharmaceutical or medical device company shoulders the major responsibility for providing an adequate response. In addition to responding to each specific observation, the quality organization should look beyond these observations. The quality assurance (QA) organization must address the 483 in a comprehensive manner. In brief, why were the observations not addressed as part of the organization's compliance program and why did the internal audit program not identify the deficiencies? Were these systemic problems or were they the result of poor audit management during the regulatory agency visit? These and associated questions should be addressed by the quality and compliance organization.

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 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 agency 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 (3).

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 483s 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 (4).
- Responses demonstrate to FDA and other stakeholders an understanding and acknowledgement 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.

There is concern on the agency's part that there may be a general lack of understanding as to what the FDA Form 483 represents. It is only one piece of the overall inspection process that the agency employs to make its decisions on the compliance status of the inspected firm.

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 to the agency 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, a hold on approvals of other of the firms 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 regulatory actions (5, 6) that resulted in a significant financial loss to the St. Louis-based company in late November 2008.

A company also needs to recognize the importance of handling GMPs in terms of disclosure to its shareholders. In 1999, Schering-Plough recalled an inhalation product due to manufacturing deficiencies. In 2001, the company disclosed the full extent of its manufacturing problems which apparently were more severe than originally reported and resulted in FDA withholding final approval for a new product. This resulted in lower earnings and prompted a class action lawsuit against Schering-Plough for violating federal securities laws by failing to disclose the alleged depth and severity of manufacturing issues. The lawsuit was settled for $165 million (7).

HOW DOES FDA PROCESS 483 RESPONSES?

Responses to FDA 483s are handled internally by the agency as follows.

If the agency receives the Form FDA 483 response prior to submitting the draft "final" warning or untitled letter to Office of Chief Counsel (OCC), a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response accompanies the draft "final" warning or untitled letter.

If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" warning or untitled letter, the center may notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) may be submitted to the assigned attorney, added into the case file for the proposed action within Compliance Management System (CMS). The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any change to the proposed letter as a result of the FDA 483 response is discussed with the initiating office.

WHAT TO DO FOLLOWING AN INSPECTION

A firm has many options for responding to a 483 that is issued following an inspection. The following are some suggestions based on Ms. Richardson's presentation (2):

- Develop an action plan to achieve immediate, short-term, and long-term correction and to prevent recurrence (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, one of the best actions a company can take is to assemble a team immediately, 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 (2) provided the following suggestions for effectively responding to a 483:

- 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. Be specific (observation by observation), complete, realistic, able to deliver what you promise, and address affected products.
- Provide timeframes for correction
- Provide method of verification and 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 the inspector may have so as to minimize surprise observations. However, if a 483 is issued, then it is really 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 very high priority.

DISPUTE RESOLUTION

Disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements or during the agency's assessment of corrective actions undertaken as a result of such inspections. As these disputes may involve complex judgments and issues that are scientifically or technologically important, it is critical to have procedures in place that will encourage open, prompt discussion of disputes and lead to their resolution.

Manufacturers are encouraged to seek clarification of scientific or technical issues with the inspection team at any time during an inspection. Although there are existing processes to encourage dialogue between FDA and manufacturers, the processes described in this document apply to CGMP questions raised during inspections and are intended to supplement the dispute resolution processes currently in place, including the following:

- 21 CFR 10.75, *Internal Agency Review of Decisions*. Allows manufacturers to ask for a review of agency decisions at each successive supervisory level through the chain of command, ending with the FDA Commissioner's office.
- Center for Drug Evaluation and Research (CDER)/ CBER guidance for industry entitled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). Describes procedures a sponsor may use to formally appeal disputes to the office or center level

on scientific and procedural issues that arise during drug development, new drug review, and post-marketing oversight processes. The guidance may be found on CDER's and CBER's websites.

- *Investigations Operations Manual* (IOM), Chapter 5, Subchapter 510. Describes processes for discussing inspectional observations with a manufacturer. The IOM is available on the FDA ORA website (8).

INDUSTRY PERFORMANCE

FDA has issued *The Enforcement Story, Fiscal Year 2008* (9) 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 listed in Table I.

WARNING LETTER REVIEW

A total of 104 warning letters were posted on the FDA website associated with CGMP violations during 2008 and were issued to drug product manufacturers, active pharmaceutical ingredient (API) manufacturers, medical device manufacturers, and other firms. These warning letters often included comments on previous industry responses to 483 observations and addressed inadequacies in the responses.

The FDA *Enforcement Story* (9) provides the following example of an inadequate 483 response:

"On May 8, 2008, the FDA Dallas District sent a warning letter to a Texas firm. An inspection conducted January 14 through February 14, 2008, revealed that the methods for the manufacture, processing, packing, or holding of product did not conform to CGMP regulations. The firm was also marketing new drugs and misbranded drugs in violation of the Act. Violations of CGMP regulations included:

- Failure of the quality control unit (QCU) to follow written procedures
- Failure to conduct complete investigations
- Failure to conduct adequate identity testing for API containing tannates
- Failure to provide 100% of the labeled amount of the active ingredient for drug product containing tannates
- Failure to conduct accelerated stability studies as necessary

TABLE I: Most frequently cited categories of FDA observations.

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

- Failure to correct deficiencies in dissolution testing and establishing specifications
- Failure to qualify reference standards used in the testing of products containing tannates
- Failure to maintain stability indicating testing methods
- Failure to establish the reliability of the supplier's analysis.

"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 from major companies available on the FDA website (10). In all cases, the warning letter specifically stated deficiencies in the firm's responses to the FDA 483. Again, this indi-

TABLE II: FDA warning letters citing deficiencies in the firm's response to an FDA 483.

#	API	Drug product	Country	Procedures/ Records	Scientific Approach	Facilities/ Systems	Article Ref. #
1		7	USA	5(2 repeat)	1	1 (1 repeat)	(11)
2		5	USA	2	2	1	(12)
3	2	8	USA	6	2	2	(13)
4		3	Canada	1	2	0	(14)
5	6	18	USA	10	12	2	(15)
6		7	USA	5	2	0	(16)
7		5	USA	4	1	0	(17)
8		12	USA	8	4	0	(18)
9		5	USA	1	4	0	(19)
10		6	India	2	3	1	(20)

cates the need for industry to improve their responses to FDA 483 observations.

A 2009 analysis conducted by the law firm of Hogan & Hartson (1) indicates that almost all of the more than 25 FDA-issued GMP related warning letters were issued because responses failed to adequately address FDA concerns. Their report emphasizes the importance of having a written response that demonstrates a commitment to manufacturing high quality drug products and to implementing a robust quality system with aggressive corrective actions. Other points of the analysis include the following:

- 80% of all warning letters were issued to domestic facilities
- Warning letters to drug product manufacturers exceed those written to API manufacturers
- FDA is taking a more holistic, systematic and risk-based approach to assessing GMP compliance, paying close attention to the quality function, validation, and investigations.

FDA WARNING LETTER UPDATE PAGE

FDA reorganized the warning letter section on its website in September 2009. Changes include the following:

- **New postings.** New postings occur every Tuesday. These are found under "Recently Posted" with the date posted.
- **Closed out date.** The warning letter table includes a "Close Out Date" column.
- **Additional changes.** Additional formatting and navigation improvements to help users search this section.

The FDA "Warning Letters" page can be found at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

Warning Letter Close-Out Program

The Warning Letter Close-Out Letter Program applies to warning letters issued on or after September 1, 2009. FDA may issue a close-out letter to firms when FDA has completed an evaluation of corrective actions done by the firm in response to a warning letter. The letter will not be issued based on the content of the firm's response to the warning letter. The corrective actions must have been actually completed and verified by FDA, usually by a follow-up inspection. If the warning letter contains violations that are not correctable by their nature, then no close-out letter will be issued. Future FDA inspections and regulatory activities may further assess the adequacy of the corrections. If violations are observed during a subsequent inspection or other means, FDA may initiate enforcement action without further notice.

OTHER FDA ACTIONS

The *FDA Enforcement Story* (9) provides examples of other FDA actions following an FDA warning letter. These examples demonstrate the breath 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* (9):

"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 ingre-

dients 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 the 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* (9):

"On May 27, 2008, the FDA requested that a pharmaceutical firm in Miami, Florida recall all Xiadafil VIP Tabs sold in eight tablet bottles (lot #6K029) or blister cards of two tablets (lot #6K029-SEI) 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, 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 stores 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."

THE SITE COMPLIANCE PROGRAM

The cornerstone for the quality assurance organization of a firm is their site compliance program. The program should minimally include the maintenance of procedures, company processes, and policies that may encompass raw material acceptance, product release, and even product recall. The program should outline strategies to ensure compliance by use of tools such as statistical process controls, annual product reviews, corrective and preventative action (CAPA), change management and control, and internal audits, and vendor audit programs. A 483 observation suggests specific CGMP deficiencies implicating one or more of the site quality systems. However, it further represents a deficiency on the site quality program—why did the organization not detect this deficiency before the regulatory agency found

the deficiency? The site internal audit program should be the firm's simulation of an external regulatory agency audit, and a final check on the site quality systems. The importance of a site internal audit program has been recently discussed by O'Donnell (21). FDA 483 observations may also involve the quality organizations of suppliers, outside vendors and contractors, and third party manufactures, adding even more complexity to the entire situation. The 2007-2008 global heparin and glycerin incidents exemplify the complex and far-reaching scope of site compliance programs.

THE REGULATORY INSPECTION MANAGEMENT PROCESS

A company may influence the inspector's judgment regarding the firm's commitment to quality by how the regulatory agency inspection is managed. Is it clear who the lead representative of the company is and who will facilitate the inspection? Usually the soft "people" skills of this person are more of an asset than their actual technical competence. The facilitator role is critical because this person controls the tempo and mood of the inspection. It is important that the inspector facilitator try to keep emotion out of the inspection and be sure that information is supported by hard data. They should ensure that information is provided to the regulator in a timely manner, and that it is the proper information to address the inspector's concerns. When it is necessary to have an expert address the inspector's concerns directly, it is the facilitator's role to ensure that the best person is chosen to address the question and is available to do so. Timely retrieval of supporting documentation is critical during regulatory inspections. For example, how quickly can research and development reports from other site locations be obtained and are appropriate contact people identified? Other considerations such as meeting room facilities, location and atmosphere of the meeting environment, facility tours, computer availability, fax availability, other necessary facilities, etc. should be addressed to prepare for an actual audit.

CONCLUSIONS

The 2009 Anita Richardson presentation provides useful suggestions for a framework for responses to observations, which has been identified as a major reason for FDA to issue warning letters. 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 ICH 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 very familiar with their product supply chain. This includes the API, excipients, and container and 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 for writing clear, valid procedures to manufacture 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). The site compliance program including internal audits and the audit management process are basic to regulatory audit preparedness.

The reader may consult Medina's series on FDA inspection readiness and responses for a more complete discussion of these topics (22,23,24), as well as her "Compliance Handbook for Pharmaceuticals, Medical Devices, and Biologics" (25).

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