

Welcome

FDA Regulations, Humidity Monitoring and FDA Form 483



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VAISALA

Humidity 101

\ webinar series

VAISALA

Agenda

1. Why monitor humidity in the Life Science Industries?
2. Overview of Regulations and Guidelines
3. Inspections
4. Responding to the FDA Form 483

Why Monitor Humidity in Drug Production & Storage?

- Many drugs are adversely affected by moisture during development phases, manufacturing, shipping and storage.



(Photo courtesy of Purdue News Service file photo/David Umberger)

Why monitor humidity?

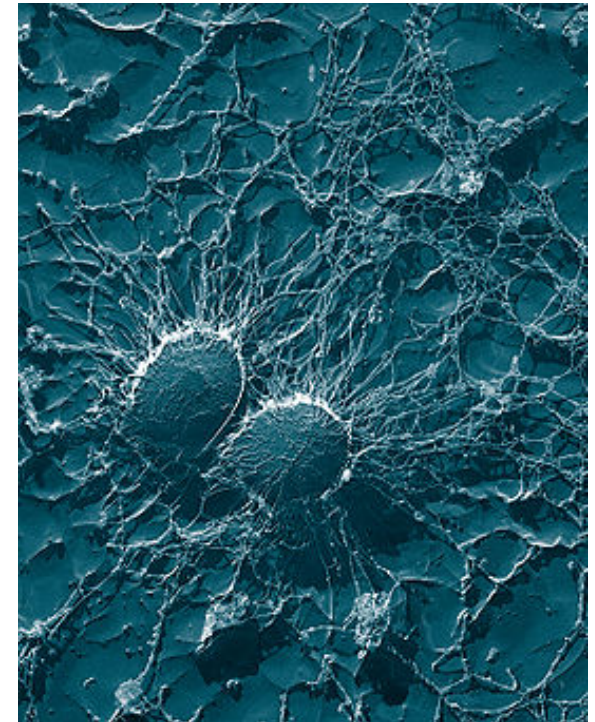
- **Humidity can cause**
 - Degradation of product
 - Impurities in the product



Why monitor humidity?

Water Activity & microbiological growth

0.97	<i>Clostridium botulinum</i>
0.95	<i>Clostridium perfringens</i>
0.93	<i>Bacillus cereus</i>
0.92	<i>Listeria monocytogenes</i>
0.86	<i>Staphylococcus aureus</i>
0.80	Most molds
0.50	No microbial proliferation



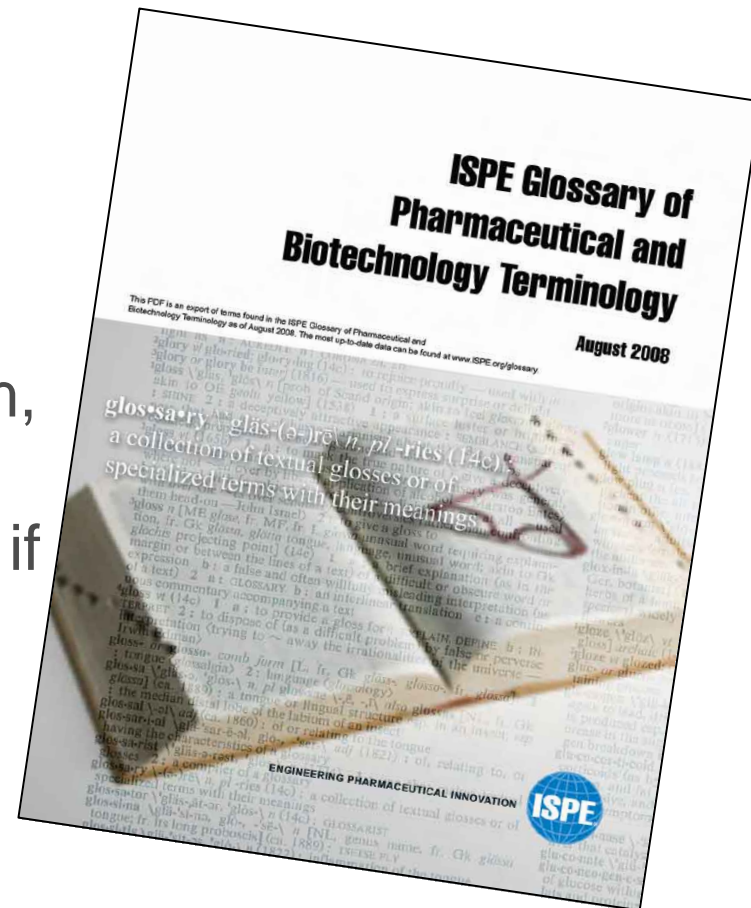
You must justify why you do not monitor humidity

- Include RH monitoring in your quality system *unless* you have:
 1. Documented justification for not monitoring/mapping RH with temperature.
 2. Assurance that humidity has little to no impact. IE: hermetically sealed, Low RH.



Some definitions

- Excursion
 - An excursion occurs if the average parameter value measured is above a maximum, below a minimum, or outside another established value; OR if insufficient data are collected.
- Deviation
 - Departure from an approved instruction or established standard.



Some definitions

- **Out of Specification (OOS)**
 - An examination, measurement, or test result that does not comply with pre-established criteria
 - Includes all test results that fall outside specifications or acceptance criteria established by the manufacturer and /or laboratory

Regulations Overview

- cGMP (current Good Manufacturing Practice)
- FDA (Food & Drug Administration)
- WHO (World Health Organization)
- ICH (International Conference on Harmonization)
- USP (United States Pharmacopeia)
- Code of Federal Regulations Title 21
 - Part 210
 - Part 211
 - Part 820
 - Part 11
- ISO 900X
- EudraLex (European Union Legislation)
- GAMP (Good Automated Manufacturing Practice) – ISPE trademark
- SFDA (State FDA) China

Regulations Overview

cGMP – current Good Manufacturing Practice

- United States
- Canada
- Australia
- European Union
- India
- China
- Japan

cGMP – United States

21 CFR Part 210

New Search	Help More About 21CFR
<p>TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER C--DRUGS: GENERAL</p> <p>PART 210 <u>CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS: GENERAL</u></p> <p>§ 210.1 - Status of current good manufacturing practice regulations. § 210.2 - Applicability of current good manufacturing practice regulations. § 210.3 - Definitions.</p> <p>Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264. Source: 43 FR 45076, Sept, 29, 1978, unless otherwise noted.</p>	

cGMP – United States

21 CFR Part 211

[New Search](#)

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL

PART 211 CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED
PHARMACEUTICALS

Subpart A--General Provisions

- [§ 211.1](#) - Scope.
- [§ 211.3](#) - Definitions.

Subpart B--Organization and Personnel

- [§ 211.22](#) - Responsibilities of quality control unit.
- [§ 211.25](#) - Personnel qualifications.
- [§ 211.28](#) - Personnel responsibilities.
- [§ 211.34](#) - Consultants.

Subpart C--Buildings and Facilities

- [§ 211.42](#) - Design and construction features.
- [§ 211.44](#) - Lighting.
- [§ 211.46](#) - Ventilation, air filtration, air heating and cooling.
- [§ 211.48](#) - Plumbing.
- [§ 211.50](#) - Sewage and refuse.
- [§ 211.52](#) - Washing and toilet facilities.
- [§ 211.56](#) - Sanitation.
- [§ 211.58](#) - Maintenance.

Subpart D--Equipment

- [§ 211.63](#) - Equipment design, size, and location.
- [§ 211.65](#) - Equipment construction.
- [§ 211.67](#) - Equipment cleaning and maintenance.
- [§ 211.68](#) - Automatic, mechanical, and electronic equipment.
- [§ 211.72](#) - Filters.

 **U.S. Food and Drug Administration**

cGMP – United States

21 CFR Part 820

NEW Search Help | More About 21CFR

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES
PART 820 [QUALITY SYSTEM REGULATION](#)

Subpart A--General Provisions

- [§ 820.1](#) - Scope.
- [§ 820.3](#) - Definitions.
- [§ 820.5](#) - Quality system.

Subpart B--Quality System Requirements

- [§ 820.20](#) - Management responsibility.
- [§ 820.22](#) - Quality audit.
- [§ 820.25](#) - Personnel.

Subpart C--Design Controls

- [§ 820.30](#) - Design controls.

Subpart D--Document Controls

- [§ 820.40](#) - Document controls.

Subpart E--Purchasing Controls

- [§ 820.50](#) - Purchasing controls.

Subpart F--Identification and Traceability

- [§ 820.60](#) - Identification.
- [§ 820.65](#) - Traceability.

Subpart G--Production and Process Controls

- [§ 820.70](#) - Production and process controls.



cGMP – United States

21 CFR Part 11

New Search	Help More About 21CFR
<p>TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER A--GENERAL PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES</p>	
<u>Subpart A--General Provisions</u>	
§ 11.1 - Scope.	
§ 11.2 - Implementation.	
§ 11.3 - Definitions.	
<u>Subpart B--Electronic Records</u>	
§ 11.10 - Controls for closed systems.	
§ 11.30 - Controls for open systems.	
§ 11.50 - Signature manifestations.	
§ 11.70 - Signature/record linking.	
<u>Subpart C--Electronic Signatures</u>	
§ 11.100 - General requirements.	
§ 11.200 - Electronic signature components and controls.	
§ 11.300 - Controls for identification codes/passwords.	
Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.	
Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.	

FDA Inspections

U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration A-Z Index Search go

[Home](#) | [Food](#) | [Drugs](#) | [Medical Devices](#) | [Vaccines, Blood & Biologics](#) | [Animal & Veterinary](#) | [Cosmetics](#) | [Radiation-Emitting Products](#) | [Tobacco Products](#)

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Inspections

- Investigations Operations Manual**
- Foreword
- Vision/Mission/Values
- Chapter 1 - Administration
- Chapter 2 - Regulatory
- Chapter 3 - Federal and State Cooperation
- Chapter 4 - Sampling
- Chapter 5 - Establishment Inspections
- Chapter 6 - Imports
- Chapter 7 - Recall Activities
- Chapter 8 - Investigations
- Exhibits
- Appendix
- ORA Directory
- Sample Schedules

Investigations Operations Manual

Search Investigations Operations Manual go

The IOM is the primary guidance document on FDA inspection policy and procedures for field investigators and inspectors.

Important disclaimer: The IOM Adobe pdf by chapter files provided represent a duplicate of the HARDCOPY 2010 IOM content. Be aware that the pdf files have not been updated although these files may be updated in the future. The IOM html version shown in the left navigation area is the most current version.

We have recently redesigned the FDA Web Site. As a result, some Web links (URLs) embedded within guidance documents are no longer valid. If you find a link that does not work, please try searching for the document using the document title. For more assistance, go to [Contact FDA](#).

IOM PDF Version

- Chapter 1 - Administration (PDF - 457KB)
- Chapter 2 - Regulatory (PDF - 662KB)
- Chapter 3 - Federal and State Cooperation (PDF - 422KB)
- Chapter 4 - Sampling (PDF - 1018KB)
- Chapter 5 - Establishment Inspections (PDF - 2170KB)
- Chapter 6 - Imports (PDF - 466KB)
- Chapter 7 - Recall Activities (PDF - 183KB)
- Chapter 8 - Investigations (PDF - 2176KB)
- IOM Appendix (PDF - 241KB)
- IOM Index (PDF - 475KB)
- IOM ORA Directory (PDF - 259KB)
- IOM Sample Schedules (PDF - 9049KB)

Inspections – What is inspected?

- What will the inspector look at around humidity measurement and monitoring?
 - Standard Operating Procedures
 - Understanding & Documentation for chosen thresholds
 - Records
 - Do they exist
 - What is the condition
 - Completeness
 - Integrity (CFR Part 11 compliance for example)

Inspections – What is inspected?

- Does your SOP include deviation reports & related documentation
- Humidity measurement device maintenance records
- Justification for calibration interval
- Calibration process & documentation

Sample Form 483.

“Test devices are deficient in that apparatus not meeting established specifications are used Qualification studies for the...room temperature stability chamber were deficient in that they did not always include specifications, acceptance criteria, or raw data [2 CFR 211.160(b)(4). Specifically:
(a) **There was no data to demonstrate that the chamber alarm would perform as required in the event of a humidity excursion.**”

483 (Rev. 05-08-07)

Facility Name: MYLAN, INC. - 31000000
Inspected by: MYLAN, INC. - 31000000
Date of Inspection: 05/15/2008
Inspector: [Signature]
Facility Representative: [Signature]

OBSERVATION 1

Failure to incorporate specific test conditions and include acceptance criteria for growth of microorganisms and moisture.

Specifically, the data on container closure testing from the following:

- Submittal 1: Product name: [redacted] lot: [redacted] tested on [redacted] at [redacted] on [redacted]. The test protocol did not specify the use of a humidity excursion test device.
- Submittal 2: Product name: [redacted] lot: [redacted] tested on [redacted] at [redacted] on [redacted]. The test protocol did not specify the use of a humidity excursion test device.
- Submittal 3: Product name: [redacted] lot: [redacted] tested on [redacted] at [redacted] on [redacted]. The test protocol did not specify the use of a humidity excursion test device.
- Submittal 4: Product name: [redacted] lot: [redacted] tested on [redacted] at [redacted] on [redacted]. The test protocol did not specify the use of a humidity excursion test device.

SEE REFERENCE ON THIS PAGE

05/17/2008

How to Respond to (and avoid) Form 483

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, optimized and ready for any critical evaluation, internal or external. The records and reports that this type of system should provide are part of your detailed response to quality concerns outlined in a Form 483 letter, or – preferably – provide any observation of non-compliance conditions during an inspection.

For example, the 483 excerpt noted in this article regarding the point audit device stated: "Relative humidity readings of 99% and 99% – which fall below your specified limits." A continuous monitoring system would provide accurate, gap-free relative humidity data recording in records that can be shared and retrieved easily, for a given timeframe. Data loggers that are equipped with internal batteries, memory and sensors can continue to record conditions at the point of measurement, which reduces the data transfer to network or power failures. Fixing an inspection with gap-free records can mitigate the risk of any observations of inadequate records.



Isolated monitoring system requires a dedicated HVAC 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 show an organization's commitment to quality.

For more information on continuous monitoring systems contact technical@vaisala.com or call 800-645-8374. Visit us online at vaisala.com/us/en

Time	Temp	Humidity	Temp	Humidity	Temp	Humidity	Temp	Humidity
00:00	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:05	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:10	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:15	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:20	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:25	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:30	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:35	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:40	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:45	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:50	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
00:55	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0
01:00	14.29	99.0	14.29	99.0	14.29	99.0	14.29	99.0

Reports can be automated to fit the needs of your company, but your compliance documents and recordkeeping.

PHARMACEUTICAL MANUFACTURING DIVISION

Site Name: **Site 100** | Date: **11/27/2009**

Inspected by: **John J. Smith** | Inspected on: **11/27/2009**

Product: **Product 100** | Batch: **Batch 100**

Inspection Type: **Final Release**

Inspection Summary: **Final Release**

Inspection Status: **Final Release**

Inspection Results: **Final Release**

Inspection Comments: **Final Release**

Inspection Date: **11/27/2009**

Inspection Time: **14:29:00**

Inspection Location: **Site 100**

Inspection Room: **Room 100**

Inspection Equipment: **Equipment 100**

Inspection Operator: **Operator 100**

Inspection Supervisor: **Supervisor 100**

Inspection Reviewer: **Reviewer 100**

Inspection Approver: **Approver 100**

Inspection Date: **11/27/2009**

Inspection Time: **14:29:00**

Inspection Location: **Site 100**

Inspection Room: **Room 100**

Inspection Equipment: **Equipment 100**

Inspection Operator: **Operator 100**

Inspection Supervisor: **Supervisor 100**

Inspection Reviewer: **Reviewer 100**

Inspection Approver: **Approver 100**

How to Respond to (and avoid) Form 483

References:

“FDA 483 Responses—Compliance Considerations” by Richard Poska and Ballard Graham, as published in the Journal of Validation Technology, Winter 2010

FDA Presentation “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

Note: used with permission

10 Steps for an Appropriate Response

The initial response must accomplish 3 things:

1. Establish Credibility
2. Demonstrate acknowledgement and understanding of the objectionable condition(s)
3. Show commitment to corrective actions

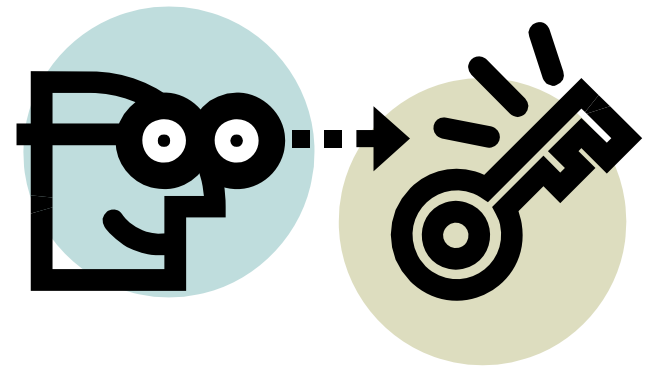
10 Steps for an Appropriate Response

- 1. Get your response in on time and in writing**
 - You have 15 days



10 Steps for an Appropriate Response

- 2. Demonstrate understanding and desire to comply**
 - Be explicit in the first paragraph of your response letter



10 Steps for an Appropriate Response

3. Respond *individually to each item* that was addressed in the warning letter

“Failure to ensure that drug products are stored under appropriate conditions of temperature and humidity so that the identity, strength, quality and purity of the drug products are not affected [21 CFR 211.46(b)], in that

- (1) your firm has not determined that the temperature/humidity equipment used to monitor the storage area is adequate to monitor the entire area;*
- (2) the monitor is not equipped with an alarm to alert your firm to environmental control failures;*
- (3) your firm has no written procedure for calibration of the monitor.”*

10 Steps for an Appropriate Response

4. Respond in order of importance

- Prioritize observations most likely to impact product quality.

“Failure to ensure that drug products are stored under appropriate conditions of temperature and humidity so that the identity, strength, quality and purity of the drug products are not affected [21 CFR 211.46(b)], in that

- (1) your firm has not determined that the temperature/humidity equipment used to monitor the storage area is adequate to monitor the entire area;*
- (2) the monitor is not equipped with an alarm to alert your firm to environmental control failures;*
- (3) your firm has no written procedure for calibration of the monitor.”*

10 Steps for an Appropriate Response

5. Outline how and when each deficiency will be corrected

- Be detailed and concise
- Do not discuss how the deficiency happened
- Provide documentation of the corrective action

“Failure to ensure that drug products are stored under appropriate conditions of temperature and humidity so that the identity, strength, quality and purity of the drug products are not affected [21 CFR 211.46(b)], in that

- (1) your firm has not determined that the temperature/humidity equipment used to monitor the storage area is adequate to monitor the entire area;***
- (2) the monitor is not equipped with an alarm to alert your firm to environmental control failures;***
- (3) your firm has no written procedure for calibration of the monitor.”***

10 Steps for an Appropriate Response

6. Use positive statements

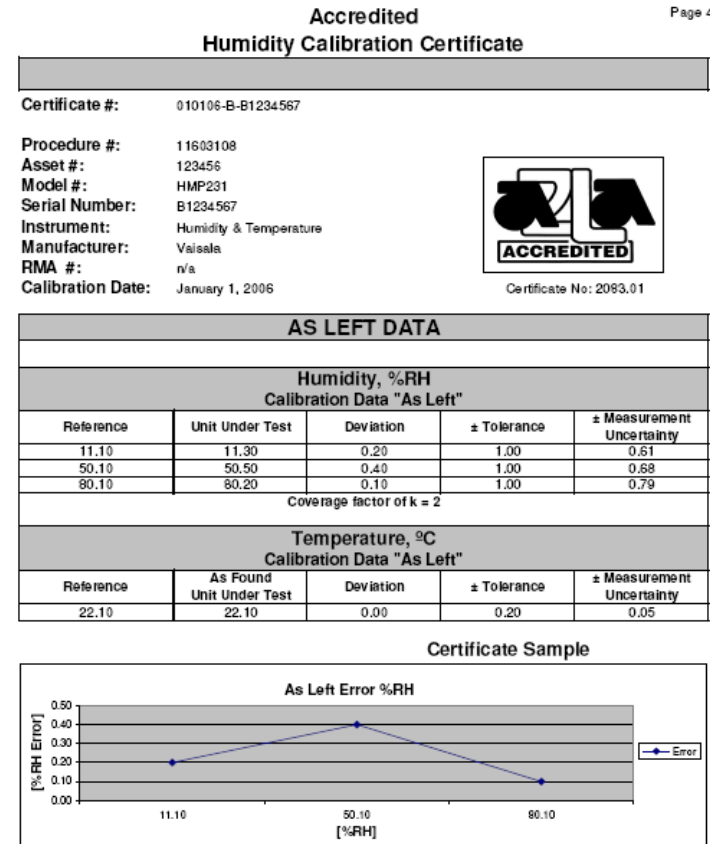
- Avoid language that implies fault
- Address each item in the 483 as an opportunity to fine-tune your quality and compliance systems and personnel



10 Steps for an Appropriate Response

7. Include reference documents to support the corrective action

- Sample report from a continuous monitoring system (CMS)
- Specifications for the measurement instruments or loggers that will be utilized for monitoring system
- A2LA Accredited Lab certification

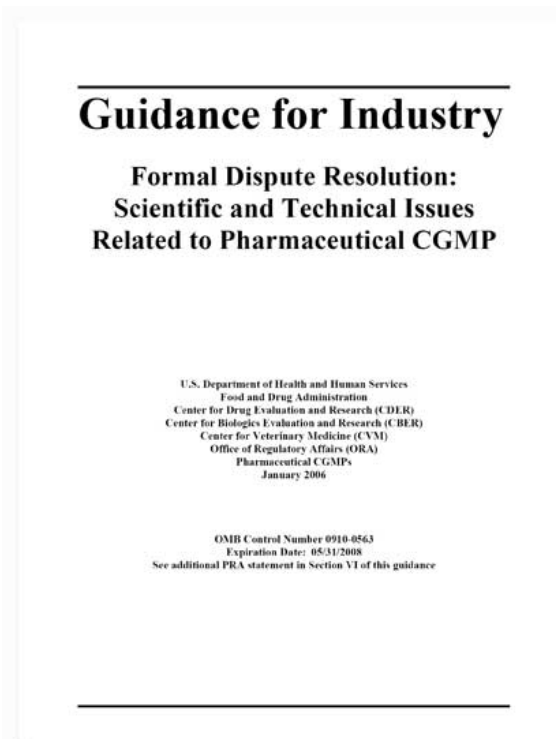


10 Steps for an Appropriate Response

8. If you disagree or feel it is an isolated incident

- Be ready with complete and accurate data to support your
- Be aware of the formal dispute resolution

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



10 Steps for an Appropriate Response

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
- Reviewing the IOM is a good place to start for improving a quality system

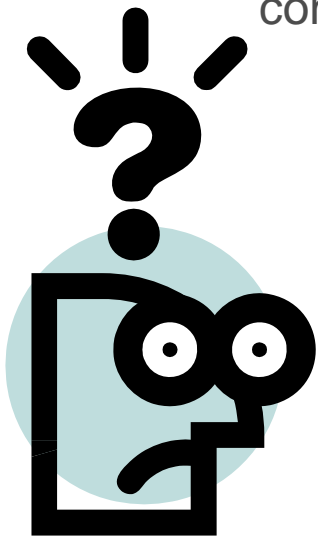
Investigations Operations Manual

- The guide to what FDA inspectors are looking for

10 Steps for an Appropriate Response

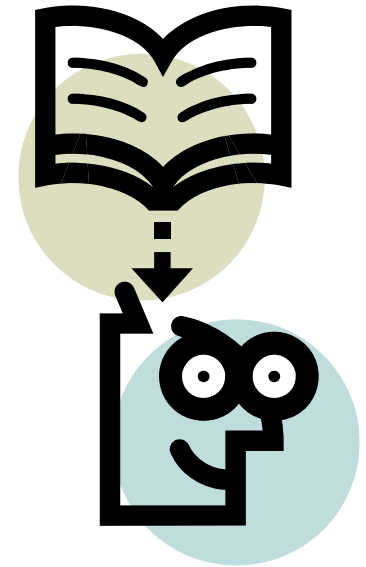
10. If you need clarification, seek it on the spot

- Get clarification in writing
- Ask a lot of clarifying questions
- Be sure you understand each deviation *before* the inspector leaves your facility
- If your questions involve policy, contact the FDA headquarters — don't contact your local FDA because policy is set at HQ.



10 Steps for an Appropriate Response

- Do you need an industry expert?



How to Avoid Form 483 about Humidity and Temperature

- Install and utilize an automated monitoring and alarming system
- This system will produce required reports and documentation required by cGMP
- Take the human element out of the monitoring and alarming system
- Ensure proper documentation about calibration and maintenance of measurement instruments
 - Consider using an accredited lab

Summary

1. Why monitor humidity
2. Regulations
3. FDA Inspections and humidity
4. Responding to a Form 483
5. Some ways to avoid the Form 483

Summary of Questions from the Audience

Vaisala Humidity Measurement Resources

- On-line Humidity Calculator www.vaisala.com/humiditycalculator
- Slide Rule Calculator to order – <http://forms.vaisala.com/forms/RequestSlideRule>
- Psychrometric Chart - <http://forms.vaisala.com/forms/RequestPsychChart>
- Humidity Conversion Formulas - http://forms.vaisala.com/forms/humidity_conversion

For expert assistance with your humidity measurement:

North America:

Email: instruments@vaisala.com

Direct telephone: 800-408-9454

Web: www.vaisala.com/instruments

Global – www.vaisala.com/contact

Next Webinar – (Stay tuned for the 2011 Schedule)

www.vaisala.com/webinars

Everyone who registered for previous webinar will get the invitation for all subsequent webinars.

You will receive a follow up email with all of the resource links & link to recording.

Live Humidity Seminars

Los Angeles – December 1st

<http://vaisala.com/seminars>

Thank you!

This concludes the webinar.

Follow-up email will arrive shortly with the resource links & further contact information.

Link to the recorded version will follow.