# Guide for US FDA-Regulated Organizations—

## *"How to Avoid and Respond to FDA Warning Letters—for Temperature, Humidity and other Controlled Environments"*

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VERITEQ
Superior Temperature & Humidity Monitoring

## Guide for US FDA-Regulated Organizations—
### *"How to Avoid and Respond to FDA Warning Letters—for Temperature, Humidity and other Controlled Environments"*

No regulated business wants to receive an FDA Warning Letter (or Form-483) of Inspectional Observations. In such controlled industries as food, agriculture and pharmaceutical, 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]

The following article shows three excerpts from some of the more common "observations" noted in Warning 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 monitor temperature at food processing facilities 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'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 Food processing facility:

"…your firm's HACCP plan for…this product… lists monitoring procedures and a frequency at the refrigerated storage CCP that is, not adequate to control histamines. 21 CFR 123.6(c)(4) Specifically, the HACCP plan for…this product… to control the hazard of histamines lists monitoring the temperature of the cooler by a, "Visual Wall Temperature Thermometer Check" at a frequency of [redacted] times per day, rather than continuous monitoring of the storage temperature with a continuous temperature monitoring and recording device, such as a recording thermometer or a digital time/temperature data logger."

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[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.gxpandjvt.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)

**Sample Deviation #2**
To a Seafood processing facility:

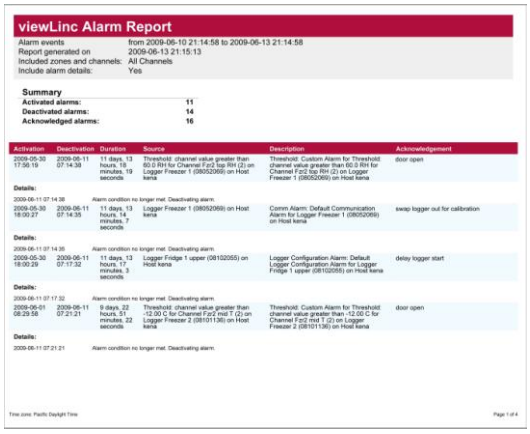
"…your firm's HACCP plan for products "Not Fully Cooked and Not Shelf Stable"…, do not list the critical control point of refrigerated storage of cooked seafood ingredients for controlling the food safety hazard of pathogen growth and toxin formation. FDA recommends implementing controls which assure the product has not been exposed to temperatures above 40°F while in storage. These recommendations include monitoring the adequacy of the ice surrounding the product or continuous temperature monitoring of ambient temperature to control the growth of pathogens and toxin formation in cooked seafood products."

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

**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]…"*


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 Fz2 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 Fz2 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 Fz2 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 Fz2 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 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[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 + (warning 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.

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

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.

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.[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/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.

Tip 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.

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

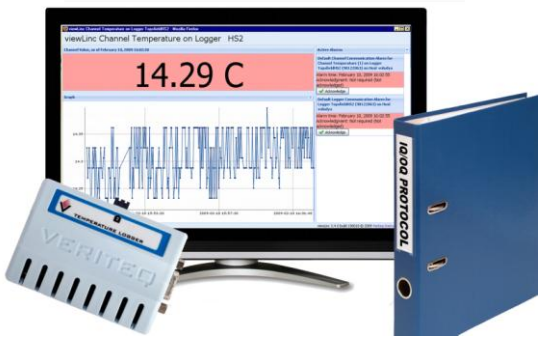
For example, in the 483 excerpt of the food facility, which noted that "*…monitoring procedures and a frequency at the refrigerated storage CCP that is, not adequate…"* A continuous monitoring and alarming system would provide gap-free temperature data recording. Data loggers with long-life batteries (up to 10 years) can continue to record temperature at the point of measurement, rendering environmental data immune to network or power failures.

| | Channel Fzr1 fnl T (1) on Logger Freezer 1 (08062069) on Host kena (C) | Channel Fzr1 rear T (1) on Logger Freezer 2 (08062119) on Host kena (C) | Channel spec fzr1 T (2) on Logger Freezer 2 (08101136) on Host kena (C) | Channel spec fzr2 T (1) on Logger Incubator 1 (08101136) on Host kena (C) | Channel spec fzr2 T (1) on Logger Incubator 2 upper (08102066) on Host kena (C) | Channel Fzr1 RH (2) on Logger Room 1 (08062119) 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 seafood processing example, the rooms can be validated with the same equipment used to monitor. Self-contained data loggers with internal sensors, memory and battery can be equipped for "periodic testing" or mapping the temperature distribution of the containers.

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




*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 storage, processing and critical manufacturing can stave off misgivings about a facility's commitment to quality. It will also lower your financial risk of product damage, inspection costs and brand reputation when temperature- and humidity-sensitive products are at stake.

For more information on how to avoid Form 483's, click www.veriteq.com/avoid-fda-483s or call 800-683-8374, or email FoodIndustryCompliance@veriteq.com.

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