VAISALA / APPLICATION NOTE

LIFE SCIENCE

How to Avoid (and Respond to) FDA 483s for Temperature, Humidity and other Controlled Environments

No cGMP compliant manufacturer wants to receive a Form 483 ("Notice of Inspectional Observations"). In such stringently controlled industries as pharmaceutical/ biotechnical development, manufacturing and warehousing, 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].

As technologies emerge for monitoring and documenting controlled environments, the expectations of regulatory bodies rise.

The following article shows three excerpts from some of the more common "observations" noted in Form 483 Letters. (The names have been left out in this application note, but are a matter of public record)[3]. Each of these deviations involved environmental conditions (temperature, humidity, etc.) in a variety of GxP settings; they range from failure to properly validate containers for Human Cell & Tissue Products to a lack of temperature records in an aseptic processing area of a drug manufacturing facility. None of the deviations excerpted here are unique, but all are avoidable.

After the excerpts, we outline some best practices of a 483 response, providing a 10-point checklist (to make that 15-day time limit more manageable) with some links to further resources. Finally, we'll look at ways to simplify and automate monitoring, alarming and reporting on FDA regulated environments. Options range from low-tech manual methods, to hybridized systems that combine written and electronic methods of documentation, to fully automated systems for compliance with 21 CFR Part 11 and cGMPs.

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)..."

Manufacturing, processing, and storage facilities must be monitored continuously for critical parameters.

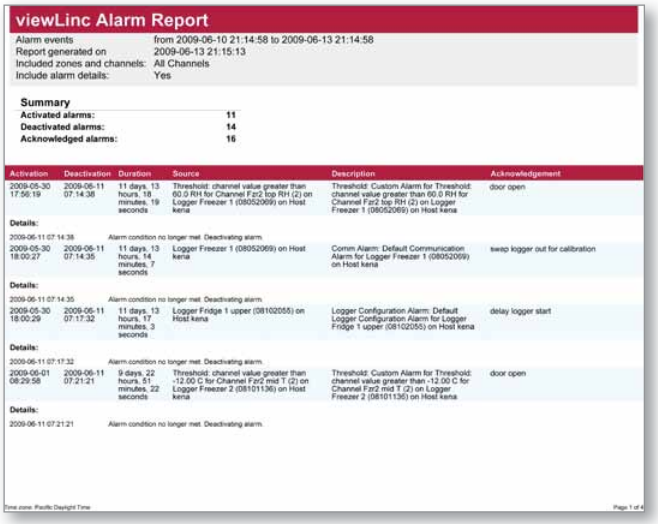
Sample Deviation #3

To a major manufacturer of OTC Pharmaceuticals:

"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 sterilization chamber. We also observed that your firm was not maintaining or reviewing the temperature recorder charts generated during your sterilization process of [product x]..."

There is no regulatory requirement to respond to a 483. According to the agency, they are merely *"…inspectional observations, and do not represent a final agency determination regarding your compliance."* Sort of like an



viewLinc Alarm Report

Alarm events: from 2009-06-10 21:14:58 to 2009-06-13 21:14:58
Report generated on: 2009-06-13 21:15:13
Included zones and channels: All Channels
Include alarm details: Yes

Summary

Activated alarms:	11
Deactivated alarms:	14
Acknowledged alarms:	16

Activation	Deactivation	Duration	Source	Description	Acknowledgement
2009-05-30 17:56:19	2009-06-11 07:14:38	11 days, 13 hours, 18 minutes, 19 seconds	Threshold: channel value greater than 60.0 RH for Channel Fzr2 top RH (2) on Logger Freezer 1 (08052069) on Host kena	Threshold: Custom Alarm for Threshold: channel value greater than 60.0 RH for Channel Fzr2 top RH (2) on Logger Freezer 1 (08052069) on Host kena	door open
Details:					
2009-06-11 07:14:38	Alarm condition no longer met. Deactivating alarm.				
2009-05-30 18:00:27	2009-06-11 07:14:35	11 days, 13 hours, 14 minutes, 7 seconds	Logger Freezer 1 (08052069) on Host kena	Comm Alarm: Default Communication Alarm for Logger Freezer 1 (08052069) on Host kena	swap logger out for calibration
Details:					
2009-06-11 07:14:35	Alarm condition no longer met. Deactivating alarm.				
2009-05-30 18:00:29	2009-06-11 07:17:32	11 days, 13 hours, 17 minutes, 3 seconds	Logger Fridge 1 upper (08102055) on Host kena	Logger Configuration Alarm: Default Logger Configuration Alarm for Logger Fridge 1 upper (08102055) on Host kena	delay logger start
Details:					
2009-06-11 07:17:32	Alarm condition no longer met. Deactivating alarm.				
2009-06-01 08:29:58	2009-06-11 07:21:21	9 days, 22 hours, 51 minutes, 22 seconds	Threshold: channel value greater than -12.00 C for Channel Fzr2 mid T (2) on Logger Freezer 2 (08101136) on Host kena	Threshold: Custom Alarm for Threshold: channel value greater than -12.00 C for Channel Fzr2 mid T (2) on Logger Freezer 2 (08101136) on Host kena	door open
Details:					
2009-06-11 07:21:21	Alarm condition no longer met. Deactivating alarm.				

Time zone: Pacific Daylight Time — Page 1 of 4

Controlling environmental conditions can include notification of OOT/OOS conditions in the form of an alarm. An Audit Trail will include all alarms, notifications and responses.

offer to help you with your compliance concerns. However, not responding quickly and carefully could result in further investigation. In addition, all Warning Letters are posted on the FDA's site[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's Name] + FDA (or +483) into the search box, and your organization's name and quality shortcomings are part of the public domain.

10 ½ Tips for a 483 Response

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

One indicator of commitment is your organization's willingness and ability to work cross-departmentally. A response should include statements from all relevant department heads that briefly but specifically address the form observation pertinent to their area. Acknowledgement is demonstrated by your initial corrective actions – planned or accomplished – outlined in the response. These must be feasible and deliverable within a predetermined time-frame.

Here is a checklist of items – some simple, some in depth – for creating a thorough response to a Form 483:

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 10.

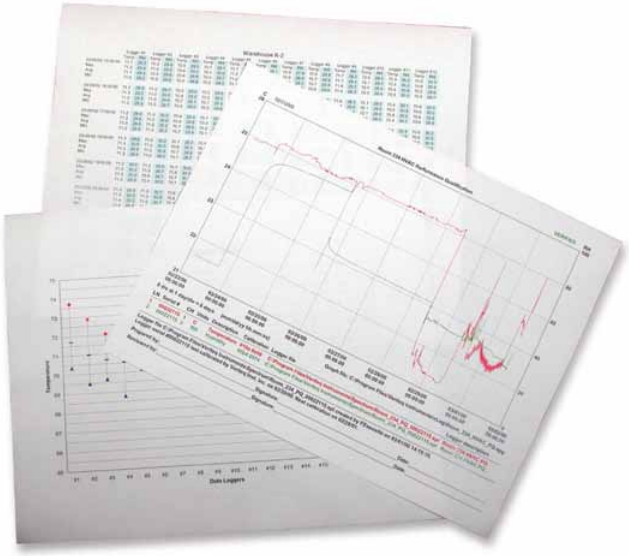
2. In the first paragraph of the response letter, be explicit in your understanding of and desire to comply with FDA regulations.
3. Respond individually to each item that was addressed in the Warning letter. Be specific. Do not try to solve all issues in one paragraph or your response may be rejected, 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 your 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 Vaisala's continuous monitoring and alarming system to provide reports on temperature recordings taken at 10 minute 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."
9. Be proactive. Reassess your internal compliance programs – why were 483 deficiencies not detected internally? Mention this in your response letter, noting your commitment to QC/QA audit management. The[6] definitive guide to what FDA inspectors are looking for (at least in theory) is the agency's "Investigations Operations Manual."
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 specialize 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 & remediation, internal GLP/GMP auditing and pre-approval inspections.

Avoiding 483s with Environmental Monitoring

An automated monitoring and alarming system that records data at the point of measurement and includes back-up recording – can make your QA/QC system for regulated environments efficient and ready for any critical evaluation, internal or external. The continuous records that this type of system provides can also form part of a detailed response to a Form 483.

For example, in the 483 excerpt of the CMO (sample deviation #1), which stated "documentation that stability samples are maintained at the designated temperature"; a validated monitoring and alarming system would have provided 21 CFR Part 11 compliant documents on all temperature data for the samples' storage and handling



Reports can be customized to fit the needs of your organization, but once configured, should be consistent and standardized.

areas. Data loggers with long-life batteries (up to 10 years) can continue to record temperature at the point of measurement, rendering environmental data immune to network or power failures and thereby ensuring gap-free records and a full audit trail.

Regarding the blood bank 483 excerpt (sample deviation #2), the storage units should have been validated regularly. An efficient solution is to perform thermal mapping with the same equipment used to monitor – provided that such equipment has stable sensors and tamper-proof files, and the software is validatable. Self-contained data loggers with internal thermistor sensors, with on-board memory and battery, can be used to regularly map the temperature distribution of the containers.

For the 483 issued to the OTC Pharmaceutical manufacturer (sample deviation #3), the issue of inadequately documented temperature conditions would be solved by following the detailed IQ/OQ and SOPs that are ideally provided with the monitoring, alarming and reporting system.

Some organizations 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 will continue to be problematic. The FDA, with its "strong recommendations" cannot mandate that organizations 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. For more information on Vaisala's monitoring and validation solutions for GxP and FDA compliant environments, visit: **www.vaisala.com/lifescience-hitech**

Validated monitoring systems require a detailed IQ/OQ change control document.

Sources:

[1] Parts of this article were sourced from two documents **1) "FDA 483 Responses – Compliance Considerations"** cited with permission by the authors: Richard Poska and Ballard Graham, as published in the Journal of Validation Technology, Winter 2010 available with subscription at: http://www.gxpandjvt.com/ivtnews/templates/IVTNews.aspx?articleid=1896&zoneid=27 and

[2] **"Writing An Effective 483 Response"** also cited with permission, was presented by Anita Richardson, Associate Director for Policy, Office of Compliance & Biologics Quality at the 5th Annual FDA University RI Pharma Conference, January 2009 available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM102921.pdf

[3] **"FDA's Enforcement Crackdown To Increase Inspections, Delays"**, Drug GMP Report - Issue No. 210, January 2010; http://img.en25.com/Web/Vaisala/FDANews_Enforcement_Crackdown_article.pdf

[3] From the FDA's Warning Letter web page: **"Inspections, Compliance, Enforcement, and Criminal Investigations"** http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?filter=temperature&sortColumn=&qryStr=21+CFR+Part+11)

[4] See the ORA FOIA Electronic Reading Room at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

[5] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf

[6] "Investigations Operations Manual" http://www.fda.gov/ICECI/Inspections/IOM/default.htm

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