Achieving Meticulous Aseptic Standards & Control in a Filling Isolator – Lessons for Design

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Background Classification – Is Grade D Good Enough?

Sterilize Vs Surface Biodecontamination of Indirect Parts

Gloves & Pinholes – a Real Risk?
EU Grade D

EU Grade A
<table>
<thead>
<tr>
<th>ISPE Classification Grade</th>
<th>FDA, CDER September 2004 Guideline on Sterile Drug Products for Aseptic Processing</th>
<th>European Commission Annex 1, 2008 – Manufacture of Sterile Medicinal Products</th>
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<tbody>
<tr>
<td></td>
<td>In Operation</td>
<td>Descriptive</td>
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<tr>
<td>Grade 8</td>
<td>3,520,000 ISO 8 (100,000)</td>
<td>100 (50)</td>
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An Open, Positive Pressure Isolator is a Closed System

- Room Environment
- HVAC System
- Product Protection
- Facility / Building
Aseptic Processing Complexity –

The Holistic Facility*

* R. Friedmann- FDA, 2014
Consequences
RISK ASSESSMENTS INPUTS

- Set-up Bioburden load
- Integrity breach during processing
- Integrity breach during transfer / interventions
- Area Practices
Autoclave Prior to VHP?
Guidance Documents


PHSS Technical Monograph No 20: Biodecontamination (2014)
• The application of a sporicidal process is not considered to be a sterilization process

• ...lacks the penetrating capabilities of steam sterilization

• ...be mindful of the limitations of surface sterilants

• ...their inefficiency in penetrating obstructed or protected components
What Limitations?
VHP Controls

- Temperature & Humidity
- Airflow
- Slow Motion during VHP to ensure hidden areas are exposed
- Chemical indicators
- BI's – Mitigation Against Variance
- VHP Dosing Rate / Exposure Time
- Biological Indicators – Establishment of Edge of Failure
- System D Value Determination
Consistently Delivers at least a 6 log BI Reduction

Is this no longer good enough?
Longer Batch Turnaround Times
Increased Risk of Damage due to Handling
Opportunities for Error in all of the above

CONSEQUENCES

Autoclave Loads – Cycle Development / PQ / Requalification/ Hold time studies by Media Fill

Storage Requirements with Control post Autoclaving

Longer Batch Turnaround Times

Increased Risk of Damage due to Handling

Opportunities for Error in all of the above
CONSEQUENCES

Greater Aseptic Control?

Greater Product Quality & Patient Safety?
RISK ASSESSMENTS

INPUTS

- Ineffective sanitisation as part of isolator set-up
- Increased Bioburden load for VHP
- VHP Cycle not effective
- Product Contamination
How Risky are Pinholes in Gloves? A Rational Appeal for the Integrity of Gloves for Isolators

Following 12 batches over two weeks, less than 20% of the gloves (103) showed more than 5 CFU/sample.

Migration of microorganisms through damaged gloves with pinhole was established with high bioload (3.6 x 10⁴ CFU/cm²)

Medium (4.3 x 10³ CFU/cm²) and Realistic (5.0 x 10¹ CFU/cm²) bioloads did not result in contamination.
Conclusions

• Pinholes as a source of contamination does not consider real world situations and may also have enormous economic consequences.

• Defective Gloves will not contaminate a product if proper control of the glove inner side and properly evaluated techniques are respected.
EM Data (Viable & Non-Viable)

Review of Glove Spec & Previous Test Data

Leak Location on Glove

Process Data - Alarms

Sequence of Events - Interventions

Previous Deviations
Glove Failure Investigations

Batch is saved – no microbial contamination

The reason the gloves failed in the first place was not helped by excessive environmental monitoring inside the isolator

Where is the contamination going to come from in the first place?

Is this embracing new technology?
As long as some people erroneously insist on immeasurable perfection, we will have unreasonable expectations.