PDA India Chapter

# The Quality Edifice and Sterility Assurance of Parenterals

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*Connecting People, Science and Regulation*

**Session: I (B)**

**Investigations- The ABC of expectations**

PDA India Chapter

Case Study : Common issues in aseptic processing- Examples: Glass particles/ Sterilization/ Media Fill

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## Purpose of this session

PDA India Chapter

- Understanding the steps to be followed for the media fill failure
- Understanding the Regulatory Requirements
- Understanding the FDA expectations in handling Media fill failure investigations

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# Media fill failure

- How many have of you have experienced a media fill failure?
- Bad luck or Good luck?

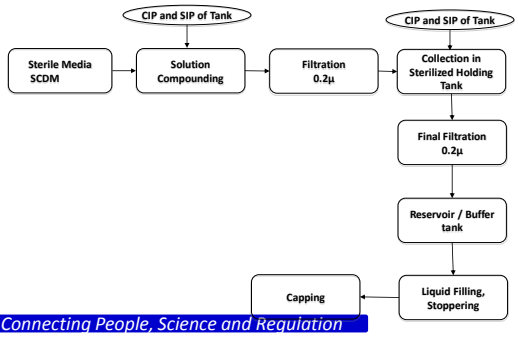


# Case Study

- Media fill was taken as part of routine media fill requalification
- Batch details
  - 5 ml Vial
  - Batch size : 7000 vials
  - Media used: Soyabean Casein Digest media
  - Filling time 24 hrs



# Case Study Process flow



## Case Study

- Observation on 7th Day
  - 122 Vials contaminated
  - 1.7% vials with contamination



## What is the first step?



## Which site procedure defines this?

## First few step?

**Management Notification (Within 24 hrs)**

- Done within an hour after the observation of the contaminated vials

**Initiation of deviation (Within 24 hrs)**

- Taken on the same day of the contaminated vials observation

**Hold Notice (Except for TS product)**

- Done on the 2nd day of observation of the contaminated vials



## First few step?

**Field Alert (within 3 working Days)**

- Done on the 3rd day of observation of the contaminated vials

**Manufacturing stopped**

- Till investigation / impact assessment completed.



## Investigation

- Investigation Initiated on the same day
- Meeting with the department Heads
- Investigation Team of 10 people was formed consisting of Production, Quality Control, QA, Engineering, Microbiology.
- The strategy was finalized to decide for the investigation methodology.

# Investigation

The investigation was divided into Six Steps

**Step-1 [Information Collection & Review]**
Thorough review of the failures from documentation and linking the facts from the previous media failure(s) in the series

**Step-2 [Identification of most probable cause(s)]**
Identifying the most probable cause(s) for failure, their assessment

**Step-3 [Hypothesis Testing]**
Designing and conducting the necessary experiments, to prove the most probable cause identified in step-3, as the reason for failure.



# Investigation

**Step-4 [Establishing the route/ mechanism of contamination]**
Identify and/ or establish the route / mechanism of contamination

**Step-5 [Risk Assessment]**
Perform a Risk assessment of the route of contamination and similar type of risks available in your system

**Step-6 [Recommendations for CAPA]**
Recommend and implement the corrective / preventive actions to avoid reoccurrence and take 3 consecutive, successful media fill batches



# Investigation

**Step-1 [Information Collection & Review]**
Thorough review of the failures from documentation and linking the facts from the previous media failure(s) in the series

- Batch records review and comparison of the important batch manufacturing aspects
- Identification of deviations, if any occurred during manufacturing of the affected batch(s).
- Identification of downtimes and/ or repairs, if any occurred during the manufacturing of affected batch(s).
- Identification of problems, if any in the critical support system (HVAC, Water System, and Compressed air) during the manufacturing of affected batch(s).

# Investigation

**Step-1 [Information Collection & Review]**

Thorough review of the failures from documentation and linking the facts from the previous media failure(s) in the series

- Review of Sterility Assurance Information from the corresponding batch manufacturing records and additional associated documents, such as log books, lab notebooks etc. (additional testing done for media fill)
- Review of environmental monitoring results in the filling line and in the surrounding environment
- Identification of organisms
- Review of changes to the plant and/ or the manufacturing processes
- Identification of the causative organism and comparison with normal environmental microbial flora
- Review of the personnel involved in various manufacturing operations1111



# Investigation

**Outcome of Step-1**

**Abnormality found**

- Abnormal counts were observed in the Environmental monitoring in the Grade B area
- 1 count was observed in the RABS.
- Maintenance was done for the Buffer vessel
- 2 filling machine operator was found to have microbial counts in their gloves
- Filling room coving was painted before this media fill as part of the annual maintenance program

**Identification of organism**

- In all media fill contaminated vials the organism found was Bacillus sp.
- In the EM and Personnel monitoring all organism were either cocci or Bacillus sp.



# Investigation

**Step-2 [Identification of most probable cause(s)]**

- EM and Personnel's were considered to be the most probable cause

**Is it right?**

# Investigation

**Step-2 [Identification of most probable cause(s)]**

**What about modifications done to the buffer vessel?**



# Investigation

- **What was the modification?**
  **Top dish was replaced (like to like )**
- **Was the buffer vessel sterilized?**
  **Yes**
- **Is the sterilization process Validated?**
  **Yes**



# Investigation

**Step-2 [Identification of most probable cause(s)]**

- Comparing the organisms identified

| S. No. | Identified organism | RABS | Personnel | Media fill vials | EM |
|---|---|---|---|---|---|
| 1 | *Staphylococcus auricularis* | -- | √ | -- | √ |
| 2 | *B. cereus* | -- | -- | √ | √ |
| 3 | *Staphylococcus epidermidis* | √ | √ | -- | √ |
| 4 | Micrococcus sp. | -- | √ | -- | √ |

**This gives sufficient evidence that EM is the Most Probable cause?**

## Investigation

Step-2 [Identification of most probable cause(s)]

Few Questions to be asked?

- Are these organism your NMF?
- Have we seen this high microbial count in EM and PM before?



## Investigation

### Have we looked at Interventions?

(Which can take the contamination from the outside env. to RABS?)

There were no non routine interventions. The vials taken and incubated separately during the interventions were all passing



## Investigation

Results of Investigation Step-3 [Hypothesis Testing]

How can we simulate the contamination of vials because of environment and personnel?

## Investigation

### Where does this lead us?

**Was there was some problem which happened during the initial phase of filling?**

**All routine Interventions happened in the later part of the filling activity.**

**So, from where this contamination came from?**



## Investigation

What are the possibilities

- Possibility of insufficient sterilization of items post sterilizing grade filter?
- Machine setup and contamination by the operator
- Tunnel, initial vials?

- Anything else

Risk Assessment



## Investigation

Most Probable reasons

1. Environment / Personnel
2. Buffer vessel top dish change.

## Investigation

**Results of Investigation Step-3 [Hypothesis Testing]**

- Revalidation of Sterilization of Buffer vessel?



## Investigation

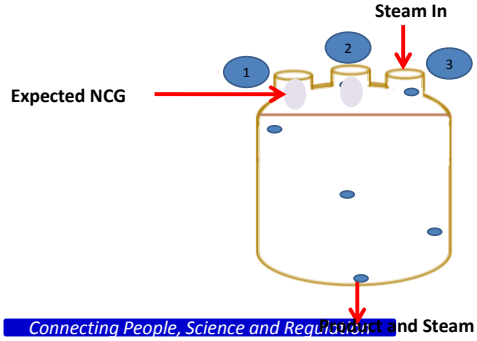
**Why was the top dish changed?**

**There was a minor leakage in valve 1 hence the dish was changed**

**Post change of Top dish the leakage test was carried out and found to be passing.**



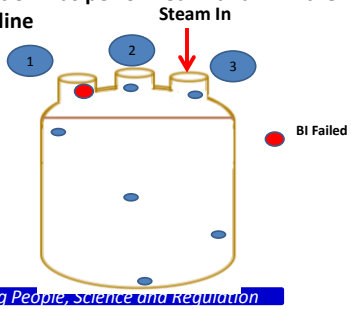
## Investigation (Hypothesis)



## Investigation

Step-4 [Establishing the route/ mechanism of contamination]

**Revalidation was performed with a BI in the product line**






## Investigation

Step-4 [Establishing the route/ mechanism of contamination]

- **Water run was carried out.**
- **Bioburden was carried out:**
  **Counts observed in the initial vials filled**
- **Swab samples were taken from the product inlet:**
  **Counts observed**

**Proves the Hypothesis!**



## Investigation

Step-5 [Risk Assessment]

- Risk identification : More than 20 other risks identified
- Risk analysis : 40% of the risk identified were high
- Risk control and mitigation

## Investigation

**Step-6 [CAPA]**

- Sterilization procedure revised
- New procedure for handling of failures
- Various actions identified as part of the Risk assessment mitigation plan
- Impact assessment of the changes to be strengthen



## Closing the items

- After the CAPA was closed
  - Repeat media fill (3 runs)
  - Investigation report shared with FDA
  - Manufacturing resumed.

What to do with the old batches ?



## Summary-Handling of media fill failure

- Immediate actions
  - Management Notification (Within 24 hrs)
  - Initiation of deviation (Within 24 hrs)
  - Hold Notice (Except for TS product)
  - Field Alert (within 3 working Days)
  - Decision on future Manufacturing
- Investigation
  - Investigation Initiation
  - Investigation Team creation.
  - Brain storming

## Summary-Handling of media fill failure

- Investigation methodology
  - Step-1 [Information Collection & Review]
  - Step-2 [Identification of most probable cause(s)]
  - Step-3 [Hypothesis Testing]
  - Step-4 [Establishing the route/ mechanism of contamination]
  - Step-5 [Risk Assessment]
  - Step-6 [Recommendations for CAPA]
- Investigation Closeout
  - CAPA closure
  - Repeat media fills
  - Information to the Regulatory agency's



## Summary-Learnings

- Always listen to any type of suggestions during investigation
- Risk assessment should be performed.
- Robust impact evaluation of the changes



## Media Fill Observations

- Media fill failure investigation did not include the impact of all the batches in market
- The company failed to initiate a field alert within 3 working days of a media fill failure.