WHITE PAPER

THE TOP THREE MISTAKES TO AVOID WHEN RESPONDING TO AN FDA FORM 483

By David Elder, Vice President Strategic Compliance Services, PAREXEL
ON YOUR MARK: YOU HAVE 15 DAYS TO AVERT A NON-COMPLIANCE CRISIS

For biopharmaceutical and medical device companies, the cost of non-compliance with current good manufacturing practice (cGMP) regulations can be devastating. In addition to compromising patient health and safety, unresolved cGMP problems can land foreign firms on the FDA's import alert list, banning them from shipping products to the US until corrective actions are implemented and verified. And product recalls create a vicious cycle of loss: Remediation costs skyrocket while revenues, reputation and stock prices sink. Last year, one foreign-based generic drug maker struggling with regulatory sanctions at facilities in both the US and India reported a 94% drop in net profit year-over-year.

In the US, the cGMP enforcement process involves a staged escalation that begins with the FDA's Form FDA-483. The 483 is a set of observations regulators compile after inspecting a manufacturing facility and, importantly, before sending a Warning Letter. Warning Letters, while not considered formal agency action per se (Regulatory Procedures Manual, Section 4.1.1) constitute a notice of violations that the agency expects to be corrected. They lay the groundwork for other enforcement actions. The FDA posts all Warning Letters online.

The 483 ("Notice of Inspectional Observations") lists observed conditions or practices that in the opinion of the FDA investigators may constitute violations of law. However, the 483 observations are not a final determination of noncompliance. There may be extensive further review before the agency takes action. Companies have opportunities (both oral and written) during and after the inspection to make their views known, to offer plans to remedy 483 observations, or even to dispute observations they believe inaccurate or not representing violations of law or regulation.

While roughly half of FDA inspections result in 483s, only a fraction of those lead to a Warning Letter or other serious enforcement action. For example, in fiscal year 2014 (10/1/13-9/30/14), the FDA issued a total of 1,617 Form-483s to medical device and drug manufacturers (972 and 645, respectively) but sent out just 208 Warning Letters (114 and 94, respectively). There is not a perfect correlation between 483s and Warning Letters as 1) Warning Letters may be issued without a corresponding 483, e.g. by policy, some potentially violative conditions are not reported on the 483 (see Investigations Operations Manual Section 5.2.3.3; advertising and promotion Warning Letters are typically not associated with an inspection); 2) 483 totals on the FDA's website may not include some reports prepared outside the FDA's automated system; and 3) 483s may be issued in a different fiscal year than the related Warning Letter. But even with those caveats, the data show that a complete and timely 483 Response offers a real chance to avert trouble.

However, there's a catch: Your company only has 15 days to prepare a 483 Response. The FDA will consider your analyses, corrective actions, and explanations when deciding whether or not to initiate compliance actions, but only if you hit that deadline. Submitting a sloppy, incomplete or otherwise inadequate response could make matters worse. And although responding to a 483 is not mandatory, the vast majority of companies do respond. This makes non-responders appear uncooperative, from which regulators likely may draw a negative inference.
Here are three of the most serious mistakes companies make and how you can avoid them:

1. **Tunnel Vision**

   Yes, the 483 included an observation that batch test results were improperly deleted from the computer at Station 5 on April 22 and FDA investigators found a record of that deletion in the trash bin, not the automatically generated audit trail. But your response should go well beyond the unfortunate trash bin incident to analyze how it was possible for those deletions to occur in the first place. Was it a systemic failure or a fluke? Was it a single rogue employee, an inadvertent keystroke or a system-wide computer software deficiency that allowed the audit trail function to be disabled? And what about the product on the market that relied on those test results? Is it impacted and, if it is, how should that be addressed?

   Your company needs to avoid offering corrections or corrective actions that address a single incident. The goal of your response should be to propose comprehensive, systemic actions that demonstrate your company’s resolve to get at the root cause of the problem to prevent anything like that from ever happening again. In the above example, remedies should both prevent further noncompliant deletions at Station 5, but also ensure the audit trail function works across your entire computer system so that no lab technician in any facility can either intentionally or accidentally delete data without an electronic record of the event. Your analysis should encompass your procedures, policies and personnel qualifications to explain why the issue wasn’t detected (or was detected but not remediated) through internal auditing or via management oversight.

   The requirement for this degree of diligence in 483 responses is made explicit in FDA Warning Letters, which are posted online, exposing the alleged manufacturing problems of your company to public scrutiny (another excellent reason to try and avoid them). The Letters often outline how and why 483 Responses fall short. In cGMP Warning Letters issued to biopharmaceutical and medical device companies, one phrase pops up repeatedly: “You failed to identify the root cause.” Conducting an accurate and actionable root cause analysis requires an open mind, holistic thinking and deep expertise. And once the root cause is discovered, it’s not sufficient to describe it in one sentence. A 483 Response should include a detailed description of the root cause analysis, along with data substantiating the findings.

   For example, in 2011 the Center for Drug Evaluation and Research (CDER) cited one firm’s explanation of a product contamination incident as inadequate. In a 483, FDA investigators observed that: 1) 13 batches of the company’s active pharmaceutical ingredient (API) contained “black particles”; and 2) hydraulic oil was...
leaking in the manufacturing area. In response, the company stated that it had repaired the leaking equipment and that each time new leaking oil was detected it would revise its procedure for process deviation investigations “to address documentation of the investigations, root cause analyses and corrective and preventive actions.”

Not good enough. According to CDER, the firm’s response was “inadequate” because it “assumed that the black particles are hydraulic oil contamination, without an investigation or any identification of the contaminant. Furthermore, you did not describe what steps you will be taking with regard to the API manufactured using defective production equipment.”

Although the company took care of the leaking oil, it failed to prove that the black particles were, indeed, connected to the leaking oil. CDER wanted a deeper analysis, broader corrective measures and a full accounting of the final disposition of the defective 13 lots.

**FIGURE 1:** NARROW 483 RESPONSES DON’T WORK

<table>
<thead>
<tr>
<th>Language Used to Describe Inadequacy of 483 Response</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Your response… only addresses the five entries specifically discussed on the Form-483 issued… your response <strong>does not discuss any investigation into the missing records or address the root cause or extent of these deficient practices</strong> throughout your facility.”</td>
<td>Warning Letter July 2014 (CDER)</td>
</tr>
<tr>
<td>“Your response is inadequate in that your investigation was primarily limited to the discarded CGMP records cited in the Form FDA-483… The investigation **did not include a comprehensive review of all records in the waste area or a thorough review of your firm’s practice of destroying cGMP records...”</td>
<td>Warning Letter May 2014 (CDER)</td>
</tr>
<tr>
<td>“Your firm’s response did not address why these activities were not documented. In addition, <strong>your firm did not consider a systemic corrective action</strong> to include a retrospective review of other CAPAs to ensure that these reports were adequately documented.”</td>
<td>Warning Letter July 2014 (CDRH)</td>
</tr>
</tbody>
</table>

*KEY: CDER = FDA’s Center for Drug Evaluation and Research; CDRH = FDA’s Center for Devices and Radiological Health*
One of the most common errors companies make in responding to 483s is failing to provide documentation, i.e. evidence of corrective action. For example, if a company has revised its Standard Operating Procedures [SOPs] and retrained employees, the 483 Response should include the new SOP document and concrete proof of the retraining sessions (e.g., times, dates, and attendance records for the sessions.) It’s that simple.

**FIGURE 2: WHERE’S THE PROOF?**

<table>
<thead>
<tr>
<th>Language Used to Describe Inadequacy of 483 Response</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>We acknowledge your response that you have performed smoke studies... However, your response... failed to provide a video of the new smoke studies you indicated that you performed.</td>
<td>Warning Letter March 2015 (CDER)</td>
</tr>
<tr>
<td>We reviewed your firm’s response and conclude that it is not adequate. Your firm revised its CAPA procedure. However... your firm did not provide training records on the revised procedure.</td>
<td>Warning Letter March 2015 (CDRH)</td>
</tr>
<tr>
<td>We acknowledge the revisions made to SOP No. SGL-IMS-04 (section 2.3), “Control of Records,” however, your firm provided no evidence demonstrating that all operators have been trained on the revised procedure. Provide documentation...</td>
<td>Warning Letter October 2014 (CDER)</td>
</tr>
</tbody>
</table>
Time lines proposed for corrective action in a 483 Response must be finely calibrated to the problem at hand. Too often companies propose deadlines that are either unrealistically short or, at the other end of the spectrum, needlessly put off so that they’re robbed of their urgency. It’s best to commit to goals, time lines and milestones that are aggressive but achievable. If extensions are needed, ask for them: If a problem can be fixed on an acute basis, fix it.

Let’s start with the 483 Response deadline itself. The FDA gives companies 15 days to craft a comprehensive response and propose a plan to correct all the deficiencies listed in the 483. Yet it’s highly improbable that complete investigations and implementation of corrective actions can be completed within that time. Some cGMP violations may be amenable to a thorough analysis and swift repair in less than two weeks and some may not. If all that is needed for compliance is a revised procedure and additional employee training, that can often be accomplished in days, not weeks. (But don’t forget to document the process and include your evidence!)

When corrective actions take longer, the response submitted within 15 days must present clear, comprehensive corrective action plans with milestones, time lines and accountability for completion. For such fixes that need longer time frames, a risk assessment may indicate the need to propose and implement an interim controls plan with appropriate assurance of quality, review, and accountability. If you later realize a milestone can’t be met despite your firm’s best efforts, ask for an extension, but be sure the request is justified and the new deadline can be met without further delay.

For example, pharmaceutical manufacturers procure materials and services to make their products. As a result, they must continually monitor their suppliers through testing, oversight and audits of suppliers’ facilities in order to ensure that their specifications for the quality of materials and services are met. If the 483 cites cGMP problems with the qualification and monitoring of suppliers, corrective actions often are extensive. For projects of this magnitude, only commit to what you are sure you can deliver and establish interim controls to provide assurance of quality and conformance until permanent corrective actions can be implemented. Missed deadlines, lack of management and/or staging for longer-term projects and poor performance can destroy your company’s credibility (as in the sample Warning Letters in Figure 3).

Your Last, Best Chance to Avoid Escalation of Regulatory Sanctions

An effective 483 Response represents your company’s cooperativeness and concomitant commitment to quality and patient safety. It is potentially your last, best chance to avoid a Warning Letter after an inspection. A Warning Letter can delay product launches, harm your reputation and incur hefty damage control costs. If you can avoid the three most significant mistakes in your 483 Response, and take corrective action in a comprehensive and timely manner, you will be on your way to achieving compliance and restoring your company’s credibility with the FDA.
Responding to EU GMP Inspection Reports

Although procedures for handling inspections and compliance in the EU differ slightly from the US, the same criteria for an exhaustive, compelling and acceptable response to observed GMP problems apply.

In the EU, the competent authorities (CA) of the member states – analogous to the US FDA – perform Good Manufacturing Practice (GMP) inspections for drug manufacturing facilities (devices are generally handled by Notified Bodies and are not discussed here). Although the European Medicines Agency (EMA) can request inspections, one (or in some cases, several) of the CAs will conduct the actual investigation and record observations. Foreign inspections may involve teams consisting of inspectors from more than one CA. Inspectors will present their findings at the end of the inspection orally, and company officials can present a tentative remedial action plan at that time, based on the feedback received from the inspectors during the inspection.

The GMP Inspection Report is the final outcome of EU inspections and inspectors typically send the contents of the initial report to companies for comment, along with a tentative date for the issuance of the final document. Given that the findings already have been presented orally, the company should be in a position to provide a comprehensive remediation plan when they receive the draft inspection report for comment. Although there are no defined timelines, inspectors typically expect a response within a two-week timeframe. In general, the timelines are quite similar to the FDA’s 15 working days. If applicable, inspectors will issue a GMP certificate within 90 days, according to statute.

The worst-case scenario for a company is when the CA refuses to issue a GMP certificate or revokes an existing one. Without the GMP certificate, the drug product cannot be put on the market in the EU. Although EU agencies do not publish their inspection reports, they enter the outcome of the inspection in a database with limited public access (EudraGMDP). In principle, although it is possible to obtain heavily redacted inspection reports from EU CAs under freedom of information laws, this is extremely time consuming and is a course very rarely pursued. In case of serious deficiencies posing possible safety risks for patients, inspectors may take immediate action.

Siegfried Schmitt, Ph.D., PAREXEL Consulting
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.

CORPORATE HEADQUARTERS
195 West Street
Waltham, MA 02451
USA
+1 781 487 9900

Offices across Europe, Asia and the Americas

www.PAREXEL.com