

FOOD AND DRUG LAW JOURNAL

*Analyzing the Laws, Regulations, and Policies
Affecting FDA-Regulated Products*

Responding to a Form 483 or Warning Letter: A Practical Guide

*Richard M. Cooper
John R. Fleder*

Responding to a Form 483 or Warning Letter: A Practical Guide

RICHARD M. COOPER *

JOHN R. FLEDER **

I. INTRODUCTION

In general, in responding to a Food and Drug Administration (FDA) Form #483 (notice of inspectional observations, commonly called simply a #483) or to an FDA warning letter, the main goal is to give the agency reason to believe that the responding company henceforth will comply with all of the applicable legal requirements administered or enforced by FDA.¹

FDA employs different procedures for issuing a #483 and a warning letter. A #483 is issued by one or more FDA investigators at the conclusion of a site inspection, and usually is not reviewed by a compliance officer, district director, or an official in FDA's headquarters before it is issued. An FDA warning letter, on the other hand, is issued by a district director or headquarters official of similar seniority, and only after review by FDA's Office of Chief Counsel.² Although a warning letter reflects a greater institutional investment on FDA's part, is approved at a higher level, and, therefore, is a more serious and threatening document than a #483, the same general considerations in forming a company's response to the agency apply to both kinds of document.³

FDA's issuance of a #483 or warning letter signals that one or more employees of the agency actively disbelieve that the company was, or currently is, complying with the

* Mr. Cooper is a Partner in the law firm of Williams & Connolly LLP, Washington, D.C.

** Mr. Fleder is a Director in the law firm of Hyman, Phelps & McNamara, P.C., Washington, D.C.

¹ Form #483 derives from section 704(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 374(b) (2000). For a general discussion of Form #483, see FDA, INVESTIGATIONS OPERATIONS MANUAL § 512 (2005), available at http://www.fda.gov/ora/inspect_ref/iom/ChapterText/510part2.html#512 (last visited Nov. 28, 2005).

For a general discussion of FDA warning letters, see FDA, REGULATORY PROCEDURES MANUAL § 4-1 (2004), available at http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf (last visited Nov. 28, 2005).

Although "Notice of Violation" letters and "untitled" letters, in which an FDA official informs an addressee that it appears to have violated the law, do not receive as elaborate an FDA review before issuance as do warning letters, most of this article's comments about responding to a warning letter apply also to responding to such letters.

In this article, the term "company" is used to include any responding entity or individual, including, e.g., a university laboratory, an institutional review board, a clinical investigator, as well as a manufacturer, packer, or distributor. Similarly, comments referring to "good manufacturing practices" may (with some adjustment) extend to good laboratory practices, good practices for the conduct of clinical investigations, and, in general, good practices for conducting any activity subject to regulation by FDA. Although the obvious focus of this discussion is a #483 or warning letter addressing deficiencies in manufacturing practices, the discussion has relevance to #483s, warning letters, and other regulatory communications addressing other types of issues relating to compliance, such as whether a marketed product previously has been approved or cleared by FDA.

² FDA, REGULATORY PROCEDURES MANUAL, *supra* note 1, at § 4.1 & Ex. 4-1.

³ A #483 "is intended for use in notifying the inspected establishment's top management in writing of significant objectionable conditions, relating to" products or violations of the FDCA observed during an inspection. FDA, INVESTIGATIONS OPERATIONS MANUAL, *supra* note 1, at § 512. Sections 512.01 and 512.02 outline what FDA believes are "reportable" and "non-reportable" observations for purposes of a #483.

law. The company's response should be designed to persuade the agency that the company now is, or soon will be, in compliance, and that a finding of past noncompliance should not lead FDA to expect future noncompliance by the company.

II. GENERAL POLICIES FOR DEVELOPING A RESPONSE

Although it often is appropriate for a company to explain why past noncompliance occurred and why full compliance cannot be achieved instantly, the theme of excusing past or continuing noncompliance generally should be, at most, subordinate to the theme that the responding company has now achieved or will achieve, and then will maintain, compliance.⁴ Because an important part of FDA's mission is law enforcement, the agency generally cannot be expected to tolerate prolonged substantial noncompliance, whatever excuses may be offered for it by the company.⁵

Generally, the benefit of satisfying FDA that the company is on the road to compliance is that, thereafter, the company is likely to be subject only to an ordinary intensity and frequency of inspections, and is unlikely to be the target of an enforcement action based on the earlier violative conduct. The cost of not satisfying FDA is that the company is likely to be subject to extraordinarily intense and more frequent inspections until either FDA's active doubt is removed or the agency takes regulatory action against the company. In addition, failure to remove doubt may delay or prevent approvals of applications to market new products and supplements for modified or additional products.

Despite temptation, the goal of removing FDA's doubt normally should not be compromised by venting exasperation with the agency, seeking to undermine FDA's confidence in its own investigator(s), or trying to show that the agency is incompetent in the relevant scientific or technical discipline. Such digressions are likely to be counterproductive.

The company's response is an attempt to persuade—its task is one of advocacy. Offending the audience is unlikely to achieve a favorable reaction from that audience. Company personnel involved in drafting the response to the agency should imagine themselves in the positions of FDA compliance officials, who receive an endless stream of such responses—sometimes filled with invalid denials of deficiencies, unpersuasive excuses for failures, attacks on the performance and competence of FDA investigators, and unrealistic assertions of lofty commitments and promises of future improvements. Those involved at the company should ask themselves what it would take to persuade *them* that their company henceforth really will comply (not just *try* to comply, but *succeed* in complying and staying in compliance).

Nevertheless, it is crucial to examine whether a blanket agreement with FDA's criticisms of the company's past performance will have serious adverse consequences for the company in future litigation against FDA or others (e.g., plaintiffs in products liability or securities actions). Agreement with FDA's criticisms generally can be used against the company as an admission. FDA usually is more interested in explanations of what a

⁴ Of course, in unusual situations where a company believes FDA may seek punishment for past conduct (through, e.g., criminal prosecution or a civil penalty) or where the circumstances of past conduct are material to other kinds of agency action (e.g., disqualification, withdrawal of approval of a product), it is likely to be desirable to make a full presentation of exculpatory and mitigating circumstances and any other reasons why an enforcement action is unwarranted.

⁵ The agency's willingness to tolerate continuing noncompliance by a company may be increased where the product at issue fills a critical medical need that cannot otherwise be met, the noncompliance does not, to a material extent, adversely affect the ability of the product to meet that need, and the company is making all reasonable efforts to achieve compliance at the earliest feasible time. A company asking FDA to acquiesce in prolonged noncompliance on the ground that the company's product fills a critical medical need that otherwise cannot be met bears a heavy burden of persuasion, and the company should prepare its argument with particular thoroughness and care.

company will be doing in the future to comply with regulatory requirements than in confessions of past sins.

Commonly, however, a shared understanding by the company and FDA as to why observed noncompliance occurred in the past is necessary for agreement that a company's plan for remedying past noncompliance and ensuring future compliance is adequate. Consequently, avoiding damaging admissions, while simultaneously satisfying FDA, often requires considerable thought and careful writing by the company.

Sometimes, the proper way to remove doubt as to a company's commitment and competence to comply with regulatory requirements is to persuade the agency that the asserted basis for its #483 or warning letter is mistaken: that, when FDA examines the situation properly, the agency will conclude there is no basis for doubt about the company's future compliance because there was no earlier violation. The #483 or warning letter may be wrong about what is required by the relevant statute, regulation, guidance document, agency policy, company commitment in a marketing application or other previous interaction with the agency, or accepted standard applicable to the matter at issue. It also may reflect a misunderstanding or disregard by the agency of certain facts or an incorrect factual assumption. It may reflect a scientific error. A district office may be pursuing a legal interpretation or policy contrary to that of the relevant headquarters office. Generally, where it appears that one of these circumstances has led to the #483 or warning letter, the company response should point it out—in the manner most likely to persuade the agency to recognize and acknowledge its mistake (i.e., calmly, respectfully, clearly, cogently, and with supporting citation(s) and documentation).

In most circumstances, the agency has not made a mistake: the deficiencies it claims to have observed are real. In those circumstances, the removal of doubt generally depends mainly on three elements: understanding, commitment, and resources.

A. Understanding the Problem

A showing that a company has the ability to, and probably will, comply with the law generally begins with a demonstration to FDA that the company understands four things: 1) what the applicable law requires, 2) what aspect or aspects of the company's operations were deficient, 3) what the root cause or causes of the deficiency were, and 4) what is needed to bring the company into compliance and keep it there.

1. Applicable Requirements

Fundamental to the company's future compliance is its understanding of what the applicable law requires. Removal of FDA's doubt about a company's ability to comply depends on the company's exhibiting such an understanding to the agency. If FDA continues to doubt that a company really has grasped what the law requires, the agency will continue to doubt the company's ability to bring itself into, and consistently maintain, compliance, no matter what commitments the company makes and what resources it brings to bear on the situation.

Thus, there is a serious credibility cost to an attempt to defend the plainly indefensible—whether an indefensible interpretation of applicable legal requirements or of scientific principles or of factual matters observed by FDA. The attempt suggests that the company truly does not understand what the applicable legal requirements or scientific principles are or cannot face the plain facts, and, in effect, does not know the difference between right and wrong. When a response argues that a deficient manufac-

turing practice complies with good manufacturing practices or quality system requirements, it intensifies doubt by FDA instead of reducing it.

Where the facts and the science are not in dispute, the #483 or warning letter has taken the position that a violation has occurred, and serious adverse collateral consequences are not a risk, generally it is far preferable to acknowledge (or at least not dispute) the violation, and to move on to address the root cause(s) and corrective action(s).⁶

In some fields (e.g., manufacturing, clinical investigations, and laboratory procedures), what the law requires are "current good" practices. Those practices are not specified in the Federal Food, Drug, and Cosmetic Act (FDCA) and are described only in very general terms in FDA's regulations. However, companies can resort to a variety of other kinds of materials, principally FDA guidance documents and professional literature. In those fields, understanding what the law requires involves familiarity with what those materials require. In-house or outside experts familiar with FDA guidance documents and the professional literature may make valuable contributions to a company's response, and may even sharpen and strengthen a company's understanding of the applicable requirements.

2. *The Deficiency*

Ordinarily, a #483 or warning letter specifies a deficiency by quoting or paraphrasing a general requirement and stating certain factual particulars that, in the FDA employee's view, constitute a violation of that requirement. Where the applicable facts are not in dispute, the response should confirm the company's understanding of the nature of the problem observed by the agency, or at least not suggest a lack of such understanding. If FDA doubts that a company understands a problem, it is likely that the agency will doubt that a company's proposed solution is adequate.

If a company truly is confused about the meaning of a poorly worded observation in a #483 or warning letter, it may be wise to call FDA to obtain clarification from the official who signed the document. Oral clarification by FDA may quickly remove the company's confusion, and make possible a timely and effective written response by the company. An assertion in the *written* response that the company does not understand FDA's observation in a #483 or warning letter may be poorly received by FDA, particularly if the agency believes that the company's claim of confusion is unreasonable.

In most circumstances, although a #483 or warning letter signals that a company needs to rectify deficient conditions, it does not signal that FDA has concluded that particular company personnel are unwilling or unable to comply in the future. If asked about specific company personnel, FDA employees usually will state, in substance, that the agency is not in the business of making personnel decisions for regulated companies. Nevertheless, where FDA personnel, in fact, have no confidence in a company's employees responsible for compliance, they may well question the company's ability or willingness to comply and may indirectly convey doubts about particular company employees. Company management should listen carefully for any signals from FDA personnel that question the competence, motivation, or integrity of company personnel. Where senior company management suspects, but is not certain, that FDA distrusts company personnel responsible for compliance, senior management may seek to obtain

⁶ A company undergoing an FDA inspection should be vigilant about hearing and quickly acting on oral comments by the FDA investigator(s). When possible, a company should correct an observed deficiency during the inspection. Doing so may persuade the investigator(s) not to include the corrected deficiency on a #483. Even if the deficiency appears on a #483, the company should ask the investigator to acknowledge on the #483 that the deficiency was corrected during the inspection.

more information by requesting a meeting with FDA officials for an overall discussion of the company's compliance.

There may be circumstances where a company should relieve employees whose performance has been seriously deficient of those responsibilities that relate to the violation(s) observed by the FDA investigator(s). Although generally it is unfair and unwise to treat one or two employees as scapegoats, in some circumstances FDA will not conclude that a company is on the path to compliance until it has replaced the individual(s) who caused the past violations.

These considerations also bear on the question of who should sign a company's formal response to a #483 or warning letter. Commonly, the response should be from the management of the operating unit whose performance is criticized in the #483 or warning letter or, sometimes, if different, the addressee on the warning letter. The company's response should demonstrate the operating unit's awareness of its deficiencies and its willingness and ability to comply henceforth.

Where, however, noncompliance has been observed repeatedly in FDA inspections of that operating unit's operations or where a particular instance of noncompliance is egregious, FDA may strongly doubt the willingness or ability of the management of that unit to achieve and maintain compliance, and a response from that management may leave FDA dissatisfied. In this situation, it may be best that the signatory be a more senior official above the level of the operating unit in which the violation(s) occurred.⁷

It may even be warranted for senior management to demonstrate direct personal involvement in addressing FDA's concerns. Involvement of senior management may be especially beneficial for medical device manufacturers. FDA has been following whether senior managers of device manufacturers are involved in compliance issues.

One way a company can demonstrate to FDA its understanding of a problem is to recount to the agency a search by the company for similar or related problems at the same or other facilities operated by the company. If the agency has observed that certain machinery was cleaned inadequately between batches made during the day shift at a particular facility, the company should investigate and report to FDA whether there has been a similar deficiency in the cleaning of other machinery on that shift, or in the cleaning of machinery on other shifts in the same facility, or at other facilities. This point will be considered further in the discussion of coming into compliance.

Demonstrating an understanding of a deficiency reflects a kind of competence. Earnest good will is not sufficient under the FDCA; those who market regulated products also must show competence, including competence in correcting deficiencies noted by FDA.

3. Root Cause(s) of the Problem

Simply correcting an observed violation and telling FDA that it has been corrected is not, by itself, an adequate response to a #483 or warning letter. FDA has told regulated firms repeatedly that FDA investigators are not a company's quality control department.

⁷ It is theoretically possible, but almost always counterproductive, for a company to have an outsider sign the company's response. Such an approach might be considered where FDA's observations suggest a very real risk of criminal prosecution, the company has very few employees who might sign the response, and any of them who did sign it would risk self-incrimination. A response signed by an outsider surely would be a signal to FDA that conditions at the company are dire, and the agency would have no basis for confidence that current management would achieve compliance. Even in the scenario described, it might be better for a current manager to sign a response that does not discuss past events and only makes statements about the future (e.g., that the company will not operate until an inspection by a reputable consultant shows that it is ready for an inspection by FDA and the agency has an opportunity to conduct an inspection).

FDA expects that, when it reports to a company an observation of an apparent violation, the company will correct that violation *and* seek out (and correct) any similar violations that were not noted by the agency. FDA expects a company to focus on the root cause(s) of the observed violation, so that similar violations that were not observed by FDA will be corrected before the agency discovers them in future inspections.

Critical to persuading FDA that a proposed corrective action plan will address the problem observed by the agency in an adequate manner, and will bring the company into sustained compliance, is a persuasive showing that the plan addresses the root cause or all root causes of the observed problem. The company needs to show the agency, therefore, that it has identified, or at least has made an adequate effort to identify, the root cause(s).

The elements of such a showing to FDA may include: 1) a thorough description of the company's investigation to determine the root cause(s), including any testing that was done; 2) a discussion of alternative theoretically possible root causes that were rejected; and 3) a discussion of any additional circumstances that support the conclusion that the identified root cause is the correct one. The very discipline of describing these elements to FDA may suggest further lines of inquiry or analysis that the company should pursue. A company's exhibition to FDA in the response to a #483 or warning letter of its logical, analytically sound, systematic, and comprehensive approach to identifying the root cause(s) and developing a plan of corrective action(s) is an important element in the effort to remove the agency's doubt that the company can, and will, prevent most deficiencies on its own, will find those that do occur, and will correct them appropriately.

An axiom of adequate systems for the assessment of human conduct is that deficiencies do not just happen; always, there is a cause or set of causes. The logic of the inquiry into the root cause(s) of an observed deficiency in manufacturing practices is a series (commonly, a long series) of questions that begin with "why," such as:

- *Why was the machinery not properly cleaned?* Because the standard operating procedure (SOP) was inadequate. (The inquiry does not stop with the inadequacy of the SOP.)
- *Why was there an inadequate SOP?* Because the machinery had been modified, but the old SOP had not been updated.
- *Why had the old SOP not been updated?* Because nobody thought to update it.
- *Why did no one think to update the old SOP?* Simple human error. This is not an adequate response to FDA. Precisely because humans commonly err, good practice requires that there be *systems* to prevent and correct human error, and other systems to prevent the errors that nevertheless do occur from affecting products shipped for use or other outputs of the regulated activity (e.g., data from a clinical investigation or laboratory procedure). A company's acceptance of "human error" as an adequate explanation for a deficiency reflects its failure to internalize the axiom that there always is a correctable cause. Although sustained perfection is unattainable, a failure to seek it is likely to lead to results that are less than what, in fact, is attainable. The demand of "current good practices" is to use all reasonable means to seek to achieve sustained perfection.
- *Who was responsible for ensuring that the SOP was updated?* If no one was responsible, then there was a deficiency in the assignment of managerial responsibilities. Why was there such a deficiency?

- *Why did that employee not discharge that responsibility?* Was there a lack of knowledge that SOPs must be updated when the subject matter to which they relate changes? In that case, the cause may be that the employee is unqualified for the responsibility—and should be replaced by someone more likely to ensure compliance—or at least needs further training. Why did an inadequately qualified or inadequately trained employee have that responsibility?
- *Was the employee unaware of the modification of the machinery?* In that case, the cause may relate to an inadequate system of internal communications. Why was the system of internal communications deficient?
- *Was the employee simply slow in getting around to having the SOP updated?* In that case, the cause may be a lack of motivation, a failure of communication, or a lack of resources. Why was there inadequate motivation, communication, or resources?

This series of questions can go on until the asking of a further question would be pointless. Identification of when a company reaches that juncture is a matter of common sense and judgment.

Sometimes, despite diligent efforts by the company, the root cause(s) of a problem cannot be determined. Before reaching that conclusion, however, a company should consider using outside resources (e.g., experts in the relevant technologies, systems, or scientific disciplines) to confirm the reasonableness of the company's inability to discover the root cause(s) of the problem. Where the root cause(s) cannot be determined, the response to the #483 or warning letter should describe the company's investigative efforts. The investigation should have been as systematic, comprehensive, and thorough as reasonably could be expected; and the company's response should describe the investigation in a manner that supports an inference that it was adequate even though unsuccessful.

An SOP for conducting investigations of deficiencies might usefully include a checklist of general questions to guide the company's inquiries. Reviewing the checklist may help ensure that an investigation is adequate in scope, depth, and intensity.

4. *A Corrective Action Plan*

Corrective action may encompass many types of action: 1) stop the immediate deficient performance (e.g., by shutting down an operation until it has been brought into compliance); 2) stop any undesirable effects of the deficient performance (e.g., cease shipments and conduct a recall); 3) search for, identify, and stop any similar or related deficiencies in other company operations, and stop any undesirable effects of those deficiencies; 4) design and implement a remedy or remedies for the root cause(s) of the deficiency or deficiencies and intermediate causes; 5) monitor and audit the remedy or remedies to determine whether compliance is achieved and sustained; 6) integrate what has been learned from this experience into other company systems (e.g., the design of products and manufacturing processes, quality control, quality assurance, and compliance auditing procedures, job descriptions, training, and budgeting processes); and 7) document all of the foregoing.

The response's description of the corrective action plan should reflect the company's thorough understanding not only of what is needed to correct the immediate problem, but also of the general principles (part of "current good practices") that should govern any long-term program to correct any observed deficiency. Perhaps the aspect of a response that is most likely to remove agency doubt about a company's future compliance is a

demonstration that the company really has internalized and made operational these general principles. Such a demonstration may support an FDA conclusion that a company has a reasonable expectation of substantial future compliance across the board.

Where the company cannot identify a root cause, the corrective action plan should include elements sufficient to support a reasonable belief that the unidentified cause nevertheless probably has been corrected or, at least, prevented from materially adversely affecting the company's outputs.

Where an observed problem already has been corrected by the time a company responds to FDA, documentation of the correction should be attached to the response. Ideally, a company should discover all its deficiencies before FDA finds them. Where FDA discovers an operational deficiency the company was unaware of, there may be, in addition to that deficiency, a further deficiency in the company's self-corrective system (e.g., quality assurance or auditing). If prior FDA inspections also found deficiencies, the company response might well address how the company will improve its self-corrective system.

If in the course of reviewing its operations a company discovers a deficiency FDA did not include in the #483 or warning letter and presumably is unaware of, the company faces the question whether to report that deficiency to FDA in its response.⁸ In each such situation, a judgment has to be made after consideration of all the relevant circumstances, including the recent history of the company's dealings with FDA. Disclosing the problem (and corrective action) to FDA may help persuade the agency that the company truly is committed to compliance with regulatory requirements, but also may lead the agency to inspect for any additional deficiencies and/or to demand more rigorous corrective action. Failing to tell FDA, however, may lead to serious difficulties with the agency if it later discovers the deficiency and believes the company should have disclosed it previously.⁹

Documentation of a company's actions serves multiple purposes in FDA's regulatory universe. Because FDA is not continuously present on a company's premises, documentation is a critical tool for FDA's performance of its regulatory function. Documentation generally is contemporaneous evidence that the documented activity actually occurred, and it provides useful factual details about the activity. FDA compliance personnel commonly act on the premise that a required activity that has not been documented probably did not occur.

Documentation, itself, reflects an investment of time and effort, and thus provides some evidence of the company's seriousness of purpose in attaining compliance. It also may communicate a company's awareness of the importance of documentation as a part of "current good practices," and the company's awareness of its importance to FDA. In addition, the discipline of creating formal documentation may enhance a company's performance of the documented activity by drawing attention to aspects of it that otherwise might have been overlooked or inadequately considered. Finally, because documentation normally includes the signature or initials of the person responsible for the documented activity, it provides personal accountability and the benefits thereof.

⁸ In some circumstances, a company has a legal obligation to report a problem to FDA, e.g., certain adverse events associated with a drug, *see* 21 C.F.R. § 314.80 (2005); and certain malfunctions of medical devices, *see* 21 C.F.R. pt. 803; and, where a deficiency is sufficiently serious to warrant a recall, FDA expects the recalling company to notify it so that it can monitor the recall and assess its adequacy, *see generally* 21 C.F.R. §§ 7.40-7.59. This article assumes that, in the situation discussed in the text, no such obligation applies, and no recall is involved.

⁹ *See* John R. Fleder, *A Voluntary Disclosure Program for FDA—The Time Has Come*, 54 *FOOD & DRUG L.J.* 389 (1999).

B. *Commitment*

To be persuasive, a demonstration of the company's commitment to achieve and then maintain compliance with applicable regulatory requirements must go well beyond a mere bald assertion to FDA of the company's commitment. In general, and depending on the circumstances, the company should include in its response 1) a well thought out, comprehensive, and reasonably detailed plan for addressing the observed deficiencies in a manner that will achieve and maintain compliance; 2) a reasonably detailed timetable with specific milestone dates; 3) an indication that, if the time for achieving compliance will stretch out over several months or more, periodic interim progress reports will be made to the agency; 4) an expression of willingness to expend the necessary financial and personnel resources to correct the identified problems; and 5) where warranted in a serious case, independent external verification of the adequacy of the corrective action plan and of its current and future implementation.

Talk is cheap—a detailed corrective action plan is not. The quality of the thought (as well as the overall time and effort) reflected in the plan is an indicator of the company's seriousness of purpose. An appropriate investment in the corrective action plan supports an inference that there will be an appropriate investment by the company in its implementation.

Milestone dates establish a basis for accountability. Achieving compliance may depend on a series of steps, some of which may be outside the company's control (e.g., a new machine must be ordered and received; a report must be received from a consultant). A company does not want to, and generally should not, commit to milestone dates it does not have a high degree of confidence it will meet. Yet, a company must be mindful that, for FDA, a company's noncompliance while the regulated activities continue and outputs are produced and distributed becomes progressively less tolerable as time passes. With both perspectives in view, the company should exhibit an appropriate sense of urgency, should propose a reasonable timetable, should fully justify whatever delay will occur, and should be prepared to respond to probing questions and comments by FDA.

In general, in estimating the time needed to achieve compliance, a company should estimate the time needed if all goes well, and then add a margin to provide for unforeseen contingencies. To make an informed estimate of the time needed to achieve compliance, the company needs to understand all of the actions, especially the critical path actions that are part of achieving compliance. The margin should be the smallest period that is sufficient to provide a high degree of confidence that compliance will be achieved within the specified time.

To select an appropriate margin, the company needs to understand the potential bottlenecks and other obstacles to timely achievement of compliance. Consideration of potential obstacles may extend to such matters as financial constraints (where a relatively large expenditure for equipment or the design of new systems may be involved), internal bureaucracy (e.g., processing of new personnel by the human resources department), the time needed to recruit new employees or to train current or new employees on new systems, delays by suppliers, or the time needed to qualify new equipment.

It is far better to set a target date that is realistic and very likely to be met than an earlier one that initially would be more pleasing to FDA but that is not very likely to be met. FDA will note any dates by which the company has promised compliance. Failure to meet the commitment dates probably will erode whatever confidence FDA has in the company's prospects for compliance. Indeed, the agency is likely to view a missed

commitment date as yet another (and more recent) sign that the company cannot be trusted to fulfill its responsibilities.

If FDA believes that a company has allowed itself too much time to achieve compliance, FDA generally will so inform the company, which then will have an opportunity to defend its overall estimate. To some extent, the company's credibility with FDA is likely to depend on the persuasiveness of that defense. Anticipating the defense it may have to make may help a company select an appropriate target date for a commitment.

Consequently, those responsible for preparing the response to FDA may need to consult widely within the company to confirm that all company units whose work is necessary to meet the commitment understand (and agree with) what will be required of them. Where timeliness also depends on the performance of outsiders, they, too, should be consulted and pressed for commitments to specific achievable deadlines.

Written reports generated by or for a company that assess some regulatory aspect(s) of its operations provide transparency and facilitate accountability. In serious cases where, for some reason, transparency is extraordinarily important, it can be increased by providing FDA with copies of specified types of documents generated internally or by consultants.

In some circumstances, sharing with FDA a company's consultant's independent final assessment of the adequacy of the company's corrective action plan or implementation can help reduce the agency's doubts about future compliance. Promises to share with FDA an as yet unwritten assessment, however, may carry a heavy price. For example, if a company promises FDA that the company will share written assessments by an outside consultant, the company bears the risk that one or more of the assessments will not be as favorable as the company had hoped and expected. Moreover, disclosure of such assessments to FDA may make it impossible to protect them from disclosure to other parties in litigation.¹⁰ Therefore, although such sharing with FDA may be warranted, a company should weigh the benefits and risks of such disclosure in the light of its own particular circumstances.

C. Resources

Compliance depends not only on understanding what is required in the particular circumstances and intending to comply, but also on having the resources needed for compliance. Those resources are human and material.

FDA believes that, if a company within its jurisdiction does not have and cannot obtain the resources needed to comply with regulatory requirements, the company should shut down. Willingness on FDA's part to tolerate a temporary out-of-compliance situation depends on the agency believing, *inter alia*, that the company is mobilizing adequate resources to achieve and maintain compliance. Where FDA believes that such mobilization depends on senior management, the agency will have little to no sympathy for the company if it believes that the relevant senior managers are devoting insufficient attention and resources to compliance because they are focused on selling products or other matters.¹¹

¹⁰ Where an outside expert assessment is needed solely or predominantly to enable a lawyer (whether in-house counsel or outside counsel) to provide legal advice or some other legal service, rather than to enable the company to conduct its operations properly, the assessment may be addressed to counsel and may be protected by the attorney-client privilege. An attempt to extend the privilege to documents whose sole or predominant purpose is operational, however, is likely to fail if a challenge is raised in an adversarial setting.

¹¹ Sometimes, a small company appears to be simply incapable of reaching compliance, even if it changes personnel and obtains additional compliance-related resources. In such a circumstance, management needs to consider whether to cease making FDA-regulated products. Continuance of noncompliant operations within FDA's jurisdiction runs the risk of serious enforcement action by the agency.

The human resources needed are, principally, relevant expertise and adequate staffing. To remove doubt by FDA, the company needs to demonstrate that it has the competence and the person-power to solve the identified problems and keep them solved. Where a problem has significant scientific or technical aspects, the company needs to show that it has mobilized or will mobilize people with the relevant qualifications and experience from internal sources or by retaining outside consultants, to address the problem.

Developing and implementing a corrective action plan usually draws employees away from their normal tasks. If those normal tasks must continue at full force, additional temporary staffing, perhaps from other units of the company or from outside firms, may be needed.

Where an element of the corrective action plan is the hiring of additional permanent staff, it is desirable to specify, and to report to FDA in the written response, the job descriptions and required qualifications and experience for the new positions. It also may be helpful to describe to FDA how the new employees will be trained and integrated into the company's operations.

If the success of a corrective action plan depends, to some extent, on the performance of outside suppliers (including consultants), then the plan should contain provisions that support confidence that the outside performance will be adequate. These provisions may address, for example, the qualification and monitoring of suppliers and any special provisions for ensuring the quality of their products or services.

Material resources may include additional spending for particular types of machinery, equipment, or systems. Where relevant, the company response should describe the process for adding these material resources.

The response to a #483 or warning letter reflects a mobilization of the company's resources for self-correction—the resources of knowledge, analysis, and testing necessary to understand what the company must do to achieve and maintain compliance; the managerial resources necessary to formulate commitments; and the operational resources necessary to implement all corrective actions so as to achieve and maintain actual compliance. The company response should reflect, and inspire confidence in, the company's systems for self-correction. To that end, it should reflect a well-organized, systematic approach to solving the problems raised in the #483 or warning letter.

III. THE MECHANICS OF SUBMITTING A RESPONSE TO FDA

On receiving a #483 or warning letter, a company should promptly bring together the relevant knowledgeable employees.¹² Collectively, these company employees should analyze FDA's criticisms, determine whether they are valid, and develop a plan for addressing them operationally and for preparing a timely formal written response to the agency. The plan should include assignment of responsibilities for determining immediate corrective actions, root cause(s), and permanent corrective action(s) (including the time needed for implementation), for implementing all corrective actions at the earliest practical times, and for drafting and reviewing the written response. If additional human resources will be needed (e.g., employees from elsewhere in the company, or outside

¹² In some circumstances, a company may need to consider whether any of the people who may constitute the team for developing the company's response to FDA (and who thereby may become fully aware of other deficiencies in the company's operations) is likely to become a whistle-blower against the company, perhaps due to a grievance against the company or to an impending adverse personnel action or because the employee is offended by the company's approach to dealing with its deficiencies or with FDA.

consultants), the sooner the need for them is recognized and they are engaged, the sooner the company will begin to benefit from their work.

Part of a company's demonstration of competence is the actual written response to the #483 or warning letter. Care is warranted to make sure the response is complete (i.e., responsive to all concerns reflected in the #483 or warning letter), well-organized (e.g., coherently structured, with supporting documents behind tabs or otherwise readily accessible), appropriately detailed, easy to understand, and grammatically correct and proof-read.

Each statement in the response must be factually accurate. The company should check and recheck every factual assertion to make certain there are no mistakes. FDA will look for factual errors. A factual misstatement may indicate sloppiness; in some circumstances, it may raise a question of possible fraud.

FDA generally expects a company to respond to a #483 or warning letter within fifteen business days.¹³ Where possible, a company should respond within that period. Doing so helps persuade FDA that the company has taken seriously the observed violations the agency has brought to the company's attention, and that the company has the will and the capacity to submit a timely response.

Generally, it is better, however, for the company to take more time if it is needed for preparation of an adequate response than to submit a timely but inadequate response. If, before the deadline has run, a company requests an extension for good reason, FDA normally will grant the request. In some circumstances, it is preferable for a company to submit a partial response by the deadline, and to include in the response a commitment to complete the response by a specified date as soon thereafter as possible.

In sum, it is far better to be right than to be quick. Companies should resist the temptation to rush a response to FDA simply to meet an FDA "deadline." Instead, the company should make sure that its response addresses all of the issues raised by the #483 or warning letter, addresses each one adequately (with supporting documentation as warranted), and does not make any promises that cannot be kept.

To whom should the response be addressed? In determining the proper addressee(s), the company should seek to bring its response to the attention of each FDA official likely to be influenced by the #483 or warning letter to which the company is responding, and to avoid offending any FDA employee who may expect to receive either the response or a copy.

Determining the addressee of a response to a warning letters usually is simple. FDA typically states in the warning letter where (and to whom) the response should be sent. Although a company may choose to respond only to the designated addressee, it should consider sending copies to other relevant FDA officials, such as the author of the warning letter.

Typically, a company will address its response to a #483 to the Director of the FDA district office that conducted the inspection. As a courtesy, the company generally should send copies of the response to the FDA investigator(s) who conducted the inspection. If the company knows that other district personnel (such as compliance officers) were involved in the decision to conduct the inspection or will be involved in assessing its results, the company should consider sending each such person a copy of the response. Finally, if the company knows that personnel at FDA headquarters have an interest in the results of the inspection, the company might send those persons courtesy copies of the response. For example, in the case of a preapproval inspection, the company generally should provide the original (or at least a copy) of its response to the reviewer or reviewers of the application that spawned the inspection.

¹³ Some FDA warning letters request a response within ten business days.

Biologics inspections often are driven by FDA's "Team Biologics" in the Center for Biologics Evaluation and Research (CBER). Where CBER was responsible for an inspection assignment, the #483 response could be addressed to the Director of CBER's Office of Compliance.

Occasionally, multiple FDA district offices are involved in an inspection. In those situations, a company probably should direct its response to the Directors of all the districts involved, as well as all relevant headquarters compliance officials.

In submitting a response, the company should consider whether it is providing FDA with trade secrets or confidential commercial information. FDA routinely discloses to the public responses to #483s and warning letters. Companies cannot assume that FDA will shield the company's sensitive information from the public, regardless of whether the company requests confidential treatment.

A company should: 1) consider whether there is any overriding need to include confidential information in the response; 2) where appropriate, delete confidential information from documents submitted with the response, and disclose in the response and on the altered documents that information was deleted for that reason; 3) stamp every document that contains confidential information with an appropriate notation (e.g., "Trade Secrets/Confidential Commercial Information"); and 4) as appropriate, state in the response that it contains confidential information that should not be disclosed to the public.

FDA district offices generally have an open-door policy that welcomes meetings between company personnel and appropriate FDA officials. Receipt of a #483 or warning letter may raise a question as to whether a meeting should be requested. In general, it is desirable for both FDA and company decision-makers to know one another. A serious #483 or warning letter, however, normally does not provide the optimal occasion for a first meeting, but even in that context a meeting may help alleviate FDA's doubt or mistrust. If a very senior company official requests and attends the meeting, it is likely to demonstrate that the agency's concerns have the company's attention.

Apart from emergencies, however, FDA officials generally prefer to see a written response *before* they meet with company personnel. In many situations, a written response will eliminate any need for a meeting. FDA will review the response and may indicate through a follow-up letter whether the response adequately addressed its concerns. If such a letter from FDA is not received within a reasonable period, a follow-up call to the agency is appropriate.

Even where a meeting is needed, a prior written response may narrow, or at least clarify, the issues between the agency and the company so that the meeting can focus productively on addressing those narrowed or clarified issues. A properly worded response also can help set a cooperative rather than adversarial tone for the meeting. Consequently, usually it is a mistake for a company to seek a meeting before the submission of at least a partial written response.

In some circumstances, it is appropriate for a company to meet with FDA before submitting a written response. For example, a company might request such a meeting if it has received a #483 and wants to reduce to a minimum any risk that FDA might issue a warning letter or take other enforcement action before the company submits its written response. A company also might request a meeting before sending a written response if it needs further explanation from FDA before it can prepare an adequate response, and other efforts to obtain an adequate explanation have failed, or if the company believes that its written response is likely to be acceptable to FDA only if accompanied by a face-to-face presentation.

A request for a meeting with FDA (whether before or after submission of the written response) generally should be made by telephone, but should be followed by a letter stating why the requested meeting is warranted, and proposing lists of company and

FDA participants, an agenda, and a duration for the meeting. Of course, the company also needs to consider who its principal speaker(s) will be at the meeting, and what type of presentation will be made (e.g., PowerPoint); and the company participants should be prepared to respond to FDA's questions and requests for commitments, and to enter into a productive discussion with FDA.

Once a company has submitted its written response to a #483 or warning letter, FDA may inform the company by letter that the response has, or has not, addressed FDA's concerns. If FDA is satisfied with the company's response, the company must make sure that it follows through on all of the commitments it set forth in the response. Being told by FDA that the company's response is adequate should not result in the company relaxing its commitment to comply with its obligations. FDA undoubtedly will return for another inspection at some point. Investigators will examine their file on the company before conducting the next inspection, and will check corrections of past deficiencies.

Where FDA's letter informs a company that its response to a #483 or warning letter was deficient, the letter will explain why. In response to such a letter, the company should immediately assess FDA's position and inform the agency by letter, telephone, and/or meeting whether the company agrees with FDA's conclusions.

IV. TAKING AN "APPEAL"

In some circumstances, a company will disagree with the conclusions stated by the district director or headquarters official and conclude, after exhausting pertinent discussions with those officials, that the company cannot reach agreement with them. The company then faces the question whether to appeal the disagreement within the agency, challenge FDA's conclusions in court, or acquiesce in the agency's current position.

FDA has established procedures for taking an appeal within the agency when a company and FDA officials cannot resolve a disagreement. The company may choose to present the dispute to 1) officials in FDA's Office of Regulatory Affairs; 2) the Ombudsman in the FDA Center that is involved in the dispute; 3) FDA's Office of Chief Counsel; or 4) other FDA officials who might be willing to consider the matter, up to FDA's Commissioner.¹⁴

Another option is to sue FDA for declaratory and/or other relief. Challenging FDA in court is expensive and risky, however; and it is likely that the agency will raise procedural and substantive defenses. Even success for the company in the lawsuit may leave FDA enforcement officials with the view that the company is unwilling to comply.

Nevertheless, sometimes a disagreement with FDA is so serious that the costs or other consequences of acquiescing in FDA's position are unacceptable. Further discussion of litigation against FDA is beyond the scope of this article.¹⁵

V. CONCLUSION

A company's written response typically is its first communication to FDA following receipt of a #483 or warning letter. It is the formal beginning of the process of removing agency doubt about the company's current and future compliance. It should be viewed

¹⁴ See, e.g., FDA, Draft Guidance, Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP (Aug. 2003), available at <http://www.fda.gov/cder/guidance/5804dft.pdf> (last visited Nov. 28, 2005).

¹⁵ A company that disagrees with FDA also has the option of waiting until FDA brings an enforcement action, and then raising whatever challenges it has to the agency's conclusions. Because, in general, it is difficult (though not impossible) to defeat FDA in court and because a lawsuit with FDA may be expensive and may generate adverse publicity and adverse reactions among the company's constituencies (including customers and stockholders), most companies seek to avoid resolving their disagreements with FDA in court.

as an opportunity to show FDA that the company has “gotten the message” and can be trusted to fulfill its regulatory obligations with minimal future involvement by FDA. The foundation for a successful response, however, consists of an actual understanding of the problems FDA has identified, a serious commitment to correct and prevent problems from recurring, and the mobilization of adequate resources to accomplish these goals.

