Overview of Inspection Issues with Legacy Products

Barbara Breithaupt
Consumer Safety Officer
Overview of the presentation

• The role of the Quality Unit will be discussed in the context of the inspection findings.

• Lifecycle examples will demonstrate the need for the Quality Unit to:
  • Establish controls
  • Implement surveillance programs
  • Engage in active oversight of production operations
  • Be appropriately qualified
The Role of the Quality Unit

• 21 CFR 211.22 Responsibilities of quality control unit
• 21 CFR 211.25 Personnel qualifications
• 21 CFR 211.192 Production record review
• ICH Q9 Quality Risk Management
• ICH Q 10 Pharmaceutical Quality System
During the summaries, consider:

• Did the Quality Unit meet the regulatory requirements?
  • 21 CFR 211.22 Responsibilities, quality control unit
  • 21 CFR 211.192 Production record review
• Was the surveillance information adequate for investigations leading to root cause determinations?
• Was the oversight of production operations adequate?
• Were 211.25 Personnel qualifications adequate?
If a tree falls and no one is around ....
Bulk drug substance (BDS) not purported to be sterile

• The BDS was intended to be used as the active ingredient in a sterile injectable drug product.
• The finished product was not terminally sterilized, it was filter sterilized.
• The BDS could be stored at 2-8°C up to 27 days before freezing.
• The firm permitted sub-lotting from thawed/refrozen BDS.
• In 2011, the firm provided a stability report to support refrigerated BDS storage for up to 27 days.
  – One microbial content sample was analyzed at the 14 month time point, after the BDS was frozen.
• There were no aseptic process media fills or aseptic operator qualifications.
• The firm did not have a procedure consistent with the manufacturer’s directions for returning laminar flow hoods (LFHs) to service after the blowers were turned off.
• There was no justification for the EM program:
  – The LFHs used for open-step aseptic operations were unclassified areas (no viable monitoring).
  – Viable surface monitoring was only performed on the wall opposite the LFHs.
  – There was no personnel monitoring after aseptic process operations in the LFHs.
• The Production Manager, who provided on-the-job aseptic process training, had no documented aseptic technique training.
Deficient Testing

• The BDS Material Confirmation Validation Study permitted ungoverned retests in the event of failure to meet acceptance criteria.

• Test methods were inconsistent with the USP <61> “Microbiological examination of Nonsterile products: microbial enumeration tests”

• The test results of a lab trainee were invalid for the method; however, counted as part of the employee’s required qualifications.
• The 2007 facility microbial risk assessment
  – Was based on calculated risk (no actual data).
• The 2010 addendum
  – Did not describe the open-step aseptic operations in the unclassified LFHs
    • flask inoculation
    • assembly of nutrient feeds
    • BDS sterile filtration into open 200 mL bottles
    • sampling from the bottles after sterile filtration.
  – Did not describe the risk of contamination from personnel (only the gloves were sterile)
• The 2011 Addendum
  – Did describe the flask inoculation and BDS filtration operations performed in the unclassified LFHs.
  – Reduced the risk to Low - The facility “has appropriate engineering and cGMP procedures in place to mitigate possible contamination from personnel, air, equipment and facility sources”
Four non-host contamination events:

- *Bacillus cereus/thuringiensis/mycoides*, and *Bacillus megaterium* in 2 of 6 new WCB aliquot vials
- *Bacillus cereus/thuringiensis/mycoides* in a 100L fermentation vessel
- *Enterobacter cloacae* detected in a 100L fermentation vessel
- *Bacillus cereus/thuringiensis/mycoides* detected in a 100L fermentation vessel
• Deviations were investigated and reports were written by the Production Manager who found no root cause.

• The Production Manager who conducted the contaminated WCB investigation was also the aseptic operator who failed to document cleaning of the LFH before starting to aliquot the WCB into vials.

• The Quality Unit signed off on the deviation investigations. There was no evidence the Quality unit participated in the investigation.
Outcome for the firm:

- All non-host contamination materials were discarded.
- The firm voluntarily held BDS to make a retrospective assessment.
- The firm promised not to resume manufacture until corrective actions were implemented.
• Did the Quality Unit meet the regulatory requirements?
  • 21 CFR 211.22 Responsibilities, quality control unit
  • 21 CFR 211.192 Production record review
• Was the surveillance information adequate for investigations leading to root cause determinations?
• Was the oversight of production operations adequate?
• Were 211.25 Personnel qualifications adequate?
Vaporized Hydrogen Peroxide (VHP) Decontamination for Aseptic Filling

• Since the previous inspection, the firm validated and implemented a VHP room disinfection cycle for the Class 100 and Class 10,000 areas.

• The fixed equipment had complex surfaces. The rigid barriers, from the ceiling HEPA filters to just below the filling operation level, made for difficult access to some fixed equipment surfaces.
VHP disinfection of the filling room

- VHP disinfection was performed using a portable VHP generator automatically sensing H₂O₂ vapor concentration, and programmed to cycle for a minimum H₂O₂ contact time at the target vapor concentration.
- The HEPA filters and pressure differential monitors were turned off during the VHP disinfection.
Review of the VHP Validation Study

• Review of the raw data found paired chemical indicators and or BIs failed to meet H₂O₂ exposure and kill specifications.

• When the validation was compared to the VHP disinfection section of the batch record:
  – The room was not sealed to ensure the H₂O₂ vapor concentration was maintained.
  – The volume of H₂O₂ concentrate used was not specified as a control parameter.
Review of batch records for the months of June and July found:

- Multiple VHP cycles ran ≥ 16 hours; while most cycles were completed in about 60 minutes.
- The VHP generator cycle printout showed "*******" at timed intervals instead of an injection of a volume (cc) of H₂O₂ concentrate.
- The Production Operator said the cycle was manually stopped.
- There was no documentation showing the volume of H₂O₂ concentrate used when the cycle was manually-discontinued.
"******" was not a validated condition and could not be explained.

- No deviations were raised.
- Production relied on an assumption the disinfection was adequate because the cycle time exceeded the validation time.
- Quality Unit review was described as a batch record completeness check (no review of raw data).
No documentation showing adequate $\text{H}_2\text{O}_2$ contact time at the target vapor concentration.

- Chemical indicators and BIs failed to meet acceptance criteria during validation.
- There was a visible gap under the door between an unclassified area and the area being disinfected (taped in the validation).
- Environmental monitoring samples were not scientifically justified to represent risks during aseptic filling operations.
Outcome for the firm

The week after the inspection, the firm's management and counsel appeared at the District office to announce the firm's voluntary recall of all drugs manufactured in the VHP-disinfected filling room.
• Did the Quality Unit meet the regulatory requirements?
  • 21 CFR 211.22 Responsibilities, quality control unit
  • 21 CFR 211.192 Production record review
• Was the surveillance information adequate for investigations leading to root cause determinations?
• Was the oversight of production operations adequate?
• Were 211.25 Personnel qualifications adequate?
Resources

Email: CDERSBIA@fda.hhs.gov
Phone: 1-866-405-5367
Phone: (301) 796-6707
Website: http://www.fda.gov/cdersbia
Resources

• Drug Guidance Compliance and Regulatory Information
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm

• Drug Compliance Program Guidance Manual
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm
Questions?