Sterility Assurance & Quality Risk Management Conference
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Sterility Assurance: Key Considerations to Maintain Compliance
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Agenda

• Contamination control strategy and risk assessment
• Proven engineered and automated controls
• Integrating manual and automated approaches pragmatically
• Sterility assurance with holistic thinking
Sterility Assurance & Probability

• Toss a coin
  • Heads = Sterile
  • Tails = Non-Sterile

• Roll a die
  • 1 – 5 = Sterile
  • 6 = Non-Sterile

• Probability of pulling the ace of spades
Sterility Assurance

- Minimum probability of non-sterile: 1 in 1,000,000
- Sterility assurance is not an absolute; directly linked to changes in the controls, or the introduction of variables.
- Build into the manufacturing process as variables to the process must be understood and controlled
- Anything which moves the process away from its validated controlled state has the potential to impact sterility assurance
Contamination Control Strategy

- Regulatory Requirements and Guidance
  - EC Annex 1 GMP for Sterile Products
  - PIC/S Good Manufacturing Practices
  - FDA Guidance GMPs for Sterile Products from Aseptic Processing
  - ICH Q9 Quality Risk Management
Best practices approach

• Risk Assessment
  • Map all manufacturing areas, equipment and activities (including transfers) with relevant classifications
  • Identify risk of microbial intrusion
  • Develop understanding of microbiological bioburden and their decontaminants in each area
  • Determine frequencies of cleaning and decontamination based on activities, surfaces and risk
Legacy approach
Control the aseptic core primarily

- ISO 5 Grade A/B classified areas – Aseptic Core
  - Engineered controls - HVAC, Pressure cascade
  - Full gowning and aseptic behavior expected
  - Airlocks and pass-throughs

- Risks
  - Contamination can still appear
  - Engineering controls taken for granted as ‘enough’
Better approach
Control origins of contamination as well as the aseptic core

- ISO 5 cleanroom, isolator, closed instruments are not separate entities in a GMP environment
- Pragmatic thinking of adjacent ISO 7-8 areas (Grades C-D)
- Consider control of CNC areas adjacent to cleanroom
Improvements to risk

Outside In

- Reduce source of contaminants
  People, materials, variability in cleaning and disinfection

- Influence reduction of cross-contamination

- Additive thinking for contamination control and reduction of human variability in cleaning and disinfection
Engineered design to reduce risk

• Surface materials are cleanable, maintained in good condition
• HVAC calibrated and monitored
• Doors/seals checked and good condition
• Process equipment for containment, RABS or isolators (understand limitations)
Approach for Selecting Manual Decontamination Agents

Identifying appropriate cleaning and disinfection agents

Aseptic core and beyond

- Select appropriate cleaning agent:
  detergent, surfactants

- Select appropriate disinfectant:
  ✓ Manual, broad spectrum rotated with a sporicide (automated H₂O₂ Vapor)

- Rinsing agents should be available:
  Water for Injection, IPA
Automated Approach to Contamination Control

A choice for efficiency and consistency in controlling contamination

- Use of isolators/closed systems to reduce risk of contamination to process
- Use of automated room decontamination (H₂O₂ Vapor) to reduce variability from manual disinfection practices
Hydrogen Peroxide Vapor Technology

- Bio-decontamination cycles in as little as 30 mins in isolators
- Validated, 6-log sporicidal kill* on exposed surfaces, verified with *Geobacillus Stearothermophilus*
- Compatible with sensitive materials and products
- Breaks down into oxygen and water vapor with no additional wipe downs needed
- Efficacy against a wide spectrum of microorganisms
Automated bio-decontamination can replace human intervention

- Any room decontamination with hydrogen peroxide vapor replaces manual activity with mops, wipes and spray
- Consistent, validated, efficient, cGMP
- Pass-thru or MAL decontamination
- Aseptic core, ISO 5, containment with built-in $\text{H}_2\text{O}_2$ system
- $\text{H}_2\text{O}_2$ Vapor Technology can be contracted or performed internally
Isolator Systems vs Biological safety cabinets
Environments for aseptic processing
Biological Safety Cabinets Overview

**ADVANTAGES**

- Provides some protection for a critical process
- **Lower capital cost** compared to most isolator systems

**DISADVANTAGES**

- **Open** to the environment/operator, putting critical process at risk of contamination
- Must be located in grade B cleanroom, **increasing running costs**
A Systems approach to contamination control
A choice for efficiency and consistency in controlling contamination

Use of isolators/closed systems

- A **complete barrier** eliminates risk of environment/operators contaminating process

- **Pressure cascades** prevent entry of ‘dirty’ air into isolator

- Note: EU GMP Annex 1 requires ‘open’ isolators to be in grade C cleanroom, but ‘closed’ isolators can be in grade D
Use of Isolators for Sterility Testing

Must be performed to release all sterile medicines and products to the market.

Failed test due to a false positive results in unnecessary investigation, halting production, loss of product.

Isolators should be used to protect process from environmental contamination.

Minimising the risk of false positives.
Best Practice

All manufacturing-related areas

- Develop a full facility control approach based on risk assessment of adjacent areas and potential for cross contamination
- Clean areas based on risk
- Automate disinfection for consistency and fit for manufacturing schedule
- Combining automated and manual approaches in a robust, efficient plan
- Train and maintain personnel aseptic practices in any classified area

How can you drive contamination control?
Significance of infrastructure control

Infrastructure and people

Adjacent to aseptic core

- Maintenance
- Cleaning
- Disinfection
- Operator traffic flow and restrictions
- Physical controls for manufacturing rooms
  - Diff. pressure
  - Temperature
  - Humidity
  - Air changes

Courtesy of Class One Cleanroom Systems Inc.
Monitor and observe contamination control

**Consistency is key!**

- Monitor engineered controls from Grade A to CNC
- Observe facility design and personnel aseptic behavior, skills and gowning
- Training ongoing
- Material decontamination and transfer
Your Bio-decontamination Program

Summary

- Holistic contamination control
  Integrated across your facility and processes

- Pragmatic cleaning with combined automated and manual decontamination meets your needs for efficiency and consistent, effective facility control

- Impact your key parameters of concern:
  - reduced chemicals, reduced residues
  - validated processes
  - efficient and effective labor (resources)
  - more production ‘run time’
Thank you!

Any questions?