USP <1115> Bio-burden Control of Non-sterile Drug Substances and Products

Leonard W. Mestrandrea, PhD., RM(NRM)
Mestrandrea Consulting
Disclaimer

- I am an independent consultant.
- I have been involved with the USP for many years.
- I do not represent the USP or any other organization.
- Opinions expressed at this conference are mine alone, and should not be interpreted as the policies, positions or whims of any other organization.
Presentation Overview

- Why Risk Based control
- Industry survey results
- Risk Assessment
- Microbial Control Considerations
Why Risk Based Control?

- No well defined regulatory standards or guidance exists for the microbiological control of non-sterile pharmaceutical manufacturing environments.
- Environmental control and monitoring of non-sterile processes either range from non-existent to parallel programs to aseptic processing.
- Data generated from some programs may be of little value for the control of the microbiological quality of non-sterile environments in which the product is manufactured.
Points to Consider when Performing a Risk Assessment

- The route of administration of the drug product
- The synthesis, isolation and final purification of the drug substance
- The microbiological attributes of the pharmaceutical excipients
- The formulation, chemical and physical attributes of the drug product
- The manufacturing process
- The dosage regime
Points to Consider for Performing a Risk Assessment  
(continued)

- The age and medical status of the intended recipients of the drug product
- The administration of immunosuppressive agents and/or corticosteroids
- The presence of disease, wounds, organism damage and invasive medical devices associated with the recipient
Risk Assessment

The order of risk of pharmaceutical products based on the invasiveness of the route of administration:

- Metered-dose and dry powder inhalants
- Nasal sprays
- Otics
- Vaginal suppositories
- Topicals
- Rectal suppositories
Risk Assessment (con’t)

- Oral liquids (aqueous)
- Liquid filled capsules
- Oral tablets and powder-filled capsules
Microbial Control Considerations in Routine Monitoring

Manufacturing risk factors in descending order:

- Ingredient water
- Pharmaceutical ingredients
- Process equipment
- Manufacturing personnel
- Manufacturing environment
Non-Sterile Product Microbial Influences

- Facility Design & Maintenance
- Personnel Flow
- Equipment Design
- HVAC
- Storage Conditions
- Personnel Practices & Training
- Equipment Cleaning & Maintenance
- Manufacturing & Filling Processes
- Tools & Utensils
- Influences From Adjacent Areas
- Seasonal Effects
- Process & Cleaning Water
- Facility Housekeeping / Sanitization
- Non-Product Contact Equipment
- Validation
- Product & Material Flow
- Personnel Gowns & Hygiene
- Primary Packaging Components

In-Process Materials

Products

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Water Systems and Usage

Quality or type of water utilizes for non-sterile product formulation and final rinse of equipment should be chosen based upon product risk.
Water Systems and Usage

(continued)

- Purified water used in manufacturing, i.e., Mix Bed, RO, UF
- Chlorinated potable water may be appropriate for:
  - Early stage cleaning
  - Housekeeping
  - Sanitization activities
Active Pharmaceutical Ingredients

Vendor audits, specifications, testing, package selection, shipping, storage conditions and expiry dates are all critical in the reduction of microbial risk.
A limited number of USP/NF items have microbial limits / controls indicated as part of the monograph, but others do not: e.g.,

- Lactose Monohydrate - The total aerobic microbial count does not exceed $1 \times 10^2$ CFU/g, the total combined molds and yeasts count does not exceed $5 \times 10^1$ CFU/g, and it meets the requirements of the test for absence of *Escherichia coli*.
Microbial Limits on Materials - 2

• While some items have limits the majority do not

• Even having and passing a limit doesn’t help much considering the difficulties in obtaining a representative microbial sample from a large shipment

• It’s somewhat akin to the sterility test. The sample results may not mean much at all

• It is impossible to rely on testing to assure the microbial quality of materials!!
Microbial Limits on Materials - 3

- The suppliers of raw materials to the pharmaceutical industry are faced with the similar objectives.
- The approaches described throughout are largely appropriate for pharmaceutical raw materials.
- Where there is no defined limit, the progress for improvement will be slower.
Microbial Limits on Materials - 4

- Raw materials directly derived from natural substances represent more of a risk (i.e., starch, acacia, etc.)
- Generally the more processing a material goes through the lower the contamination risk
- Inorganic materials are usually less of a concern
Sampling and Control Conditions

- Control conditions for weighing and compounding of product
- All sampling and weighing equipment should be properly cleaned and sanitized, stored and labeled relative to status
Facility Layout & Design

The facility layout and overall design should aim to:

- Minimize risks of errors (proper material flow)
- Permit effective cleaning (using appropriate materials of construction)
  - Avoid contamination, build-up of dirt and dust
- Permit effective maintenance (ease of access)
- Avoid any adverse effect on the quality of products
Manufacturing Areas
Production Areas - 1

- Raw materials, packaging materials, intermediates and other items exposed to environment:
  - Interior surfaces (walls, floors, ceilings) – smooth, free from cracks and open joints.
  - No shedding of particles.
  - No wood surfaces /
  - Avoid sheetrock / drywall if possible
  - Easy and effective cleaning must be possible

- Housekeeping / disinfection on scheduled basis
Production Areas - 2

- Design of pipe work, light fittings and ventilation points for access and cleaning
- Access for maintenance from outside production areas is preferred
- Drains of adequate size, and equipped to prevent back-flow
- Open drain channels to be avoided
Production Areas – 3

- Effective ventilation with air throughout the facility
- Including filtration of air to a sufficient level to prevent contamination and cross-contamination. Also as protection from the external environment
- Control of temperature and relative humidity where necessary
- Regular monitoring of conditions during production and non-production periods
HVAC
HVAC Systems - 1

- Classified environments are not required.
  - If provided, they should be confirmed in static mode only when facilities are clean

- Temperature control is required

- RH control is desirable especially in tropical climates
HVAC Systems - 2

- Pressurization scheme as needed to protect from cross-contamination rather than to provide microbial protection. Generally:

  - Liquids / Semi-solids – positive to corridors
  - Powders– negative to corridors
  - Washrooms should be negative to corridor where equipment is still dirty and positive to corridor after equipment is clean
Housekeeping
Rule #1 in Housekeeping

- Nothing matters more than keeping the facility clean on a daily basis. That means:
  - Corridors largely free of materials
  - Dust plumes largely contained during material transfer
  - Drums, bins and other containers externally clean
  - No discolored surfaces, or streaked windows
Housekeeping and Sanitation

An effective means for housekeeping and sanitation must be established for all area of drug facilities: warehousing, manufacturing and laboratories. The program should cover:

- Facilities
- Equipment and apparatus
- Production materials and containers
- Products for cleaning and disinfection
- Potential sources of contamination
Housekeeping - Overall

- The entire facility should be subject to a formalized housekeeping program. The objective is to minimize the presence of soil, dust and waste in all areas.

- This can be accomplished by vacuuming, sweeping, mopping, etc. of all surfaces on a periodic basis.
Sanitation - Overall

- The entire facility should be subject to a formalized sanitization program. The objective is to control microbial proliferation throughout.

- This can be accomplished by sanitization with disinfectant / sporicide after housekeeping as needed to maintain desired conditions.
Process Equipment
Equipment Design and Use

- Should include sanitary design.
- Removal of contaminants
- Should use sanitary fittings and designed for use of cleaning and sanitary agents.
- Preferred material for construction of equipment and utensils is stainless steel.
Equipment Cleaning

Cleaning of the equipment plays a critical role in microbial control.
Equipment Cleaning and Drying

- Equipment design should promote easy cleaning
- Facility flows must avoid cross-contamination
- Cleaning on scheduled basis, procedures and records
- Drying is important for microbial control.

Cleaning
- *Manual*
- *Automated - Clean in place CIP*
What items are being removed?

- Excipients
- Detergent/cleaning agent/rinse fluid
- Microbial contamination
- Viruses
- Particulate
- Sanitizing agents
- Lubricants
- Active ingredients
Microbiology & Cleaning
Microbiology – Rinse Samples

- Sampled at various points in the system
  - Include beginning and end

- Sampled over time during the cleaning process
  - Demonstrate a reduction in microbial levels

- Collect a minimum of 200 mL for microbial counts in sterile flasks or bottles

- Negative control samples of rinse water taken for comparison to the solution/rinse samples
Microbiology - Swabs

- Should use sterile cotton or alginate swabs
- Area swabbed typically 4 square inches
- Medium for extraction chosen to maximize recovery of microorganisms
  - 0.1% peptone water, PBS,
  - Extraction volume dependent on counting technique
- Care taken to swab areas that may harbor organisms
  - e.g., weld joints, sharp angles, and areas not well swept by solution flow
Microbiology – Clean Hold Time

- Establishment of clean hold time

- Verify length of time clean equipment can be held without a significant increase in microbial counts

- When combined with appropriate protective measures post-cleaning this period can be quite lengthy
Background Cleaning

- In conjunction with cleaning of product contact surfaces for equipment, non-product surfaces and rooms should also be cleaned.

- In sterile plants, this is done so frequently it deserves no further mention.

- Non-sterile facilities should receive similar attention to assure that microorganisms have limited opportunity to proliferate.
Cleaning & Facilities
Cleaning & Facility Design

- The flow of equipment to/from cleaning areas typically hasn’t been given proper consideration in N/S facility design

- Dirty equipment and clean equipment should not use the same corridor

- A single door washroom is always inadequate

- Even with double doors, the flow of items with the washroom must be well defined
# Gowning in Manufacturing Areas

<table>
<thead>
<tr>
<th>Protective Clothing</th>
<th>Operators in formulation and packaging areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant uniform or plant uniform with overall for higher risk product and environment</td>
<td>Yes</td>
</tr>
<tr>
<td>Hair/beard covering</td>
<td>Yes</td>
</tr>
<tr>
<td>Safety glasses</td>
<td>Yes</td>
</tr>
<tr>
<td>Dedicated shoes or shoe coverings</td>
<td>Yes</td>
</tr>
<tr>
<td>Gloves</td>
<td>Yes (if in direct product contact)</td>
</tr>
<tr>
<td>Face Masks</td>
<td>Yes (if in direct product contact)</td>
</tr>
</tbody>
</table>
Working in Production Areas

- Avoid direct contact with raw materials, API, intermediates and finished product
- Avoid touching product contact surfaces without gloves
- Arm, head and beard covers are always in order
Monitoring is the act of conducting a planned sequence of observations or measurements of control parameters.
Where Does Contamination Come From?

- There is no correlation between particulate air classification and viable contamination levels.
- Air enters through HEPA filters that are of the same efficiency in different grade rooms.
- Microorganisms do not colonize well maintained environments. That’s why housekeeping is vitally important.
Where to Monitor by Priority

• All production / packaging areas,
  • Emphasis on rooms where materials, intermediates and drug product are exposed
  • Corridors, storage area, washrooms, gowning areas including closets & machine/mechanical rooms directly accessed

• Warehouse; laboratories; production/quality support areas; mechanical areas surrounding production / packaging

• Non-production/quality areas, maintenance shops, mechanical rooms, machine closets, cafeteria, canteens, lavatories
Monitoring

- Steps to identify monitoring procedures:
  - Identify best monitoring procedure for each critical control point
  - Sampling location
  - Determine frequency of monitoring
  - Determine procedures
  - Identify responsibilities
What to do with the results

- Not a part of release decision
- Primarily for trending, awareness, and data gathering
- Do respond to unusual data
- Enhancement of housekeeping and sanitation programs
- Formal limits are likely years away
Active Measures for Microbial Control
What are Active Measures?

- In the preparation of sterile products, aside from the design and monitoring there are active steps taken to eliminate microorganisms from the drug products.

- The control strategy has to include procedures designed to eliminate microbial intrusion.

- The same type of thinking is beneficial and can be applied to non-sterile products with a less absolute outcome.

- They can mitigate risk substantially.
Active Measures

- Process time limits (especially for aqueous materials).
- Decontamination / sterilization of product contact surfaces, materials, and containers
- Bioburden reduction treatments for raw materials and actives.
- Use of closed systems for handling and transfer of materials.
- Improved gowning materials and procedures for operational personnel
- Use of classified environments in high-risk operations
Summary

Overall Management of a Microbiological Program

- Identification of suitable suppliers of ingredients and excipients.
- Environmental contamination is by no means the most significant cause of non-sterile product recalls or contamination.
- Program should be developed with identifying and controlling product risk-based assessment.
- Control of the microbial quality of ingredients and water, and the development of a proper cleaning and sanitization procedures.
Questions?
THANK YOU!