

How to Respond to (and Avoid) FDA Form 483s

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Introduction:

No FDA-regulated manufacturer wants to receive a Form 483 at the end of an inspection. In such stringently controlled industries as pharmaceutical, biotechnical, and medical device manufacturing, receiving a list of deficiencies can be a heavy blow to your quality system. Unfortunately, with the recent increase in enforcement staff¹ and the new 483 response time —now 15 days — it's clear that the agency is ramping up its enforcement mandate.² The likelihood of receiving a post-inspection 483 is now more likely than ever before.

The following article offers three excerpts that represent common deviations observed in recent Form 483s. (The names have been left out in this article, but are a matter of public record).³ Each of these deviations involved environmental conditions in a variety of manufacturing settings — from failure to properly document calibration results for Class 1 sterile devices to a lack of humidity control for manufactured patient-assist devices. None of the deviations excerpted here are unique, but all are avoidable.

¹ Parts of this article were sourced, with permission, from two documents 1) “**FDA 483 Responses—Compliance Considerations**” by Richard Poska and Ballard Graham, as published in the *Journal of Validation Technology*, Winter 2010 “available with subscription at: <http://www.gxpan djvt.com/ivtnews/templates/IVTNews.aspx?articleid=1896&zoneid=27>

and the FDA Presentation 2) “**Writing An Effective 483 Response**” 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>

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**” <http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?filter=temperature&sortColumn=&qryStr=21+CFR+Part+11>

After the 483 excerpts, we’ll outline some best practices for creating an appropriate response, providing you with a 10-point checklist that should make the 483 response time-frame more manageable. We also provide links to agency guidances and for further research. Finally, we offer some solutions that can simplify and automate your monitoring, alarming and reporting requirements for FDA regulated environments.



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

Sample Deviation #1

To a medical device manufacturer:

“Procedures for the control of manufacturing and storage areas where environmental conditions could be reasonably expected to have an adverse effect on product quality were not adequately followed [21 CFR 820.70(c). Relative Humidity readings of 19% and 20% -- which fall below your specified...limits -- were disclosed in your failure investigations work area...”

Sample Deviation #2

To a testing lab:

“Failure to adequately test, calibrate and standardize equipment used for the generation, measurement, or assessment of data. [21 CFR § 58.63]. Adequate written records are not maintained of all equipment inspection, maintenance, testing, calibration and/or standardization operations. Specifically, there are no maintenance records for the equipment in the... Laboratory...that were used for the inspected non-clinical laboratory study.”



Manufacturing, processing, and storage facilities must be monitored continuously for critical parameters. Are you monitoring and recording the necessary parameters and locations?

Sample Deviation #3

To a contract device manufacturer:

“Failure to establish and maintain procedures for monitoring and control of process parameters for standard processes to ensure that the specified requirements continue to be met, as required by 21 C.F.R. § 820.75(b). Your firm did not present any procedures for the monitoring and control of process parameters used during ETO sterilization and packaging of your finished devices. For example, during the inspection we observed that your firm was recording the relative humidity (RH) in the processing room and not the RH 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 sterile implants.”

viewLinc Alarm Report					
Alarm events:	from:	2009-05-10 21:14:58	to:	2009-05-13 21:14:58	
Report generated on:		2009-05-13 21:15:13			
Included zones and channels:		All Channels			
Include alarm details:		Yes			
Summary					
Activated alarms:		11			
Deactivated alarms:		14			
Acknowledged alarms:		18			
Activation	Description	Duration	Event	Description	Acknowledgment
2009-05-02 17:06:18	Threshold alarm value greater than 10.0 for Channel 1 (2) on Host name: Logger Fridge 1 (20090205) on Host name:	11 days, 13 hours, 14 seconds, 19 milliseconds	Threshold Alarm for Threshold Channel value greater than 10.0 for Channel 1 (2) on Host name: Logger Fridge 1 (20090205) on Host name:	Threshold Custom Alarm for Threshold Channel value greater than 10.0 for Channel 1 (2) on Host name: Logger Fridge 1 (20090205) on Host name:	door open
2009-05-11 08:00:27	Alarm condition no longer met. Deactivating alarm.	11 days, 13 hours, 14 seconds, 9 milliseconds	Logger Fridge 1 (20090205) on Host name:	Comm Alarm: Default Communication Alarm for Logger Fridge 1 (20090205) on Host name:	sleep trigger out for calibration
2009-05-02 18:00:26	Alarm condition no longer met. Deactivating alarm.	11 days, 13 hours, 14 seconds, 3 milliseconds	Logger Fridge 1 Upper (20090205) on Host name:	Logger Configuration Alarm: Default Logger Configuration Alarm for Logger Fridge 1 Upper (20090205) on Host name:	sleep trigger start
2009-05-01 08:29:58	Threshold alarm value greater than 12.00 for Channel 1 (2) on Host name: Logger Fridge 2 (20091113) on Host name:	8 days, 22 hours, 14 minutes, 22 milliseconds	Threshold Alarm for Threshold Channel value greater than 12.00 for Channel 1 (2) on Host name: Logger Fridge 2 (20091113) on Host name:	Threshold Custom Alarm for Threshold Channel value greater than 12.00 for Channel 1 (2) on Host name: Logger Fridge 2 (20091113) on Host name:	door open
2009-05-11 07:21:21	Alarm condition no longer met. Deactivating alarm.				

A detailed history of all events and changes is crucial in proving that environmental conditions are continuously monitored and fully documented.

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.*” From a certain perspective, a 483 can be viewed as an unsolicited offer to help you with your compliance concerns. (Who better to help than the enforcer?) However, not responding quickly and carefully can result in an in-depth investigation, which can lead to warnings and further enforcement action. In addition, all Warning Letters are posted on the FDA’s site⁴ in html format and as such, are indexed by search engines. Once you receive a 483, all anyone needs to do is type [Your Company’s Name] + FDA (or 483) into the search box, and there you are— likely in the top results.

10.5 Tips for Formatting 483 Responses

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. To do this, ensure that you include a statement from all relevant department heads or team leaders that briefly (but specifically) addresses each observation. Each observation must have a corrective action— either planned or accomplished— and it must be feasible and deliverable within a predetermined time-frame. List the time-frame for execution, as well as relevant personnel.

Here are 10 steps — some simple, some a bit more complex — for responding appropriately to a 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

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

regulations. How? Simply state that your organization is taking immediate corrective action. Then, elaborate...

3. Respond *individually to each item* that was addressed in the form. Be specific. Do not try to solve all issues in one paragraph or your response may be rejected, prompting further action from the FDA. Give a corrective action and time-frame for each observation.
4. Respond by importance. Prioritize observations that are most likely to impact product quality. These may not be the first items on the Form 483, but they should be first on your response.
5. Be detailed, but concise. Outline how and when each deficiency will be corrected, rather than how the deficiency came to be. Provide documentation of a corrective action commitment from the person responsible for it, preferably signed by that person.
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 any reference documents to support the corrective action taken. For example, "<Your Company>will use Vaisala's continuous monitoring system to provide reports on temperature at 10 minute intervals, month-by-month..." and supply a sample report. Product specifications, protocols and calibration plans can be offered in support of the corrective actions.
8. If you feel that a 483 item was an isolated incident, note it in your response. Be certain that your data is accurate. If an observation was in error, 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 programs — Why were 483 deficiencies not detected internally? Mention this in your response letter, noting your commitment to 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" accessible at: <http://www.fda.gov/ICECI/Inspections/IO/OM/default.htm>
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 your understanding of each item. Try to be 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 (rather than your local FDA representative 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 strategies, 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 right.

As FDA compliance becomes more complex, many companies have been created to provide solutions in common regulatory areas like: responding to agency queries and help with agency meetings, regulatory gap analysis & remediation, internal GLP/GMP auditing and pre-approval inspections.

⁵<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf>

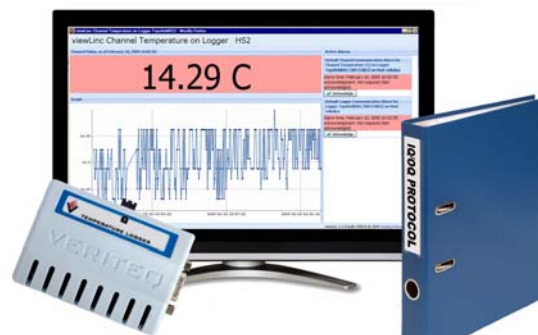
Avoiding 483s in Controlled Environments

Ideally, you welcome an inspection to show how your regulated environments and equipment are always in full compliance. An automated monitoring and alarming system that measures accurately and records data at the point of measurement — can make your QA/QC efficient, optimal and ready for any critical evaluation, internal or external. The records and reports that this type of system should provide can form part of your detailed response to quality concerns outlined in a Form 483 letter, or— preferably— preclude any observation of non-documented conditions during an inspection.

For example, the 483 excerpt noted in this article concerning the patient assist device stated: *“Relative Humidity readings of 19% and 20% -- which fall below your specified...limits.”* A continuous monitoring system would provide secure, gap-free relative humidity data recording in records that can be stored and retrieved easily, for a given time-frame. Data loggers that are equipped with internal batteries, memory and sensors can continue to record conditions at the point of measurement, which renders the data immune to network or power failures. Fielding an inspection with gap-free records can mitigate the risk of any observations of inadequate records.

In the excerpt from the testing laboratory, the observation stated: *“...temperatures...will be manually recorded... each researcher [is] responsible for checking the temperature...[and] recording daily temperatures.”* An automated monitoring system would remove the burden from individuals having to record data manually. In addition, an alarmed system gives 24/7 protection and all archived data are easily accessible for review.

In regard to the observation concerning the medical device contract manufacturer, the challenge of not having adequately documented or reviewed temperature and relative humidity conditions would be solved a system that can be monitored remotely, with all locations accessible for review via web browser.



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

Some organizations 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 quality assurance and control processes to optimize resources while ensuring compliance, relying on older technologies is and will continue to be problematic.

The FDA, with its “strong recommendations”, cannot insist that organizations upgrade to a given technology. But, a commitment to using industry-best instrumentation and systems can stave off misgivings about an organization’s commitment to quality.

For more information on continuous monitoring systems contact veriteqinfo@vaisala.com or call 800-683-8374. Visit us online at vaisala.com/veriteq

	Channel Fz1 RH T (1) on Logger Freezer 1 (08162088) on Host kana (C)	Channel Fz1 rear T (2) on Logger Freezer 2 (08162119) on Host kana (C)	Channel Csoo Tzr1 T (2) on Logger Freezer 2 (08162119) on Host kana (C)	Channel Csoo Tzr2 T (1) on Logger Incubator 1 (08162119) on Host kana (C)	Channel Csoo Tzr2 T (1) on Logger Incubator 2 (08162119) on Host kana (C)	Channel Fz1 RH (2) on Logger Room 1 (08162119) on Host kana (RH)
2009-07-20 08:11:43	-24.84 *	-26.78 *	-70.51 *	70.51 *	70.80 *	70.80
2009-07-20 08:12:44	-24.84 *	-26.86 *	-70.22 *	70.22 *	70.80 *	70.80
2009-07-20 08:13:43	-24.84 *	-26.71 *	-69.71 *	69.71 *	70.22 *	70.22
2009-07-20 08:14:43	-24.90 *	-26.78 *	-69.15 *	69.15 *	69.54 *	69.54
2009-07-20 08:15:43	-24.90 *	-26.78 *	-71.21 *	71.21 *	71.51 *	71.51
2009-07-20 08:16:43	-24.97 *	-26.78 *	-71.15 *	71.15 *	71.93 *	71.93
2009-07-20 08:17:43	-24.97 *	-26.78 *	-70.62 *	70.62 *	71.39 *	71.39
2009-07-20 08:18:43	-24.97 *	-26.78 *	-70.05 *	70.05 *	70.62 *	70.62
2009-07-20 08:19:43	-25.04 *	-26.78 *	-69.59 *	69.59 *	69.93 *	69.93
2009-07-20 08:20:43	-25.04 *	-26.86 *	-70.21 *	70.01 *	71.32 *	70.95
2009-07-20 08:20:47	-25.02 *	-26.77 *	-71.09 *	71.09 *	71.45 *	71.45
2009-07-20 08:21:43	-25.04 *	-26.93 *	-70.80 *	70.80 *	71.45 *	71.45
2009-07-20 08:22:43	-25.04 *	-26.86 *	-70.28 *	70.28 *	70.86 *	70.86
2009-07-20 08:22:44	-25.04 *	-26.93 *	-70.98 *	70.98 *	70.33 *	70.73

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