Investigating Loss of Vacuum in Lyophilized Products

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Abstract

A lyophilized product, stoppered under deep vacuum, experienced an increase in customer complaints due to "no vacuum," triggering a full CAPA Investigation. A causal factor was identified as being related to a shift in a vial dimension, but within the approved specifications. Root cause and contributing factors were identified and CAPAs implemented. Their effectiveness was confirmed after documenting a reduction in customer complaints due to "no vacuum." Lessons Learned were also identified and investigation was successfully presented to the Agency.

Background and Objectives

- A biotechnology-derived product was developed and transferred using lyophilization and aseptic processing. Product was stoppered under deep vacuum.
- After the first-year post approval, an increase in the number of complaints was noticed due to "no vacuum."
- The objective of this poster is to summarize the complaint investigation for this "no vacuum" event.

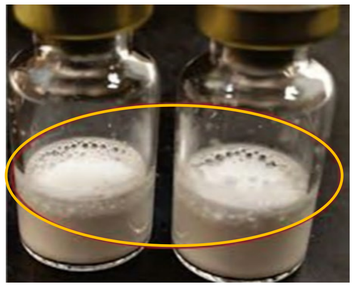
Materials and Methods

- Returned complaint samples
- Reserve samples (vials and stoppers)
- Calibrated vernier caliper
- Manufacturing batch records
- Calibration and preventive maintenance records
- Stability data/Reports

Methodology followed site CAPA-Investigation procedure:

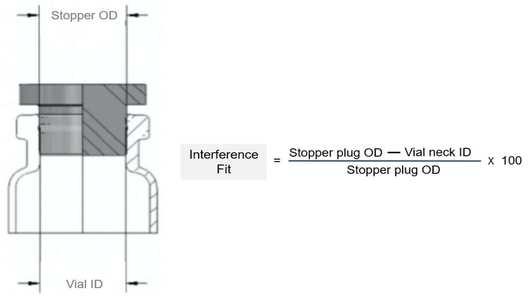
1. Event Description (4Ws/2H)
2. Impact Analysis (product/process)
3. Historical Review (R&D)
4. Root Cause Analysis (RCA)
   - Causal Factors (with 5Ms)
   - Statistical Tools and Dimensional Measurements
   - 5 Why's
5. CAPAs
6. CAPA Effectiveness

The Event (after no "hissing" sound)



Results

- Event: Increase in complaints due to "no vacuum"
- Impact Analysis:
  - No impact on CQAs (e.g., CCIT, Reconstitution time, sterility, etc.)
  - Impact on Process (PV Stage-3)
- Historical Review: Deep vacuum, needed for cake reconstitution, had been identified as a risk factor, yet actions to mitigate risk were not properly addressed during Tech Transfer
- Root Cause Analysis (RCA):
  - Causal Factors identified related to Materials (vial and/or stopper) and Machine (equipment and processes)
  - Extensive dimensional measurements conducted on "Interference Fit" elements, after multiple interactions with C/C vendors.



Conclusions

- Root Cause: After "5 Why's", RC related to a shift in vial neck ID, but within approved specifications.
- CAPAs: Readjustment in vial neck ID at vendor site, non-destructive headspace analysis, reformulation to eliminate deep vacuum
- CAPA Effectiveness confirmed after decrease in in complaints due to "no vacuum"

Epilogue

- Lessons Learned identified after "the 6th Why" related to PV Stage-1 and Tech Transfer
- Investigation successfully defended during a routine FDA inspection

References

USP, *USP* 40 <1207> "Sterile Product Packaging-Integrity Evaluation" (US Pharmacopeial Convention, Rockville, MD, 2017).

FDA, *Guidance for Industry: Process Validation: General Principles and Practices* (FDA, Silver Spring, MD, January 2011)

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