:Session 5: Investigation for source of contamination in critical areas–a case study.

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Potential Failures in an aseptically processed product

- Sterility
- Endotoxin
- Particulate matter
- Environmental condition
- Personnel Practices in aseptic area
- Personnel Hygiene
- Gowning procedures

❑ ***Many of these are inter-related and have impact on one or more parameters leading to failure in end results***

A Case Study – an experience from past

- It was reported that a batch of a sterile API, packed in 10 kg Al container failed in the test for sterility at a US customer site

- *This batch was tested before dispatch and was passing in the test for sterility and all other parameters as per agreed specifications.*

Failure Investigation Carried Out -

- A comprehensive investigation was undertaken considering all aspects of Manufacturing and Testing which could have caused sterility failure;
- This included the following :

Investigation included all potential failure areas

- Failure of Sterilization processes, CIP and SIP
- Excursions in differential pressure
- LAF – Air Flow patterns
- Cleaning and Sanitization of the aseptic areas
- Integrity of sterilization grade filters
- Disinfection of accessories
- Personnel Practices
- Malfunctioning of manufacturing equipment

Additional Investigation

- Additionally following areas were also taken into account
- Equipment qualification and re -validation
- Filter grade and Filter validation
- HVAC revalidation
- Autoclave Sterilization cycle revalidation
- SIP cycle validation for various equipment
- Trend of water monitoring system
- Trends of environmental conditions from grade D ,C ,B and A.
- Personnel Qualification and Personnel Training
- Most recent system simulation (or Media Fill Trials) and interventions .
- Container closure integrity

QC Lab investigation

- QC Sterilization process
- Differential pressure
- Cleaning and Sanitization of sterility test room
- LAF – Air Flow patterns
- Disinfection of accessories
- Personnel Practices
- Past trends of sterility test results
- Qualification of Analyst
- Past trend data for environmental monitoring , Personnel monitoring etc

Methodology Employed

- All possible areas of failure were evaluated on hypothesis basis
- Investigations were carried out
- Each of the hypothesis was reviewed and impact assessment was done through a process of elimination
- Retention sample too was tested as a part of investigation, although it was well known that a passing result in sterility was not to corroborate failure reported by customer.

Methodology - contd

- By eliminating each potential cause (or hypothesis) for the reported failure , NO “assignable” or “most probable” cause could be ascertained .
- A comprehensive report with all necessary references and data base was prepared and shared with the customer.
- A request was also made to the customer to investigate and share their OOS observations of investigation / findings – specially w.r.t identification of micro-organism in sterility test failure found in their laboratory

Further actions and disposition of the Lot in question

- ***It was found after speciation that, origin of this organism was not from Production environment in India, and instead, this was from the test environment in customer laboratory***
- Our India report was then accepted and investigational findings were appreciated by the customer
- They agreed to conduct sterility test on the additional side samples of sterile API available with them.
- Additionally, a protocol based study was conducted by customer , by drawing samples from each of the containers.
- All samples passed in sterility at customers end and finally the API lot was accepted

CAPA or continuous improvements undertaken -

- In view of the complaint following CAPA or additional measures was instituted .
- To conduct transportation study for the API containers and side samples independently .
- Gowning procedure was strengthened as “fail safe” approach by incorporating “clean or nearly sterile” pre gowns, prior to final sterile garments, both in manufacturing and in QC lab
- Filter Integrity test was made “on-line” to verify the integrity before and after sterile filtration .
- Closed sterility test equipment (Millipore) introduced .

Lessons learnt from this -

- Reliability of all data in Aseptic processing (and more so microbiological) is very CRITICAL to build Assurance and to undertake effective investigations in case of Failures
- Do not ignore any Deviations, Failures which occur in routine Environmental monitoring. Document all excursions promptly and assess impact on product safety
- Investigations should be Science based and logical
- Last but not the least, do not fear any external audits due to microbiological failures. If investigations are robust and factual, you win the hearts of inspectors and customers

What was in store for us ?

- There was a US FDA inspection soon after this complaint closure and the investigators spent initial 2 full days only to review this complaint , investigational details and response
- From the manner in which this inspection began, it was evident that, the investigators were having prior knowledge of this reported sterility failure by the US customer
- All documents were produced and investigators appreciated the approach, efforts made in a transparent manner in carrying out this investigation to find "root cause", and draw appropriate conclusion

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Road Ahead

- As is well known, Aseptic operations require high degree of discipline, above all complete "transparency" in whatever we do and document
- Continuous improvement approach , instituting good precautionary measures / controls, good personnel discipline are key for Sterility Assurance
- Design manufacturing and testing areas to minimize human interventions to the least by using Hoods, RABs, Robotic technology
- Good controls on container closures and all areas where product is likely to have exposure
- Quality of equipment and their integrity w.r.t sterility - post CIP and SIP cycles
- Quality of filters, robust Filter validation studies and online integrity test .
- Personnel Training and qualification procedures
- Media fill run with all possible interventions
- Good control on environmental monitoring systems (BMS) with alarms and interlocking with aseptic area operations

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Road Ahead - continued.....

- Review of environmental monitoring results ,both viable and non viable on continuous basis
- On line particulate monitoring
- Viable and non-viable controls progressively from class D thro' C , B and on to Class A areas
- Reliability of Data- Microbiological data is most vulnerable to data integrity issues – ***"do what you say, and say what you do in documentation"***
- Controls on calibrations of instrument and PLCs for desired performance of SIP and CIP cycles and other controls

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PDA Parenteral Drug Association India Chapter

Thank You

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