Aseptic Processing and Isolator Technology

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Disclaimer

• This presentation contains a summary of the opinion and perspective from industry representatives on the topic of Isolator Technology for Aseptic Processing.

• This presentation does not necessarily represent the opinion of the presenter nor its employers.
Agenda

• Aseptic processing for sterile drug products.
• Regulatory expectations in aseptic processing.
• Aseptic processing using isolation systems.
• Examples of isolator systems.
• Regulatory considerations for isolator systems.
• Inspection preparation considerations.
Aseptic Processing for Sterile Drug Products

- Requires separation of the operator and process.
- Presents a higher risk of microbial contamination of the product and more variables than terminal sterilization.
- Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.
- May involve manual manipulations of sterile components, containers, and closures in addition to routine operator interventions in the critical area.
- Humans are a significant source of contamination in traditional aseptic processing, especially in production lines that require operators to routinely enter critical areas (Class 100, ISO 5, or Grade A) of the filling line.¹

Regulatory Expectations in Aseptic Processing for Sterile Drug Products

- Conventional cleanrooms with gowned operators in Grade A areas with simple machine guards as separation to critical process equipment is no longer considered best practice.

- Environmental control technologies that are now available and should be utilized wherever possible include Restricted Access Barrier Systems (RABS) and isolators. The use of so-called conventional cleanroom technology may be acceptable for the processing of terminally sterilized products and APIs and products where there are technical issues which prevent the use of barrier technology for aseptic processing.¹

Aseptic Processing Using Isolation Systems

- Separates the external cleanroom environment from the aseptic processing line and minimizes its exposure to human interaction.
- Fewer opportunities for microbial contamination during processing.
- A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.

Aseptic Processing Using Isolation Systems (cont.)

• Uses vaporized hydrogen peroxide (VHP/ vH202) at greater than 6 log sporicidal reduction for a high level of surface disinfection.

• Containment attributes and can be configured to contain toxic products processed aseptically at a slight positive pressure for CGMP.
Definition: Isolators

- **A physical separation barrier** between the process/product and the most contaminating source ‘people’ with typically an ISO8/EU-C background (EU-D Min).
- **Contamination control attributes** of HEPA filtered airflow and pressure differentials are used in Isolators to protect the critical zone (ISO5/EUA).
- **Aerodynamic protection is limited to ‘Mouse holes’** at end of barrier line. **Closed transfers** are used into the Isolator Barrier.
- Isolators have a **defined leak integrity** taken from a reference e.g. ISO10648 (classes 2 & 3) or PHSS Bio-contamination monograph 20 (larger lines).
- Isolators are typically decontaminated with **vH₂O₂ – VHP (bench mark) or other automated gaseous disinfection** processes. Some Pharmacy Isolators use manual disinfection procedures.
Isolator System

Photo courtesy of Franz Ziel GmbH
Inside a Filling Line Isolator

Photos courtesy of Franz Ziel GmbH
Critical Process Points

Point of Fill
Photos courtesy of Franz Ziel GmbH

CIP/SIP Station
Viewing Corridor

Photo courtesy of Franz Ziel GmbH
Isolator and RABS Combinations in Aseptic Processing Operations

Aseptic processing Isolator for ‘**Open systems processing**’ with Grade C background environment.

Sterilizing Tunnel direct connection to Isolator.
Photos courtesy of Franz Ziel GmbH

Closed Design and Operation RABS for Capper ‘**Closed system processing**’ with Grade C background environment.

Tilt-up Conveyor after Capper to provide Filling line walk around access.
Sterility Test Isolators

Isolator with Rapid Gassing VHP material transfer hatch.

Photos courtesy of Franz Ziel GmbH
Regulatory Considerations for Isolator Systems

- Regulatory risk-based initiatives such as QbD (Quality by Design) and QRM (Quality Risk Management) should be applied through isolator design, qualification and operation.
- Isolators are not a barrier to ALL contamination and good aseptic technique is still required.
- Surrounding environmental and operators play a significant role in contamination control.
Different isolator designs provide different contamination control (product protection and/or operator protection) and cross-contamination control.

Process design should consider material/component entries and exit that could be a potential route for environmental and sterile product contamination.

Airflow pattern movements together with the need for smoke visualisation studies should be understood.

Glove life-cycle management process should be in place.
Regulatory Considerations for Isolator Systems (cont.)

• Appropriate environmental control and monitoring assessments are necessary which characterise risks groups, risk priority number outcomes and appropriate risk assessment models.

• Vaporized hydrogen peroxide (VHP) bio-decontamination process should be understood.

• Biological indicators in cycle development and qualification studies should be understood and managed.
Regulatory Considerations for Isolator Systems in ANDA Submissions

• Isolator submission are very similar to traditional filling line submissions and should be treated like any other filling lines.
Inspection Preparation Considerations

• All normal cGMP systems are evaluated.
• Smoke (static and dynamic) studies should demonstrate proper airflow.
• Interventions (including non-routine) should be qualified (during media fill).
• Rotation of disinfectants.
• For CIP/SIP process - flow, temp and time should be stated in the procedure.
• Validation of depyrogenation of containers has same requirements and guidelines as for other types of lines.
• Preventive maintenance program for equipment.
• Bioburden limits and monitoring for components.
• Capping operation.
Design and control elements that maintain the separation or isolation of the product.

Pressure differential.

Glove integrity.

Protection of the transfer ports.

Transfer of containers, closures and supplies into an isolator.
• Effectiveness of the chamber decontamination program.
• Utensils and equipment surfaces inside the isolator.
• Sterilization validation should achieve a minimum of a 6-log reduction of the BI.
• Aseptic processing presents a higher risk of microbial contamination of the product and more variables than terminal sterilization.

• Isolator systems separate the external cleanroom environment from the aseptic processing line, minimizes its exposure to human interaction, and offers fewer opportunities for microbial contamination during processing.

• Regulatory risk-based initiatives such QbD and QRM should be applied through isolator design, qualification and operation.
References

- USP (1211) Sterilization and Sterility Assurance of Compendial Articles.
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