Inspection Trends from a Regulatory Perspective

David Matsuhiro
Cleanroom Compliance Inc.
dmatsuhiro@cleanroomcompliance.com

Warning Letters 2012-15

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

Warning Letters 2012-15

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

Media Fills

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

Media Fills

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

Media Fills

- 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

Media Fills

- 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

Media Fills

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

Personnel

- 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

Personnel

- 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

Personnel

- 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

Personnel

- 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

Aseptic Technique & Cleanroom Behavior

- 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

Aseptic Technique & Cleanroom Behavior

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

Aseptic Technique & Cleanroom Behavior

- 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

Aseptic Technique & Cleanroom Behavior

- 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

Microbiology Laboratory

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

Microbiology Laboratory

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

Microbiology Laboratory

- 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

Microbiology Laboratory

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

Microbiology Laboratory

- 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

Microbiology Laboratory

- 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

Environmental Monitoring

- Observations
  - 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

- 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

Environmental Monitoring

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

Environmental Monitoring

- Observations
  - 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

Environmental Monitoring

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

Environmental Monitoring

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

Environmental Monitoring

- Observations
  - 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.

Environmental Monitoring

- Observations
  - 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.

Environmental Monitoring

- Observations
  - 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.

Environmental Monitoring

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

Environmental Monitoring

- 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.

Environmental Monitoring

- 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.

Environmental Monitoring

- 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.

Cleaning & Sanitization

- 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

Cleaning & Sanitization

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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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 & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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 & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

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

Cleaning & Sanitization

- 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

Cleaning & Sanitization

- 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