Compliance Update – Microbiological Quality Deviations and Failures – Robust CAPAs and Real-Life Success Stories

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Background / Perspective

- PET Drug CGMP Regulations – Relatively New
- PET Drug Manufacturer OAI Rate vs. Overall Drug Manufacturer OAI Rate
- Compliance Cases – Common Thread – Microbiological Concerns
Case Studies

• Two CGMP compliance cases from 2019
• Both cases clearly demonstrate significant steps forward in quality maturity

Case #1

• Manufacturer inspected mid-2019
• 5-item Form FDA 483 (FDA 483) issued
Inspection Findings (Microbiological)

- *Staphylococcus aureus* recovered in hot cell - not investigated (21 CFR 212.20(d))
- Smoke (airflow visualization) studies not conducted for initial qualification of laminar airflow hood (21 CFR 212.30(b))
- Lack of documentation to support a major change - installation of new biological safety cabinet (21 CFR 212.20(c))
- Growth promotion testing had not been conducted on microbiological media in approximately 5 years (21 CFR 212.60(b))

FDA 483 Responses

- Contracted with 3rd party to conduct airflow visualization studies
- Revised relevant SOP to include investigation into recovery of atypical organisms
- Committed to conducting growth promotion testing on all new lots of growth media received
Remaining Concerns

- Lack of supporting documentation for FDA 483 responses
- Environmental monitoring SOP revised to include investigation of atypical organisms, but the S. aureus recovery was not addressed
- No retrospective review of equipment qualification (BSC and other pieces of equipment)

Regulatory Meeting (Early 2020)

- Producer updated FDA 483 responses and provided documentation
- FDA recommended smoke studies under most challenging conditions
- Producer conceded that they do not have appropriate microbiological oversight, but committed to ensuring appropriate technical competencies
- Producer provided retrospective review of environmental monitoring data
- FDA and producer had a productive discussion on the handling of OOS results
2021 Follow-Up Inspection

- Not there yet - some progress, but new issues
- Although SOPs are important, more than SOPs are needed for a quality system to function properly
- Producer’s overall approach to assure quality - still insufficient
- FDA 483 responses lacking

Follow-Up Inspection Findings

- Eighteen ISO 5 environmental excursions identified as “objectionable” by the producer within a 6-month timeframe
  - One investigation, which was still open
  - Producer’s SOP says all atypical organisms are action level and must have corrective actions, with evidence of effectiveness
- Six water intrusions events within the facility
  - Fungi recovered (Cladosporium spp., Aspergillus spp., Trichophyton spp., Rhodotorula bacarium, and Rhodotorula mucilaginosa)
  - Piecemeal approach to facility remediation
  - Leaking water observed during inspection
  - Evidence of water leak into materials storage room
Follow-Up Inspection Findings

- Producer had a 60% relative humidity limit for the facility; however, they exceeded that limit multiple times in a ~four-month timeframe.
- Producer’s SOP stated that “Engineers should be contacted whenever the relative humidity exceeds 60%.”

Follow-Up Inspection Findings

- Producer used a contact time of 10 minutes for a sporicidal agent, in contrast to the product manufacturer’s recommended contact time of 60-120 minutes for bacillus spores. Producer had frequently recovered sporeforming microorganisms in ISO 5 areas over the last two years.
FDA 483 Responses

- Producer responded to each FDA 483 item, but responses generally lacked full remediation plans and/or supporting documentation
- Producer updated SOP to include a CAPA close-out check, but did not address the retrospective review of past CAPAs to ensure that they had been appropriately closed and were effective
- Persistent facility issues and lack of investigations are major unresolved deficiencies

Warning Letter Issued

1. Your facilities are not adequate to ensure the prevention of contamination of equipment or product by substances, personnel, or environmental conditions that could reasonably be expected to have an adverse effect on product quality. Procedures to ensure that all equipment is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results, are not adequately followed. (21 CFR 212.30(a) and (b)).
2. Your firm failed to conduct adequate investigations and take appropriate corrective action when a failure of a production batch or any component of the batch failed to meet any of its specifications. (21 CFR 212.20(d)).
WL Follow-Up Inspection – 2023

- NAI inspection classification (No Action Indicated)
- Significant improvement in the quality of corrective and preventative actions

Findings – Good CAPAs

- Conducted engineering review
- Significant work done to address water intrusion issues and humidity control, as well as air exchange rates and differential pressure issues that the producer had identified
- Change management documented
- Qualification completed for new equipment
- Smoke studies complete
Findings – Good CAPAs

- Updated cleaning and disinfection practices
- Producer had temporarily ceased distribution of some products while remediation was ongoing

Case #2

- Inspection Mid-2019
- 6-item FDA 483
Inspection Findings

- Matter appeared in sterility test samples during incubation, sterility test samples went missing. Neither were appropriately investigated. Personnel were not adequately trained to read sterility test results.
- Water repeatedly leaking into cleanroom (ISO 7) where ISO 5 cabinets are located. Cleanroom did not appear to be clean and was cluttered. Airflow was inadequate for cleanroom design.
- Humidity uncontrolled in the area where aseptic processing occurs. High humidity measurement during inspection.

Inspection Findings (cont.)

- Not all cleaning agents used for the cleaning of ISO 5 classified equipment are sterile or sterile filtered prior to use
- Non-sterile wipes and gloves used for cleaning ISO 5 areas
- ISO 5 smoke studies poorly captured and did not include relevant transfer operations
- Producer had repeated recoveries of microorganisms in ISO 5 areas, including Bacillus, spp.; others were not evaluated to determine whether they were atypical/pathogenic
FDA 483 Responses

- Producer submitted FDA 483 responses, but many initial responses were inadequate

Concerns Remaining

- Investigations – scope and timeframes
- Facility design – assessment of risk
- Environmental monitoring program – responses to recoveries
Regulatory Meeting Held / Additional Responses Submitted Several Weeks Later

- Very productive discussions during regulatory meeting
- Producer committed to immediate QA responses to deviations warranting immediate action
- Producer committed to short-term, medium-term, and long-term facility renovations (a new facility)
- Producer committed to better understanding EM recoveries in their ISO 5 areas, including trending ISO 5 recoveries and speciating them

Reinspection - 2022

- Not there yet
- Findings indicate room for higher quality maturity
- However, FDA 483 responses indicated producer was headed in the right direction
perhaps change to "higher" quality maturity

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Specific Findings

- Humidity remains an issue and producer is seeing fungal recoveries in cleanroom areas
- Frequent ISO 5 settle plate recoveries, but no investigation into this adverse trend
- Several month trend of an increase in microbial recoveries on glove and surface samples, just below action level, but no investigation into the adverse trend
- Contact times for sporicidal agents less than what product labeling indicated

FDA 483 Response

Findings themselves could have led to a final violative inspection classification

However,
- Overall, producer’s response was acceptable and far superior to their FDA 483 responses to 2019 inspection
- Specific dates provided for each CAPA to be completed
- Firm response noted that their goal was “exceeding the agency’s expectations in ensuring sustained cGMP compliance”
- In addition, the producer “recognizes the 483 identifies opportunities to further enhance the site’s facilities, operations, and quality systems”
- Firm engaged subject matter experts for each observation
- Ongoing comprehensive risk assessment of operations
Specific Corrective Actions

- Engaged a third party to identify weaknesses in current process for identifying and handling deviations
- Updated SOPs now require any mold recovery to be investigated and ISO 5 action limit reduced to anything greater than 0 cfu
- More routine recordings of humidity levels. >70%RH requires action to reduce humidity; engaging contractor to get further control over humidity.
- Had a 4 cfu ISO 5 excursion. Investigated, speciated, determined it came from personnel, retrained personnel on proper gowning, hygiene, and cleaning
- Committed to using disinfection contact times supported by scientific studies

Summary

- Quality maturity is the key to sustainable compliance.
- The 212 regulations do not prescribe everything needed to meet CGMP.
- Avoid “tunnel vision” when addressing deviations or findings of non-compliance.
- Engage appropriate experts (e.g., microbiological, engineering) when needed.
- You got this!
Thank You!