USFDA 483 OBSERVATIONS -2023

MICROBIOLOGY

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USFDA 483 OBSERVATIONS -2023 (Microbiology)

Investigator/inspector: Michael A Charles

Observations:

- Out of limit investigations for recurring environmental viable monitoring results are not complete infully investigating root cause and determining preventative actions. Root cause was identified as human error, aseptic behaviour during activities in the area and aseptic behaviour during environmental monitoring, but the investigation did notcontinue to determine which aseptic behaviour exactly is in need of correction to prevent recurrence
- During cleaning/disinfection operations in the injectable filling area, it was observed that contact times for disinfectant are not fully achieved, nor do written procedures (SOP-Cleaning and Sanitization of Aseptic Processing Area) describe how contact times are to be achieved for disinfection. Forexample, contact time for disinfectant used was shown by your disinfection study to be 10 minutes, but while observing disinfecting operations during this inspection on Jan 12, it was observed that surfaces received as little as 3 minutes of contact time.

Investigator /inspector (s) : Saleem A.Akhtar, Joshe E melendez

Observations

- For samples results are not entered contemptuously in LIMS for plate after reading it . The analyst read all samples under colony counter (that includes verification of sample ID, Sample location, , dater of analysis and reading the plate for growth) , wrote the number of colonies observed on each plate , made an entry on equipment usae log book indicating strat time and end time and then entered results in LIMS. The firms microbiological best laboratory practices sop requires that the QA reviewer shall verify the count on plates/test results against reported results However there is no evidence that QA reviewer verified microbial count on all plates.the only evidence of QA review for reported results against actual results available in LIMS.
- The Firms SOP requires images/photographs of the media plates be after reading the plates by using software. The micro lab manager stated software sometimes does not read the media plate barcode. Under these circumstances, photographs taken by manually and uploaded on a computer's drive .The significant deficiencies observed as photographs taken manually can be deleted, photographs uploaded on computer hard drive can be deleted and photograph taken date and time can be changed**.**

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Investigator /inspector (s) : Jazmine N Brown

Observations :

- No data available to support the adequacy of conducting sterility testing with sample size volumes that are less than those are required by USP <71> sterility testing method. Since microbial contamination may not be uniformly distributed throughout the drug product unit, reduced sample volumes could cause false negative sterility test results and inappropriate release of sterile injectable products into market.
- Firm does not have any scientific justification for incubation period for sterility test ,other than mentioned in USP<71>.there is no scientific rationale or data to support the use of reduced sample size .

Investigator /inspector (s) : Richard ledwidge,Arsan karapetyan,Lei zhang

Observations:

- Root cause is not identified for OOS investigation to support implementation of CAPAs . For. Example An Endotoxin result of < X EU/mL for drug substance was out of specification . During a phase-I, investigation a retest was performed and the result was within the limit . After which, further used for processing prior to identifying root cause for the original cause . The firm opened the deviation for not following SOP.
- A investigations performed are not comprehensive with respect to root cause analysis e.g. deviation was initiated for not performing endotoxin test , investigation determined root cause as mixing of s tested samples and samples to be tested and root cause observed as human error, as Microbiology manager missed an email notification from firms MODA software which tracks sample testing. Upon further review it was observed that , firm recently initiated CAPA and updated SOP as per CAPA for segregation of samples for incubation based on sample type ad sample status .However , the CAPA and SOP update not captured in above observed deviation .

Investigator /inspector (s): Eileen A Liu, Rajiv Srivastava

Observations

- Media growth promotion tests not performed for media used in media fill
- Sterility method suitability testing for ointment did not meet protocol acceptance criteria. Product positive control test was not performed during method suitability validation.
- There were no written justifications based on risk assessment for selected EM locations

- EM Alert and action limit were not based on historical data
- Swab used for viable surface monitoring does not contain disinfectant neutralizer . No study to demonstrate residual disinfectant would not interfere with test results
- Growth promotion test not performed for plates used for personnel monitoring .
- EM and PM media incubation temperature and time were not supported by corresponding media GPT

Investigator /inspector (s) : Rita K Kabaso, Justin A Boyd, Arsen Karapetyan

Observations

- When endotoxin tests are invalidated due to suitability failure, a note is written on the record and the test are repeated without documenting a incident as per SOP for handling of laboratory incidents.
- There is no further investigation when gram negative organisms that could product biofilms were identified in purified water system , including burkholderia *kururiensis*, *ralstonia pickettii,acinetobactor baumannii* and *sphingomonas paucimobilis*. After initial identification, these organisms considered normal microbial flora of the water system and if similar colonies observed again there is no identification performed .
- EM samples not counted accurately .Reported results found to be less than the number of colonies on the plate . e.g the reported result was nil but the plate was observed to have 02 CFU which the analyst had marked with marker after reading

Investigator /inspector (s) : Saleem A.Akhtar ,Rajiv Srivastava, Wenzheng zhang

Observations

- Verification of pH meter used in micro lab to test the pH of media is deficient.

Investigator /inspector (s) : Rajiv Srivastava, Kellia Hicks

Observations

- Balance used for media preparation and logbook for daily calibration verification record ,have consistent non -readable print outs which were signed by microbiologist, supervisor and QA. No action taken to rectify the problem.

Investigator /inspector (s) : Brittny C Cargo, Seneca D. Toms

Observations :

- Failure to investigate cause of discrepancy .

e.g Firm has identified objectionable organisms, during in-process testing of intermedia API on at least three occasions for the batch manufactured in the recovery area.

Serratia marcescens,
Acinetobacter guillouiae,
Enterococcus casseliflavus
Enterobacter asburiae
Enterobacter bugandensis
Citrobacter freundii

- Microbial limits have not been established for in-process API material, which have had microbes identified during the recovery phase .

Investigator /inspector (s) : Sandra A Boyd,Muna algharibeh

Observations

- Sterility test method for testing the sterile gloves not qualified

Investigator /inspector (s) : Wendy G tan, Leiyun boone,Caryn McNab

Observations

- Environmental monitoring cultural plates placed in closed boxes in the incubators. Firm has not evaluated impact of utilizing these boxes in the incubators for optimal cultural conditions to obtain recoveries that may be sensitive to sub optimal cultural conditions (e.g. strict anaerobes, temperature sensitive, slow growers etc)

Investigator /inspector (s) : Rajiv Srivastava, Eileen A Liu

Observations

- Sterility testing is deficient in that drug products are not appropriately prepared for testing and no justification for changing diluent available .
- For In-process liquid bulk bioburden testing , validated incubation conditions not followed .
- Desiccated and cracks /shrinked plates observed after completion of incubation

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Investigator /inspector (s) : Justin A Boyd,Anastasia M shields

Observations :

- Microbiologists responsible for collecting environmental monitoring and personnel monitoring samples confirmed they do not collect all samples due to workload . Microbiologists also explained personnel monitoring samples may not be collected due to production personnel that refuse to submit personnel monitoring . For samples that are not collected , a result is still recorded in the reported laboratory records that is below alert and within trend of previous data . the practice of not collecting data , but still reporting results has been occurring for at least one year.
- A microbiology manager was observed backdating entries into ‘sterility test sample inward register’.
- During sterility testing of sterile components by direct inoculation, the components were not observed to be completely submerged in the media.