Complaints – Investigations
Root Cause Analysis

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Learning objectives

- Understand failure investigation/requirements
- Identify types of OOS/deviations
- Conduct root cause analysis of sterility failure
  - Identify the general principles of an out-of-spec (OOS) sterility test
  - Distinguish between laboratory error and process contamination as cause of sterility test failure
- Corrective and Preventive action (CAPA)

FDA minimum regulations requirements

- A failure investigation to be conducted whenever an OOS test result is obtained (21 CFR § 211.192)
- To determine the root cause of the OOS result
- To identify the source of the OOS result, *whether*
  - an aberration of the measurement process
  - an aberration of the manufacturing process
- A written record of the investigation should be made, including conclusions and follow-up

FDA minimum regulations requirements

- The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy (21 CFR § 211.192)

- Investigation is necessary to determine if the result is associated with other batches of the same drug product or other products

- Batch rejection does not negate the need to perform the investigation - Even if a batch is rejected based on an OOS result

Failure Investigations

- What is Failure Investigation?

Assessment of any discrepancy or failure of a drug product (or any of its components) to meet a specification and identifying the likely causes of failure

- What is Root Cause Analysis?

An objective, thorough, and disciplined methodology employed to determine the most probable underlying cause of a problem, complaints and undesired events, to formulate corrective actions to mitigate or eliminate the causes

(Quality Management and Training, 2008)

Principles of a Failure investigation

- Identify/Understand the problem
- Determine the root cause
- Develop a plan for corrective action
- Demonstrate effectiveness of corrective action
- Written and approved investigation report

What is required?

- Written investigation SOP
- Thorough investigation of root cause (RCA)
- Extend to other batches of the same drug product
- Extend to other products sharing utilities, etc
- Conclusions and follow-up
- Enhance Training
- Written record of the investigation

What is required?

- Clear and accurate written investigation document
- Full description of the detected failure
  - Investigation completed in a timely manner
- Comprehensive Assessment - of the processes and testing
- Review of the documentation including raw data
- History of similar failures
- Impact assessment
- Implemented corrective and preventive actions

Investigations SOP should address…

- Expeditious initial review of priority complaints
- Review of retain samples of lot/lots affected
- Review of lots that might be affected –lots made just before or after affected lots
- Determination of root cause
- Timetable for completion
- Preparation of Report

Root Cause Analysis Tools

- Popular RCA tools include:

✓ Cause and effect (“fishbone” or Ishikawa)
✓ Fault tree analysis (FTA)
✓ Failure mode and effects analyses (FMEA)
✓ 5 - whys

- FDA has no requirement for use of analytical tools. The choice to use or not use a RCA tool is solely at the discretion of a firm. (Caveat: FDA may suggest a RCA tool be used during a compliance remediation)

Scenario:

- **Investigation and root cause analysis of a sterility failure**

- When a firm receives a customer complaint that indicates a possible USP sterility test product failure, some of the inevitable questions are

  - How/where did the failure happen?
  - What is the extent of the problem - How many batches are impacted? Identity of the micro-organism(s)?
  - What is the known and unknown impact on consumers?
  - FARS? Recall? Market withdrawal?

There are two areas for the review to focus on…

- …. A sterility positive result can be indicative of production or laboratory problems. The manufacturing process should be comprehensively investigated

- The laboratory that tested and released the product. Generally, should start with the laboratory data review

- It would be quicker if done concurrently

Laboratory:

Review:

- test methods and controls, including adherence to validated methods
- training and qualifications of laboratory personnel
- trending of water system test results
- systems used for recovery, identification and trending of environmental monitoring isolates

Laboratory Analytical Review

Review QC records

- For proper sterilization of all equipment and media used during the sterility test method: manifold/ SteriTest; rinse fluid, culture media, canister kits, etc

Review the EM data acquired during sterility testing

- settling plates, RODAC, simulation system controls, etc
- What are the microbial species and their normal habitat (i.e., water, plants, people, etc?). Do they match in-house QA strains used for GP?

Laboratory Analytical Review

Negative Samples

- Did the laboratory run the positive QC on the enrichment media?
- Did they perform the positive controls at time of use?
- How did they ensure a negative was negative (not false –ve?)

EM Plates

- Selective media?
- Non-selective media?
- Counting errors…(if plates still available)
- Recording errors
- Isolation errors

Laboratory Analytical Review

- Review training records of analysts and management who performed/ evaluated the test
- Review qualification of analysts and management who performed/evaluated the test

  -Are they qualified in that area?
- Review the qualification of the bio-clean room facilities or isolator chamber used during testing

  -Were there any leaks in the gloves?

  -improper sanitization of product container before placement into work station or isolator?

Laboratory Analytical Review

Review cleaning and sterilization of reusable glassware and equipment

- Poorly cleaned glassware will make sterilization of media more difficult and possibly shelter trapped microbes from the killing effect of the sterilant

Review laboratory areas used for sub-culturing the sterility test medium onto enrichment plates

- Cluttered work space or un-sanitized surfaces may cause plate contamination
- Check the remaining plates of the same batch of original plates used for isolation for possible pre-existing contamination

Laboratory Analytical Review

- Check to see if the medium had been recalled or has had past problems with contamination during manufacturing

- It may be necessary to perform a genotype identification on the two isolates (product source and manufacturing area isolate) if they are the same species

Laboratory Analytical Review

- Did the analysts manipulate or exclude some of the data used in the final QC report?
  - Perhaps raw data was averaged to bring the bioburden count below the alert or action levels?
- Review the aseptic process simulation studies trend
  - Did the microbial species recovered in past simulation studies match the microbe(s) recovered from the current product test failure?

Laboratory Analytical Review

- If laboratory operations are identified as the cause of the nonconforming test outcome, a corrective action plan should be developed to address the problem(s)
- Following approval and implementation of the corrective action plan, the situation should be carefully monitored and the adequacy of the corrective action determined

- http://app.uspnf.com/uspnf/pub/index?usp=40&nf=35&s=2&officialOn=December%201,%202017

Manufacturing Facility Review

(**aseptically filled pharmaceuticals**)

- Review *material*, *facilities & equipment*, and *production* systems
- Review environmental monitoring (EM) data taken from production areas and the testing environment (i.e., S-T-A, settling plates, RODAC, etc) for microbial contamination that matches the microbe isolated from the finished product sterility test

Manufacturing Facility Review

(aseptically filled pharmaceuticals)

If no microorganism detected, check adequacy of EM method used during manufacturing for proper sensitivity and applicability

- Did they use the proper medium (ie non-selective)?
- Did they perform growth promotion?
- Did they use appropriate incubation time and temperatures?

Manufacturing Facility Review

- Did they perform filter integrity test on the membrane used for the product sterilization?
- Review the recorded product pre-filtration bioburden levels
- assure that the concentration of bacteria in the bulk did not exceed the membrane filtration capacity determined in the validation studies
- Did they change the source or model for the membrane filter cartridge used in the process?

Manufacturing Facility Review

- Review Maintenance log
  - Were there any interventions by maintenance or other personnel during production of the contaminated lots?
  - Review glove/uniform monitoring results
  - Review CCTV footage - Was there a breach in the personnel barrier system to protect the product?
  - Review alarm logs – Was the aseptic core breached during production?

Facilities and Equipment System:

Review:

- cleaning and disinfection logs
- facility/equipment layout and air handling system material flow on days of manufacture/testing
- quality control of classified areas, including air pressure balance and HEPA filtration on days of manufacture/testing
- trending data supporting the adequacy of clean room quality – at least 4 weeks of data

Materials System:

Review:

- microbial and bacterial endotoxin control of incoming materials and components
- quality of water supply, maintenance, qualification
- operation of the systems that provide the requisite water and process gases

Production System:

- operator behavior and aseptic techniques during manufacturing
- production line operations and interventions
- personnel training in aseptic techniques
- major production line repair or maintenance issues
- microbial and bacterial endotoxin controls, including hold times of critical steps
- validation of sterilization of equipment, container-closures and supplies

Manufacturing Facility Review

- **Terminally sterilized drug product**
  - Check autoclave validation studies for sterilization process - cold spots, heat penetration, changes in chamber load configuration, etc
  - Check maintenance records for house steam, records for autoclave repair, new plumbing

Manufacturing Facility Review

- **Terminally sterilized drug product**
  - Check Biological Indicator (BI) information- improper storage of BIs
  - changes in the culture enrichment
  - incubation parameters (i.e.,55-60 C)

Manufacturing Facility Review

- **Terminally sterilized drug product**
  - Evaluate the heat resistance characteristics of isolate recovered from the product and determine if it can survive during the process condition
  - Review product container/closure integrity data and possible recent supply source changes of glass vials or rubber stoppers

Trends

Manufacturing history

- The manufacturing history of a product or similar products should be reviewed as part of the investigation
- Past deviations, problems, or changes (e.g., process, components, equipment) are among the factors that can provide an indication of the origin of the problem

Trends

Product Presterilization Bioburden

- Review trends in product bioburden and consideration of whether adverse bioburden trends have occurred

Monitoring Personnel

- Review of data and associated trends from daily monitoring of personnel can provide important information indicating a route of contamination
- The adequacy of personnel practices and training should also be reviewed

Why is Retesting NOT an acceptable Microbiological Practice?

- Microbial contamination in a product batch is not homogeneous
- Microbial contamination is not homogeneous even within a product container-especially non-aqueous products
- Storage conditions and product composition with retain units can have adverse effects on the remaining microbes in the product
- Microbes/endotoxin clump and form Micelles respectively

Warning Letter

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations into product quality complaints are inadequate. For example, when you investigated two complaints of leaking **(b)(4)** containing **(b)(4)** batch **(b)(4)**, you did not determine a root cause for the container-closure defect. Your **(b)(4)** supplier informed you of a **(b)(4)** defect that you did not address in your investigation. The investigation also failed to include an examination of retain samples or review past complaints to identify other instances of bag integrity defects.

References

- Sterile Drug Process Inspections Compliance Program Guidance Manual https://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/UCM125409.pdf
- 21 CFR 211
- FDA Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production
- United States Pharmacopeia http://app.uspnf.com/uspnf/pub/index?usp=40&nf=35&s=2&officialOn=December%201,%202017
- Center for Drug Evaluation and Research (CDER) Guidance for Industry. Q9 Quality Risk Management https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073511.pdf

Questions may be sent to
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