Compounding Pharmacies and Laboratory Investigations

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Disclaimer

• I am making this presentation as an independent agent
• I am not making this presentation as a representative of USP, PDA, PMF, SCA or any other organization with which I am currently associated.
• The views expressed in this presentation are offered as mine alone.
Presentation Overview

- FDA Guidance on Investigations
- The Sterility Test Investigation
- Corrective Action Plan

FDA OOS Guidance

- Released October, 2006 – “Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production”
- “Chemistry-based laboratory testing of biotechnology products that are under the jurisdiction of CDER are within the scope of this guidance. However, this guidance is not intended to address biological assays (e.g., in vivo, immunoassays).” (footnote #3)

This text excludes microbiological assays

FDA OOS Document

- Phase I and Phase II Investigations
- Requirements
  - ID Root Cause
  - Determine Corrective Action
  - Implement Corrective Action
  - Monitor Efficacy of Corrective Action
  - Report

FDA OOS Guidance – Phase I

Responsibility of the Analyst

- Use only qualified analytical instruments (reference USP <1058>)
- Preserve test samples until validity of test determined
- Check results against specifications
- Immediately halt a test that is invalid and inform management
FDA OOS Guidance – Phase I

Responsibility of the Supervisor

- Confirm competence of analyst
- Examine the raw data and identify anomalous or suspect information
- Verify the calculations used
- Confirm the performance of the instruments.
- Confirm that appropriate reference standards, solvents, reagents, and other solutions were used.
- Evaluate the performance of the test method
- Fully document and preserve records of this laboratory assessment.

FDA OOS Guidance – Phase II

Review of Compounding

- Performed by Quality Group
- Review of all documentation to show that process was followed
- Report
  - A clear statement of the reason for the investigation.
  - A summary of the aspects of the process that may have caused the problem.
- The results of a documentation review, with the assignment of actual or probable cause.
- The results of a review made to determine if the problem has occurred previously.
- A description of corrective actions taken.
FDA OOS Guidance – Phase II

Additional Laboratory Testing
- Retesting a portion of original sample
  - Be very cautious – don’t “Test to Compliance”
  - Practice must be described in SOP in advance
  - Requires approval of Quality unit
- Resampling
  - Acceptable if original sample was improperly collected
  - Practice must be described in SOP in advance
  - Requires approval of Quality unit

Role of QAU

- 21 CFR 211.22(b)
  “Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.”

- The overall investigation will be coordinated though QA as per 21 CFR 211.160.
Environmental Sampling

Any cfu count that exceeds its respective action level (see Table 2) should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garments or work practices. The source of the problem shall be eliminated, the affected area cleaned, and resampling performed.

Sterility Testing

Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.
USP <797> - Investigations

The numerous notes in the back of the chapter state that an investigation is required:
• Excursions in Environmental Sampling
• Failures of media-fill studies

USP <1163> Quality Assurance in Pharmaceutical Compounding

Introduction

As a final check, the compounder shall review each procedure in the compounding process. To ensure accuracy and completeness, the compounder shall observe the finished preparation to ensure that it appears as expected and shall investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patient.
USP <1163> Quality Assurance in Pharmaceutical Compounding

Testing

pounders should conduct visual inspections and know: (1) the importance of testing in the overall quality program in the compounding facility, (2) when to test, (3) what to test, (4) what appropriate method(s) and equipment to use, (5) how to interpret the results, (6) the limits of the test, and (7) specific actions required when a preparation does not meet specifications. Investigative and corrective action should extend to other preparations that may have been associated with the specific failure or discrepancy. Testing may involve one or more quality attributes, and each test will have one or more acceptable procedures, usually with well-defined acceptance criteria.

FDA 483 Observations - 7/16/14

OBSERVATION 1

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. SOP 0.040 entitled, “Sterility Testing of a Finished Preparation” (Effective date: 6/2012) documents that an investigation should be conducted in the event that contamination is observed.

My review of approximately 23 Energy Formula Worksheets for the period between 4/16/2013 and 6/23/2014 revealed that your firm had sterility or endotoxin failures for 22 different lots of drug product. In each case, the investigations were either absent or incomplete.

All lots which failed testing for sterility or endotoxin were destroyed with the exception of the following:

- Cysteine hydrochloride, lot #804312014@14

Lot #90432014@14 was originally tested on 5/2/14. Subsequent testing for sterility failed (Test dated 9/2/14) and the lot was re-sterilized on 5/2/14. Subsequent testing for endotoxin and sterility met specifications. The lot is currently being held in inventory pending distribution.

- Folic Acid, lot #80412014@20 (Production date: 4/30/14. BUD: 10/28/14)

Lot #80412014@20 was tested on 4/30/14. Subsequent testing for sterility failed as noted on testing record dated 6/2/14. The lot is being held in quarantine pending destruction.

Each batch with the failed result is identified in the following table:
FDA 483 Observations - 7/16/14

Some examples where an investigation was absent include the following:

1. Cyanocobalamin 1mg/ml Buffered, lot #N04302014@14 (Production date: 5/2/14, Beyond Use Date: 11/1/14) Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afpiea felis*. No investigation was performed.

2. Felic Acid 10mg/ml, lot #N04172014@20 (Production date: 4/3/14, Beyond Use Date: 10/28/14) Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afpiea felis*. No investigation was performed.

3. Cyanocobalamin 1mg/ml Buffered, lot #N03272014@7 (Production date: 3/27/14, Beyond Use Date: 9/23/14) Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afpiea felis*. No investigation was performed.


FDA 483 Observations - 7/16/14

Some examples where an investigation was incomplete consist of the following:

1. Green Tea (EGCG) 10ml 10mg/ml Injectable, lot #N01202014@8 (Production date: 2/19/14, Beyond Use date: 8/9/14) Lot #N01202014@8 failed the test for endotoxin with a result of 252.64 EU/ml as documented on a Certificate of Analysis dated 2/26/14 from the contract laboratory.

Your investigation identified the possible root causes as 1) (b) (4) 2) aseptic technique, or endotoxin in the API. However, your firm's investigation was incomplete in that:

a. The raw material, EGCG, was identified as a possible source of endotoxin contamination but was never tested.

b. (b) (4) was identified as a possible source of the contamination but was not investigated.

c. Aseptic technique was also included as a possible source of the contamination but was not investigated.

d. There was no assessment of (b) (4) (glassware) which have not been validated.
FDA 483 Observations - 7/16/14

2. **L-Carnitine 500mg/ml for Injection**, lot #N12202013@8 (Production date: 1/29/14, Beyond Use Date: 7/28/14)

Lot #N12202013@8 failed the test for endotoxin with a result of 476.19 EU/ml as documented on a Certificate of Analysis dated 3/19/14 from the contract laboratory.

Your investigation identified possible root causes as 1) presence of endotoxin or gram negative bacteria in the API, and 2) excessive time between preparation and

Your firm's investigation was incomplete in that:

a. The testing of the raw material, L-Carnitine, which was identified as a possible source of contamination was not conducted.

b. Excessive time between preparation and [b](4) was identified as a possible cause but was not investigated.

c. The investigation did not include an assessment of [b](4) (glassware) which have not been validated.

d. The investigation did not extend to all impacted batches. Per your Pharmacist in Charge, the L-Carnitine, lot [b] was used in L-Carnitine, lot #N12202013@8 was also used in the product, Lipotocin Plus 10 ml for Injection, lot #N01042014@2 (Production date: 1/9/14 Beyond Use Date: 7/8/14) which was sent to consignees.

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FDA 483 Observations - 7/16/14

3. **Human Chorionic Gonadotropin 5000IU Lyophilized**, lot #NO4082014@14 (Production date: 4/17/14, Beyond Use Date: 10/15/14)

Lot #NO4082014@14 failed the test for sterility as documented on a Certificate of Analysis issued by the contract laboratory (Organism: *Staphylococcus haemolyticus*).

Your investigation identified aseptic technique by the technician as the probable root cause but failed to include an evaluation of the following areas:

[b](4)

- Room pressurization
- Laminar flow operation
- Communication and coordination
- Assessment of container closure
- Sanitization procedures (Room, equipment, product containers, etc.)
- Evaluation of other lots compounded by the same technician
FDA 483 Observations - 7/16/14

B. SOP #9.010 entitled, “Particulate Testing for Sterile Preparations” (Date: 1/2013) provides guidance for the evaluation of vials of sterile, injectable drug products for particulates. My review of 185 lots of drug products manufactured between 4/16/2013 and 6/23/2014 revealed that at least 185 lots had fibers or particulates. No investigations have been conducted.

In each case, your firm conducted a 100% inspection by [redacted]. Vials identified as containing fibers and/or particulates were then removed and discarded. However, this method has not been shown effective to detect fibers or particulates in amber vials.

The remaining vials from each lot were then distributed to consignees. Some examples consist of the following:

- Methycobalamin, lot #N01162014@21
- DMSO, lot #N01082014@1
- Cyanocobalamin, lot #N01662014@11

FDA 483 Observations - 7/16/14

C. Investigations have not been conducted for sterile, injectable drug products which were rejected due to precipitation or particulates. Some examples consist of the following:

1. Thiamine HCl 30mg 100mg/ml Injectable, lot #N02212014@10 (Production date: 2/25/2014, BUD: 8/24/2014): Particulates
2. M.I.C.A. 125 50mg Preserved 25/50/50/50/25 mg/ml Injectable, lot #N12272013@6 (Production date: 1/2/2014, BUD: 7/1/2014): Precipitation

D. A “Sterilizer Test Report” dated 2/27/14 issued by [redacted] indicated that a gram stain confirmed spore growth in one or more test strips and control strips for a test conducted on 2/19/14. No investigation was conducted.

Frequent 483 Citations - Current

84 Reports
9/25/14

References

• FDA Freedom of Information page for 2014 483s
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm384667.htm

• http://www.americanpharmaceuticalreview.com/Featured-Articles/135885-GMP-and-Compounding-Pharmacies/

Presentation Overview

- FDA Guidance on Investigations
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Lab Error or Product Failure?

- First step MUST be to evaluate the possibility of lab error
- Formal Laboratory Investigation Procedure
- Test may be invalidated only on clear proof of lab error
Potential Model for Lab Investigation
Potential Model for Lab Investigation (1)

- Potential Problem Identified
- Do the data make sense?
  - Yes → Management Informed → Begin Laboratory Investigation
  - No → Can the entries be corrected? (transcriptional, clerical, math error)
    - Yes → Correct entries, with GARP traceability → Stop
    - No →实验室 investigation

Potential Model for Lab Investigation (2)

- Lab Investigation:
  - Procedure
  - Sample
  - Culture
  - Media
  - Equipment
  - Technician

- Laboratory Issues Identified?
  - Yes → Determine Disposition of the Test (QAU)
  - No → Invalide Test

- Is the Test Valid?
  - Yes → Close out lab investigation
  - No → Complete Lab Investigation Report
  - Initiate appropriate corrective action
  - Confirm effectiveness of corrective action
General Questions

• Does Contaminant Make Sense?
  • Can it survive in product?
  • Does it form spores?
• Has this Contaminant Been Seen Before? (remember need for strain-level ID methodology)
  • Test Environment
  • Manufacturing Environment
  • Raw Material/Component

Useful information can be found in:
USP. 2014. <1117> Microbiological Best Laboratory Practices

Procedural Issues

• Correct Test?
• Correct Version?
• Method Suitability Studies Completed and Observed?
• Test Controls Within Specification?
• Does Documentation Support Valid Test?
• Does a Review of Test Failure Trends Show Any Useful Information?
Sample Issues

• Correct Batch/Product Submitted?
• Samples Taken Correctly?
• Samples Handled/Stored Correctly?
• Primary Packaging Undamaged?
• Acceptable Physical Appearance
• Other Batches Sampled in This Manner/by This Technician of Interest?
• Has this Product Shown a History of Issues?

Stock Cultures

• Identity and lineage of the cultures confirmed?
  • Traceable?
  • The number and the conditions of each passage
  • Confirmation of identity upon receipt from vendor
• Confirm that the identity of the culture in the test (strain level).
• Working slant confirmed through retrospective or prospective review?
• Sister Tests OK?
  • Working slant
  • Parent frozen culture
Media Issues

- Correct formulation for that test?
- Media preparation records (composition, autoclaving, quarantine activities) show any irregularities?
- Media released for use?
  - Physical tests
    - pH, Appearance, Integrity of container
  - Growth promotion
  - Sterility check
- The expiry and storage conditions of the media confirmed?
- Sister Tests OK?

Equipment Issues

- Were the correct instruments used?
- Were incubation temperatures correct and within specifications?
- Equipment on a regular calibration and preventative maintenance schedule?
- Sister tests (shared incubators) OK?
- Were the incubators used in this test cleaned regularly?
- Sterilization Records OK?
- Were water baths (molten agar) recently cleaned/sanitized?
Personnel Issues

- Technician Trained in Appropriate SOP (revision control)?
  - Current Proficiency Rating?
- Any technician-dependent deviations noted?
- Technician Associated with Other Failures?
- Technician Have Other Tests Recently Completed or Underway – Are They OK?
- How Many Tests Did This Operator Perform on This Day?
- Does lab have large number of investigations?
  - Leadership issue?

Potential Model for Lab Investigation (2)
Closing the Laboratory Investigation

The investigator (with QAU) should determine if the situation was the result of:

1. Laboratory error (invalid test)
2. Assay variation
3. Inconclusive causes
4. Failing product

Conclusions 2, 3, or 4 uphold data – proceed to OOS (or other) investigation
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Corrective Action Plan

Identifying a problem is not enough – cGMP requires a solution to that problem and demonstration that the corrective action was effective.
Corrective Action Plan

Address Root Cause
Identifying a root cause in most microbiology investigations is difficult

• Microorganisms are ubiquitous
• Humans are the primary source of contamination in most pharmaceutical manufacturing and testing environments
• Issues usually occur as isolated events, separated in time from recognition of the problem
• Documentation is critical.
• Show caution in assigning blame to training.
• Follow-up is required to show effectiveness of corrective action

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Thank you for your attention

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Microbiology Network

- Consulting
  - Contamination Control/Sterility Assurance
  - Quality Assurance
  - Quality Control
    - Microbiology Lab Operations/Design
    - Microbiology Process/Procedure
    - GCP/CGMP for <797> or GMP compliance
- Product Development
- Audits
  - Laboratory Preparation/Contract Lab Qualification
  - Facility Contamination Control
  - FDA Mock Systems Audit of Facility (w/team)
- Training
  - In-house Training
  - Distance Training
THANK YOU FOR YOUR ATTENTION

QUESTIONS?

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