

## **Guide for US FDA-Regulated Organizations—**

***“How to Avoid and Respond to FDA Criticisms—Form 483 Letters—for  
Temperature, Humidity and other Controlled Environments”***

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## Technical Guide for US FDA-Regulated Organizations— “How to Avoid and Respond to FDA Criticisms—Form 483 Letters—for Temperature, Humidity and other Controlled Environments”

No cGMP manufacturer wants to receive a Form 483 letter (“Notice of Inspectional Observations”). In such stringently controlled industries as pharmaceutical/biotechnical/medical device, plastics 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<sup>1</sup> and the September 2009 change to the response time—now 15 days—the FDA appears to be ramping up its enforcement mandate.<sup>2</sup>

The following article shows 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).<sup>3</sup> Each of these deviations involved environmental conditions (temperature, humidity, etc.) in a variety of GMP/GLP settings; they range 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.

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<sup>1</sup> 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.gxpanjdvt.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>

<sup>2</sup> “**FDA’s Enforcement Crackdown To Increase Inspections, Delays**”, *Drug GMP Report* - Issue No. 210, January 2010

<sup>3</sup> 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 excerpts, we’ll outline some best practices of a 483 response, providing you with a 10-point checklist that should make that 15-day time limit more manageable, and some links for further research. 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.



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

### Sample Deviation #1

To a 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 Lab testing facility:

“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 nonclinical laboratory study.”



There must be documented evidence at any point in time that an environment was within its recommended specifications.

### Sample Deviation #3

To a Contract medical 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 2009-06-13 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	Description	Duration	Source	Description	Acknowledgment
2009-05-30 17:06:16	2009-05-31 07:14:33	11 days, 13 hours, 16 minutes, 19 seconds	Threshold channel value greater than 80.0 for Channel F22 for RH (2) on Logger Freezer 1 (98002095) on Host kana	Threshold: Custom Alarm for Threshold channel value greater than 80.0 for Channel F22 for RH (2) on Logger Freezer 1 (98002095) on Host kana	door open
Details:					
2009-06-11 07:14:58 Alarm condition no longer met. Deactivating alarm.					
2009-05-30 18:00:27	2009-05-31 07:14:55	11 days, 13 hours, 14 minutes, 7 seconds	Logger Freezer 1 (98002095) on Host kana	Comm Alarm: Default Communication Alarm for Logger Freezer 1 (98002095) on Host kana	swap logger out for calibration
Details:					
2009-06-11 07:14:58 Alarm condition no longer met. Deactivating alarm.					
2009-05-30 18:00:29	2009-05-31 07:17:32	11 days, 13 hours, 17 minutes, 3 seconds	Logger Freezer 1 Upper (98100055) on Host kana	Logger Configuration Alarm: Default Configuration Alarm for Logger Freezer 1 Upper (98100055) on Host kana	delay trigger start
Details:					
2009-06-11 07:17:32 Alarm condition no longer met. Deactivating alarm.					
2009-06-11 08:29:58	2009-06-11 07:21:21	0 days, 0 hours, 0 minutes, 22 seconds	Threshold channel value greater than 12.00 C for Channel F22 for T (2) on Logger Freezer 2 (98101150) on Host kana	Threshold: Custom Alarm for Threshold channel value greater than 12.00 C for Channel F22 for T (2) on Logger Freezer 2 (98101150) on Host kana	door open
Details:					
2009-06-11 07:21:21 Alarm condition no longer met. Deactivating alarm.					

Controlling environmental conditions is more often about being notified of a problem than the actual failure itself.

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 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 site<sup>4</sup> 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 there you are.

### 10 ½ 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 a statement from all 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 time-frame.

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 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.

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

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 Veriteq’s validated 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."<sup>5</sup>
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/IOM/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 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.

### Ways to Avoid 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 high accuracy data at the point of measurement with back-up recording — can make your QA/QC efficient, optimal and ready for any critical evaluation, internal or external. The continuous records that this type of system should provide 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 patient assist device, which noted that “*Relative Humidity readings of 19% and 20% -- which fall below your specified...limits*” A validated monitoring and alarming system would provide secure, gap-free relative humidity and temperature data recording. 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.

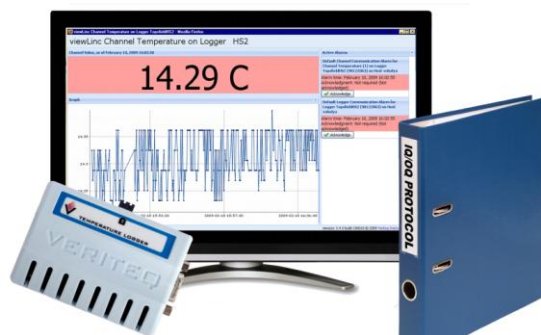
<sup>5</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf>

	Channel Fzr1 Mt T (1) on Logger Freezer 1 (08062088) on Host kena (C)	Channel Fzr1 rear T (1) on Logger Freezer 2 (08062118) on Host kena (C)	Channel sps0 fzt1 T (3) on Logger Freezer 2 (08101158) on Host kena (C)	Channel sps0 fzt2 T (1) on Logger Refrigerator 1 (08101158) upper (08105048) on Host kena (C)	Channel sps0 fzt2 T (1) on Logger Refrigerator 2 (08062118) on Host kena (RH)	Channel Fzr1 RH (2) on Logger Room 1 (08062118) on Host kena (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

*Monitoring, alarming and reporting are only as good as the measured data—accurate and continuous.*

Regarding the testing laboratory 483 example, the observation went on the say: *“You state that temperatures of freezers and refrigerators will be manually recorded, and that each researcher will be responsible for checking the temperature on the refrigerator near his or her bench...that all laboratory personnel are recording daily temperatures.”* An automated monitoring system would remove the burden from individuals having to record data. Additionally, archived data would be easily accessible for review.

In regard to the observations on the Medical contract manufacturer, the challenge of not having adequately documented or reviewed temperature and relative humidity conditions would be solved a monitoring, alarming and reporting system. All monitored points could be easily accessible for review from any location.



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

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 is and will continue to be problematic.

The FDA, with its “strong recommendations”, cannot insist that organizations upgrade to any given technology. But, a commitment to using industry-best instrumentation and systems in FDA-regulated research, storage and manufacturing processes can stave off misgivings about a facility’s commitment to quality. It will also lower your financial risk of damage to temperature and humidity-sensitive products.

For more information on how to avoid Form 483’s, click [www.veriteq.com/avoid-fda-483s](http://www.veriteq.com/avoid-fda-483s) or call 800-683-8374, or email [customersupport@veriteq.com](mailto:customersupport@veriteq.com).

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