

# 483s - Not Here

---

PDA Metro Chapter Day  
Symposium

April 6, 2010

Joel Schwartzman

---

# SOME QUICK DEFINITIONS

# What is an 483

---

- “It is a form that an FDA inspector issues to a company at the conclusion of a GMP, GCP or GLP inspection that the FDA inspector considers to be a possible violation of a regulation.”

## What happens after you receive a 483

---

- ❑ Companies do not need to reply.  
However failure to do so can be taken as a sign of indifference by FDA.
- ❑ A prompt response is usually what is done by every company.

# Warning Letters

---

- ❑ Every 483 does not result in a warning letter.
- ❑ Warning letters are sent when the FDA believes that the observations made during the inspection were significant.

---

# Recent Medical Products Warning Letters Data

# Warning Letters on medical products

---

2006	2007	2008	2009
20	13	22	26

## Major citations

- Production record review
- Responsibilities of quality control unit
- Laboratory controls
- Written procedure deviations

# Production record review

---

- “ Failure to thoroughly investigate an unexplained discrepancy or the failure of any batch to meet any of its specifications, whether or not the batch has already been distributed.”



# Quality Unit

---

- “The quality control unit failed its responsibility to reject drug products that did not meet specifications impacting quality, strength, quality and purity. It also failed to review production records to assure that no errors have occurred or, if errors have occurred, and that they have been fully investigated.”

# Written procedures

---

- ❑ “Failure to follow written procedures applicable to the quality control unit and to establish adequate procedures in writing.”

# QC Responsibilities

---

- ❑ “ Failure to extend investigations to other batches of drug product that may have been associated with the specific failure or discrepancy. Failure to include conclusions and follow up in written records of the investigations.”

---

Some examples of 483s and other  
non- conformances found

# Management Responsibility

---

- No designated management representative listed on organizational chart
- No evidence of management review minutes.
- No procedure for conducting management review meetings with suggested agenda items.

# Internal Audits

---

- No documented procedures for conducting audits.
- No evidence that these are conducted
- No evidence of training of auditors.

# Failure to implement CAPA

---

- ❑ An OOS was closed without an CAPA investigation.
- ❑ An analytical test sample size was revised; additional testing could not be conducted because of lack of sample.
- ❑ A validation test could not be repeated because of lack of sample.
- ❑ No root cause investigation was documented for improper mixing; training was orally indicate only
- ❑ An OOS closed without notation of training for the person associated with the finding.

# Document Control

---

- ❑ Two different revisions of a test method were present in a laboratory SOP binder.
- ❑ Previous Test methods were found in desks of analysts



# Missing Procedures

---

- ❑ No documented process change procedure
- ❑ No documented incoming, in-process and final product inspection procedures.
- ❑ No documented procedures to handle transfer of materials from receipt to storage.
- ❑ No procedures to define how in-house drawings are generated and controlled.

# Complaint Handling

---

- ❑ NDA Field Alert Report was not submitted within three days after receipt of field complaints.
- ❑ There was no evidence of a formal investigation conducted even though eight complaints were received.
- ❑ Trend analysis was not conducted for a series of complaints received.

# Calibration

---

- ❑ There is no documented calibration procedure.
- ❑ Equipment is missing calibration stickers.
- ❑ Out of calibration equipment is tagged but no reason for rejection is identified.
- ❑ Calibration procedure does not include a statement that customer needs to be contacted.

# Failure to thoroughly investigate

---

- ❑ Out-of-trend and out-of-specification results over a three year period not investigated
- ❑ Investigations of failures were not extended to other batches of the same product.
- ❑ A Change Authorization was issued for manufacturing without a thorough investigation into the impact on product

# Quality Control Testing Deficient

---

- ❑ Laboratory records do not include initials or signature of second person checking the original records.
- ❑ Use of a un-validated test method.
- ❑ If the first test fails, retest until it passes without further investigation  
then  
Average two results without further investigation

# Raw Material Testing

---

- ❑ A filtering aid used was not part of the incoming testing procedures.
- ❑ An incoming material is frequently contaminated with a material but its presence is not tested for potency or effectiveness of the final product.

# Product did not meet specs

---

- Product was above spec
- Product was below spec

NO ROOT CAUSE WAS DETERMINED

# In-process specifications

---

- Previously acceptable process averages and process variability estimates were not used to derive in-process specifications. Data is reported “as found”.



# Stability Chambers

---

- ❑ Written procedures are not followed regarding the humidity and temperature monitoring of the stability chambers.
- ❑ Central Alarm System signals are not responded to when received.
- ❑ The central monitoring system did not provide notification for out of range temperature. The CAPA indicated that the system would be directly connected to another system but when reviewed the system was not operating.

# Environmental Test Methods

---

- ❑ Monitoring methods were not qualified to show that a wide range of microorganisms can be detected.
- ❑ Growth promotion testing of testing media did not include documentation of incubation dates and temperatures.

# Shipping

---

- ❑ Refrigerator trucks used for transport of product were not mapped for determination of worst case locations.
- ❑ Temperature charts placed in trucks were not reviewed.
- ❑ There is no documented rationale for the number and placement of temperature monitoring devices included with each shipment.

# Lack of adequate manufacturing controls

---

- ❑ Out of Specification Lots placed on hold for in-house use

NO ROOT CAUSE INVESTIGATION  
MADE

# Equipment Cleaning

---

- ❑ Cleaning validation studies for equipment was found to be inadequate or non-existent.
  - Evaluation of water permeability data was not complete
  - There was no rationale for using pH and absorbance testing to determine if filters were clean
- ❑ Written cleaning procedures were not followed.

# Manufacturing Process Validation

---

- ❑ There is no Master Validation Plan available.
- ❑ The protocol stated that process would be validated at a minimum and maximum processing times. The study was only done on the maximum time and no protocol deviation was issued.
- ❑ Room temperatures for a process were not validated.

# Manufacturing Process

---

- ❑ Validation study for product containers and closures were not studied for extractable of leachable contamination.
- ❑ Company does not have control plans available.
- ❑ Master production and control records are not complete.

# Labeling Operation

---

- ❑ Rejected labeled vials are reworked but relabeling is not documented.
- ❑ Labeling line speed was not documented.
- ❑ Labeling line was running at a speed higher than qualified for during the validation studies.



# Purchasing

---

- No Approved Supplier List
- No purchasing procedure available to identify how risks to suppliers are assigned.

# Subcontractor Controls

---

- ❑ Subcontractors are not audited.
- ❑ Subcontractors are not required to notify customer of changes.
- ❑ No validation data available for subcontractor processes.

# How to prevent?

---

The companies with few or no 483s have incorporated into their Quality System:

Management Review meetings quarterly

Strong Internal Audit programs

Detailed documented quality procedures

Strong CAPA programs

Complete training programs

# References

---

- ❑ FDA web page which shows 483s
- ❑ Parexel Consulting Web page
- ❑ Master Control Web page
- ❑ GMP News Web page
- ❑ Personnel auditing experience

---

THAT'S ALL FOLKS

THANKS FOR YOUR ATTENTION