Letters from America

Ken Appel offers practical advice to US FDA-regulated organisations on avoiding and dealing with 'Form 483 letters' for temperature, humidity and other controlled environments

IN the US, no cGMP manufacturer wants to receive a Form 483 letter ("Notice of Inspectional Observations") from the Food and Drug Administration (FDA). If you are developing, manufacturing or even warehousing goods for the stringently-controlled pharmaceutical or biotechnical industries, receiving a list of deficiencies can feel like a heavy blow to your quality system. Worse, with the 2009 increase in enforcement staff[1] and the September 2009 change to the response time (now 15 days), the FDA appears to be ramping up its enforcement mandate[2].

This article features three excerpts from some of the more common 'observations' noted in Form 483 Letters during 2008–2009. (The names have been left out in this article, but are a matter of public record)[3]. Each of these deviations involved environmental conditions (temperature, humidity etc) in a variety of cGMP settings; they range from failure to properly validate containers for human cell and tissue products to a lack of temperature records in an aseptic processing area of a drug manufacturing facility. None of the deviations shown here are unique, but all are avoidable.

After the examples, I'll outline some best practices of a 483 response, and provide a ten-point checklist that should make the 15-day time limit more manageable. I'll also look at ways to simplify and automate monitoring, alarming and reporting on FDA-regulated environments. Options range from low-tech manual methods to hybridised systems that combine written and electronic methods of documentation, to fully-automated systems.

Form 483

Following an on-site inspection, the FDA's 'Form 483' is the List of Inspectional Observations that reports any issues of non-compliance with operational regulations such as current good manufacturing practice (cGMP), medical device reporting (MDR) regulations, and the Safe Medical Devices Act (SMDA; 1990).

The form is used to report significant deviations from applicable regulations. Following an on-site visit, the FDA investigator will present the Form-483, outlining issues identified during the inspection. A recipient of a 483 should respond to the FDA, addressing each item, indicating agreement and either providing a timeline for correction or requesting clarification of what the FDA requires. This response should be submitted within 15 calendar days regardless of the number of observations. While a response is not compulsory, a good response can usually help a company avoid receiving a warning letter from the FDA, withholding of product approval, or plant shut-down.

Sample deviation 1 – to a contract pharma manufacturer:

"Requirements for stability testing of drug products are not being met. For example, you do not have, as part of the storage condition, any documentation that stability samples are maintained at the designated temperature [21 CFR 211.166(a)(2)]; and you do not have appropriate stability data to support the 4-year expiration date for the product. [21 CFR 211.166(b)]"

Sample deviation 2 – to a blood bank:

"Failure to have quality control procedures and follow those procedures for periodic tests of containers to maintain proper temperature...as required by 21 CFR 606.160(b)(5)(iv)..."

Sample deviation 3 – to a major manufacturer of over-the-counter drugs:

"Failure to establish and maintain procedures to adequately control environmental conditions, as required by 21 CFR 820.70(c). Specifically, temperature conditions within the aseptic processing area are not being documented to ensure such conditions are consistently within established specifications... For example, during the inspection we observed that your firm was recording the relative humidity (RH) in the processing room, but not in the sterilisation chamber. We also observed that your firm was not maintaining or reviewing the temperature recorder charts generated during your sterilisation process of [product x]..."

Many opportunities are available to tighten up documentation of controlled environments with modern technology

There is no regulatory requirement to respond to a 483. According to the FDA, they are merely "inspectional observations, and do not represent a final agency determination regarding compliance." In effect it is an offer to help you with your compliance concerns. However, not responding quickly and carefully will most likely result in further investigation. In addition, all warning letters are posted on the FDA's website[4] in html format and are therefore indexed by search engines. Once you receive a 483, all anyone needs to do is type [your company/lab name] + FDA (or +483) into the search box, and there you are for all the world to see.

Tips for the right response

Your initial response must do three things: it must establish credibility; it must demonstrate acknowledgement of the observations and an understanding of the specific requirements referenced; and it must show that your facility is committed to corrective actions, any and all.

You can show commitment by working cross-departmentally. Include statements from relevant department heads that briefly but specifically addresses each observation. Each observation needs to have a corrective action – either planned or accomplished – and it must be feasible and deliverable within a predetermined timeframe.

Here are some tips – some simple, some in depth – for responding appropriately to 483 letters:

1. Get your response in on time and in writing. You have 15 days, so ensure that final proofing and substantive editing is done at least by day ten.

2. In the first paragraph of the response letter, be explicit in your understanding of and desire to comply with FDA regulations.

3. Respond individually to each item that was addressed in the warning letter. Be specific. Do not try to solve all issues in one paragraph or your response may be rejected, prompting further action from the FDA.

4. Respond by importance – that is, respond individually to items most likely to impact product quality.

5. Be detailed yet concise in each response. Outline how each deficiency will be corrected, and when, rather than how the deficiency came to be. Provide documentation of a corrective action commitment from the person responsible for it.

6. Use positive statements; avoid language that implies fault. Address each item in the form 483 as an opportunity to fine-tune the quality and compliance systems and personnel.

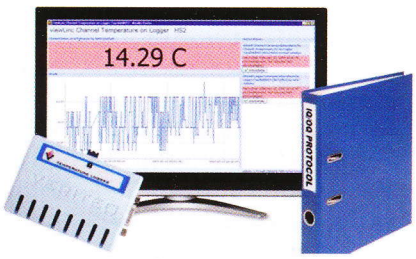
7. Include reference to how you will be forwarding evidence to support the correction. For example, "Company X will use a validated monitoring and alarming system to provide reports on temperature recordings taken at 10-min intervals month-by-month". Product specifications and protocols of any new systems can be provided or offered in support of the corrective action plan.

8. If the inspector noted something that you feel was an isolated incident, document this fact and note it in your response. Be sure your data is complete and accurate. If you find some of the observations were in error after receiving the 483, there is a formal dispute resolution process outlined in the agency's *Guidance for industry – formal dispute resolution: scientific and technical issues related to pharmaceutical CGMP*[5].

9. Be proactive. Reassess your internal compliance programmes. Why were 483 deficiencies not detected internally? Mention this in your response letter, noting your commitment to quality control/quality assurance (QC/QA) audit management. The definitive guide to what FDA inspectors are looking for (at least in theory) is the agency's *Investigations operations manual*[6].

10. If you need clarification, seek it – in writing, and from the correct party. Ideally, when the investigator gave you the Form 483 after the inspection you asked a lot of questions to clarify each observation. Try to be sure you are clear on each observation before the inspector leaves your facility and make notes while he/she is explaining the observations. If your questions involve policy, contact the FDA headquarters – don't contact your local FDA because policy is set at HQ.

10.5 You may need an industry expert. There are many companies who specialise in creating and implementing regulatory strategy, whether from the ground up or from your existing quality and regulatory systems. If it's worth doing, it may be worth hiring someone who knows how to do it really well. As regulatory compliance issues grow more complex, many companies have been created to provide solutions in common compliance areas like: response to agency queries and help with agency meetings, regulatory gap analysis and remediation, internal GLP/GMP auditing and pre-approval inspections.



Every monitoring system should have a detailed IQ/OQ change control document to make validation a straightforward process.

avoiding 483s with audit-ready environmental monitoring

Ideally, your regulated environments and equipment are always in full compliance with FDA regulations. An automated monitoring and alarming system providing data at the point of measurement can make your QC/QA efficient, optimal and ready for any critical evaluation, internal or external. The continuous records that this type of system provides could help be part of your detailed response to quality concerns outlined in a Form 483 letter.

For example, in the 483 excerpt of the contract pharma manufacturer, which noted that "*documentation that stability samples are maintained at the designated temperature*", a validated monitoring and alarming system would provide secure, gap-free temperature data recording. Data loggers with long-life batteries (up to ten years) can continue to record temperature at the point of measurement, rendering environmental data immune to network or power failures.

Regarding the blood bank 483 example, the storage units can be validated with the same monitoring equipment. Self-contained data loggers with internal sensors, memory and battery can be equipped for periodic testing or mapping the temperature distribution of the containers.

> *"as regulatory compliance issues grow more complex, many companies have been created to provide solutions"*

In regard to the observations on the OTC pharmaceutical manufacturer, the challenge of not having adequately documented temperature conditions could be solved by following the detailed IQ/OQ and SOPs provided with the monitoring, alarming and reporting system.

Some organisations compliant with GMP still use chart recorders or manual methods to track temperature and humidity. The issues with these methods are beyond the scope of this article, but as more facilities automate processes within quality assurance and regulatory compliance, relying on older technologies is and will continue to be problematic. The FDA, with its "strong recommendations", cannot insist that organisations upgrade to any given technology. But, a commitment to using industry-best instrumentation and systems in FDA-regulated research and manufacturing processes can stave off misgivings about a facility's commitment to quality. **tce**

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1. Parts of this article were sourced, with permission, from two sources: "FDA 483 responses – compliance considerations", Poska, R and Graham, B, *Journal of Validation Technology*, Winter 2010; and "Writing an effective 483 response" presented by Richardson, A, *5th annual FDA university RI pharma conference*, January 2009.

2. "FDA's enforcement crackdown to increase inspections, delays", *Drug GMP Report*, issue no 210, January 2010.

3. From the FDA's "warning letter" web page: "Inspections, compliance, enforcement, and criminal investigations", www.accessdata.fda.gov

4. ORA FOIA electronic reading room at: www.fda.gov/ICECI/enforcementactions/warningletters

5. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf

6. www.fda.gov/ICECI/Inspections/IOM/default.htm