Inspection Trends from a Regulatory Perspective



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Warning Letters 2012-15

- Ten Warning Letters cited significant cGMP deficiencies related to:
 - 1. Media Fills
 - 2. Personnel
 - Microbiology Laboratory
 - 4. Environmental Monitoring/Validation
 - 5. Non Compliance to Procedures



Warning Letters 2012-15

- Ten Warning Letters cited significant cGMP deficiencies related to:
 - Disinfectant qualification
 - 2. Supplier qualification
 - 3. Visual Inspection
 - 4. Investigations
 - 5. Sterilization of equipment



Media fill procedures fail to require performance and/or documentation of interventions that are representative of the operation



 Media fill procedures fail to require documenting when the individuals performing aseptic processing operations enter and exit the cleanroom



- Not all personnel involved in the aseptic manufacturing and filling of sterile drug products have participated in a media fill
- Failure to demonstrate the effectiveness of the agents added to media to neutralize antibiotic residues



- Lack of, or inadequate procedures for reconciliation of filled vials (total units evaluated/incubated versus total number of units filled)
 - Number of units filled did not match the number being evaluated/incubated



 Integral vials placed in a white pail labeled "to be destroyed" without documentation of the reason for destruction



- Inadequate monitoring of operators performing critical operations
 - ➤ Procedure for environmental sampling does not require that employees be sampled every time they exit the Class A clean rooms
 - ➤ Gowns worn by operators working in the aseptic processing areas are monitored only once per week



- Inadequate monitoring of operators performing critical operations
 - Failure to sample personnel gowns at the minimum frequency specified by procedure
 - ➤ Gloves are only monitored at the end of the shift



- Failure to perform gowning qualification for operators prior to working in aseptic processing areas
- Failure to re-qualify all operators for gowning on an annual basis as required by procedure



- Poor aseptic technique and/or incorrect clean room behavior during gowning and production activities
 - Operator spraying hands with sanitizing solution directly over the air viable microbial plate



- Operators exposing aseptic processing equipment and equipment parts in the Class 1000 area prior to introduction into the Class 100 area
- Excessive touching of the outside of hood and gown during gowning



- Operators moving very quickly in the aseptic area
- Operators disrupting airflow with hands and forearms over the stopper bowl while transferring stoppers



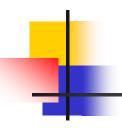
- Operators performing critical aseptic operations with exposed skin at the forehead
- Operators leaning halfway in and out of the Class A area while performing interventions over opened bottles



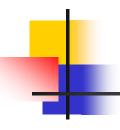
- Operator excessively shaking the stopper bag while loading the stopper bowl and knocking on the conveyor belt to fix a stuck vial
- Excessive and repeated touching of parts of the filling machine and barriers



- Traceability of microbial samples
 - Microbial plates containing environmental monitoring and personnel samples collected during production missing from incubators



- Reporting of microbial plate results
 - Failure to document positive results for a microbial plate that was confirmed as containing microbial growth



- Reporting of microbial plate results
 - Environmental monitoring data reported no alert or action level results but FDA Investigators found a high number of environmental monitoring plates with visible growth of microorganisms



- Reporting of microbial plate results
 - Microbiological growth incorrectly identified and reported as a typical microorganism when compared against library/photographs of typical environmental flora



- Sterility tests repeated before conducting a laboratory investigation
 - The quality control unit repeated the test on a new sample to confirm the original result prior to initiating an investigation



 Failure to have data to demonstrate that microbial isolates remain viable when stored for extended periods of time before testing



Cleanroom Qualification

- Failure to perform unidirectional airflow pattern studies (i.e. smoke studies) for a filling line
- Failure to identify turbulent airflow in smoke studies



Cleanroom Qualification

- Smoke studies do not demonstrate unidirectional airflow and sweeping action over and away from the critical processing areas under dynamic conditions
- The velocity of HEPA-filtered air is not evaluated proximal to the working level



Supplier Qualification

 Acceptance of endotoxin test results reported in the stopper supplier's Certificate of Analysis (CoA) without supplier qualification



Visual inspection

- Failure to include all critical defects in the challenge sets used for certification of visual inspection operators
- Visual inspection operator looking away from the vials without stopping the inspection machine



Visual Inspection

 The velocity of the conveyor (vials per minute) used for visual inspection during the qualification of operators was not documented



Investigations

 No or deficient manufacturing investigations conducted after sterility test or media fill failures



Investigations

A media fill failure was attributed to stopper bags left inside the class 100 area for a long period of time (throughout a shutdown that took place prior to the media fill)...



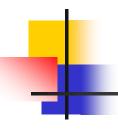
Investigations

The investigation did not include information to determine the origin of the contamination, such as the microorganisms recovered from the stopper bags and from the media fill units



Procedures

Manufacturing SOP did not require manufacturing materials to be removed to an appropriate area for storage during shut-down of operations and prior to bringing the area back into classified status



Sterilization of Equipment

 Failure to document the exact placements of the biological indicators (BIs) used for the revalidation of the sterilization cycles used for machine parts



Sterilization of Equipment

- Operators fail to follow the diagram of the validated load configuration for machine parts sterilization cycles
- The current load configuration used by production operators to sterilize filling machine parts has not been validated



Sterilization

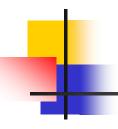
- Observation
 - ➤ Bee-Shield hand sanitizer
 - ➤ MD Quality hand sanitizer
 - Contaminated with Burkholderia cepacia



Environmental Monitoring

Observations

- Yeast and mold was recovered from the Grade-A areas, however a thorough assessment was not conducted to determine impact
- No corrective action was identified to prevent this from re-occurring

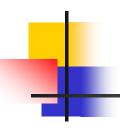


Environmental Monitoring

- Observations
 - Supervisors approving microbial ID's were not qualified on basic microbiology
 - Trending of environmental data was not performed on a consistent basis.
 - There are no written procedures for trending and what frequency it should be performed at



- Growth promotion was not performed using the recommended organisms
- Growth promotion was performed on a per lot basis and not per shipment
- Personnel in the Microbiology performing environmental monitoring were not adequately trained for aseptic techniques and clean room behavior



- Environmental monitoring program not adequate to identify the source of microbial contamination
 - Environmental monitoring locations are not adequately identified in pictures, diagrams and/or descriptions



- Observations
 - Environmental Monitoring sites were not justified in the validation report
 - ➤ No justification for sample duration and frequency in the clean room



- Environmental monitoring of the clean room identified surface samples with excessive counts. There was no follow up to this finding.
- ➤ No investigations were performed after particulate excursions in the aseptic processing areas



- Observations
 - The Quality organization failed to recognize and investigate significant environmental monitoring trends and out of specification microbial results in the sterile area



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- ➤ Investigation report was initiated on 06-Nov-06 particulate excursions in several grade areas. Corrective actions were not completed until 20-Feb-07.
- A sample collected from Room 1627 on 12-May-07, was not sent for microbial ID until 26-Jun- 07.



- Failure to establish and follow procedures designed to prevent microbial contamination of drug products purporting to be sterile
- ➤ Environmental Monitoring results for Room 1618, were not reviewed by the quality unit, within the required timeframe per SOP.



- ➤ Routine surface sampling of the Class B and C areas of the manufacturing facility is not conducted under dynamic conditions. Samples are collected after-cleaning.
- Failure to follow SOP, Trending and Reporting of Environmental Data and Establishment of Microbial Control Limits, in the quarterly trend reports are not conducted as required.



Observations

➤ Viable and particulate air sampling at the point-of-fill and personnel sampling were not taken for the vial filling line.



Observations

The active air sampling unit is not located in a critical area representative of exposure of open containers on the aseptic line. The active air sampling unit was observed positioned behind stoppered vials.



Observations

➤ Validation studies have not been performed for the testing of multiple locations with one contact plate. This practice is performed for monitoring personnel working within the aseptic core and during the monthly environmental monitoring survey.



Observations

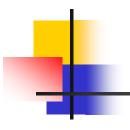
➤ A Notice of Event (NOE) and an investigation will be initiated when Action Levels are exceeded in the environmental monitoring program and the in-process product bioburden monitoring program. This response is unacceptable because it fails to provide immediate, specific corrective actions that will be taken.



- The qualification of the disinfectant failed to demonstrate that it is suitable and effective to remove organisms from different surfaces
- The disinfectant failed to meet qualification criteria when challenged with multiple organisms



- Documents associated with cleaning and validation were incomplete or unavailable
- Upon follow up visit, no corrective action was implemented
- Outcome: 483 Observation



- Incomplete deviation investigation to ensure appropriate actions implemented to remove or eliminate micro-organisms from the aseptic processing areas
- The firms SOP did not adequately define the procedures for microbial failures in the clean room



- Design of equipment and materials of construction was not taken into account for product contacting surfaces. The firm did not determine if the materials were reactive or absorptive to alter drug
 - ➤ Plastic pail from home improvement store used during sanitization
 - ➤ Silicone tubing was cleaned with alcohol, flushed with WFI and re-used



- Firm did not clean and maintained equipment at appropriate intervals to prevent microbial contamination
- Change Control system was not used when the sanitizers were changed to a new vendor
 - No disinfectant efficacy testing performed
 - No vendor audit



- Cleaning and sanitization personnel were not trained in cGMP
 - Company committed to perform training, however they did not indicate when it would take place or be completed
 - Measures taken to ensure product quality while operations continued while employees not adequately trained



- Company did not take Global Quality
 System approach
 - Failure to properly clean and sanitize equipment
 - Cleaning personnel were not properly gowned while performing the process
 - Head and arms were over previously sanitized areas and or equipment



- Inadequate equipment cleaning documentation. Many forms were missing information and not reviewed or approved
- Quality Department unable to conduct adequate investigations, determine root cause or establish adequate preventative and corrective actions for microbial recoveries in the clean room



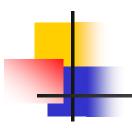
- Cleaning validation did not adequately demonstrate the procedure/system was robust enough to ensure removal of residue from previous lots
- A Deviation was generated for residue on the fill line prior to filling. The fill proceeded, however the corrective action was inadequate



- In adequate cleaning and sanitization program
 - ➤ Visible substance on the fill line noted by inspector during set up of the equipment
 - Fill proceeded as planned
 - Firms response did not address change to cleaning procedure and visual inspection, or whether detection will be possible using new process controls



- Failure to thoroughly investigate unexplained discrepancies in the cleaning and sanitization program
- SOP indicates to use WFI for cleaning and sanitization solutions. However batch records indicate PW was used to make the solutions



- Measuring devices used to make sanitizers was inadequate. Firm used graduations on the side of a large vessel
- Sanitizer failed integrity test but was used to disinfect the clean room. The Deviation report was inadequate based on the corrective action implemented. Indicated lack of understanding of the process



The fill room was cleaned and sanitized on Friday evening and held over the weekend. The firm initiated a fill on Monday morning. There was no validation data to support this hold time



- Failure to address adverse micro trends in the fill room. The solutions used to kill bacillus was in effective.
- Disinfectant efficacy program was inadequate



Sanitization solution was made improperly. The firm did not adequately address the discrepancy and the ability of the Quality Department to properly verify and evaluate the certificate of analysis to find errors



Firm failed to conduct timely micro investigation in the fill room. They were initiated 3 weeks after reading the plates and completed 4 months



Conclusions

- Develop detailed SOPs
- Follow the SOPs
- Monitor trends
- Demonstrate control over area and process
- Conduct adequate investigations
- Take corrective action in a timely fashion