Guiding Principles for the implementation of fluid management technologies for modern single use aseptic processing

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Fluid Management Technologies
Agenda

1. Aseptic processing requirements
2. Points to consider
3. Technologies for Aseptic Processing
4. Summary
1 – Aseptic Processing Requirements

1 – Regulatory requirements

2 – Process design & facility layout

3 – Examples of Process designs
A well designed barrier isolator appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing.

A Class 10,000 or Class 100,000 background is appropriate depending on isolator design and manufacturing situations.
1 – Aseptic Processing Requirements
European GMP Directive 1997 Annex 1 Manufacture of sterile medicinal products

The utilisation of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment.
1 – Aseptic Processing Requirements
Traditional Aseptic processing Isolator Layout

- Clean components in ISO 8 clean room
  - Filters
  - Mixing & transfer tanks
  - Filling machine components
- Assemble components in ISO 7
- SIP & Autoclave in ISO 7

- Formulation / Filtration in ISO 7
- Aseptic connections and final filling in ISO 5 area
- Clean
- Dismount
- Maintain equipment

Grade C Class 10.000 ISO 7
Grade D Class 100.000 ISO 8
Grade A Class 100 ISO 5
1 - Aseptic Processing Requirements

Modern Single Use Aseptic Processing

- Process components assembled by suppliers in ISO 7 cleanroom
- Single Use Systems sterilized by suppliers - gamma radiation
- Aseptic connections replaced by Sterile connectors or Tube welders
- Process in ISO 7 or 8
- Final filling in ISO 5
- Discard and incinerate

Simplified process in optimized facility layout
1 – Aseptic Processing Requirements
Modern Aseptic Processing Facility Layout

Controlled area / Class 100,000

Transition zone

Clean area / Class 10,000
Compounding and filtration zone

Critical area
Class 100
Aseptic Filling area

Stamper product

People change

Gowning

Sterile filtration

Sterilization

Sterilization

SIP / CIP

Raw materials

Packaging Components
Stoppers

Process Components
filters, bags, mixers

Utilities
Gas, Water, Steam, CIP

Waste
Clothing, materials

Waste
CIP effluents

Components
Cleaning

Repeated SIP/CIP cycles associated to multi purpose small batch facilities are eliminated
1 - Aseptic Processing Requirements

Benefits of Single Use Technologies

**Economic Benefits**
- Reduce upfront capital investment
- Minimize CIP/SIP validation efforts
- Reduce downtime, utilities & labour
- Speed up time to market, fast commercialization

**Improved Safety**
- Closed systems
- Reduced risk of cross contamination for multi purpose & small batch facilities

**Flexibility**
- Optimize facility layout
- Cost effective turn around of new products
- Ease of use and changeover for small batches
1 – Aseptic Processing Requirements

Example of Modern Aseptic Processing
2 - Points to Consider

1 - Product Robustness & Security of supply
2 - Quality system
3 - Validation & Quality Controls
4 - Extractable data & Leachable Validation Service
5 - Costs & environmental impact
6 - Single Use Process Validation
2 - Points to Consider
Product Robustness & Security of Supply

Application / Product

- Film
- Bags
- Membranes
- Filters
- Tubing
- Connectors
- Sensors
- Plastic components
- Containers

Raw Material Specification & Qualification

Product & Process Validation

Raw Material Control, Process Controls & Product Controls

Supply Chain Management
Manufacturing & Quality System Capabilities

Collaborative Demand Planning
2 - Points to Consider
Quality System

- ISO 9001: Quality Management Systems
- ISO 13485: Quality Management Systems for Medical Devices
- 21 CFR Parts 808, 812 and 820: Current Good Manufacturing Practices for Medical Devices
- ISO 14644: Clean-room environmental controls
- ISO 11137: Sterilization of Medical Devices
- ISO 11737: Bioburden
- E.P. 2.6.14 and USP<85>: Bacterial Endotoxins test
- E.P. 2.9.19 and USP<788>: Particulate
## Validation data - Mechanical & Physico-Chemical tests

<table>
<thead>
<tr>
<th>Qualification Tests</th>
<th>Tests usually performed after gamma irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical Properties</strong></td>
<td>Ultimate Tensile Strength (UTS)</td>
</tr>
<tr>
<td></td>
<td>Elongation at break</td>
</tr>
<tr>
<td></td>
<td>Secant Modulus at 2%</td>
</tr>
<tr>
<td></td>
<td>Toughness, Resistance to tearing</td>
</tr>
<tr>
<td></td>
<td>Flex Durability, Impact resistance</td>
</tr>
<tr>
<td><strong>Barrier Properties</strong></td>
<td>Barrier to Water Vapour (ASTM F1249)</td>
</tr>
<tr>
<td></td>
<td>Barrier to Oxygen (ASTM D3985)</td>
</tr>
<tr>
<td></td>
<td>Barrier to Carbon Dioxide (ASTM F2476)</td>
</tr>
<tr>
<td><strong>Integrity</strong></td>
<td>Seal Strength Integrity, 100% bag integrity testing</td>
</tr>
<tr>
<td><strong>Biocompatibility</strong></td>
<td>USP &lt;87&gt; Biological reactivity tests, In Vitro</td>
</tr>
<tr>
<td></td>
<td>USP &lt;88&gt; Biological reactivity tests, In Vivo</td>
</tr>
<tr>
<td><strong>Physico-Chemical Tests</strong></td>
<td>European Pharmacopéia (E.P.3.1.5 PE with additives for Containers)</td>
</tr>
<tr>
<td></td>
<td>BSE/TSE Status (E.P.5.2.8)</td>
</tr>
<tr>
<td></td>
<td>USP &lt;661 &gt;</td>
</tr>
<tr>
<td><strong>Stability of WFI</strong></td>
<td>USP and EP</td>
</tr>
<tr>
<td><strong>Chemical Resistance</strong></td>
<td>ASTM D543-06 &quot;Method for resistance of Plastic to chemical reagents&quot;</td>
</tr>
</tbody>
</table>
### 2 - Points to Consider
Validation Data - Gamma Sterilization

<table>
<thead>
<tr>
<th>PROCESS VALIDATION</th>
<th>PROCESS CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STERILIZATION CYCLE DEVELOPMENT</strong></td>
<td><strong>MAINTENANCE OF STERILITY</strong></td>
</tr>
<tr>
<td>1. Bioburden Quantification</td>
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</tr>
<tr>
<td>2. Bioburden Identification</td>
<td>2. Identification &amp; resistance</td>
</tr>
<tr>
<td><strong>SHELF LIFE</strong></td>
<td><strong>PRODUCT PERFORMANCES</strong></td>
</tr>
<tr>
<td>1. Functional performances</td>
<td>1. 100% Visual inspection of bags</td>
</tr>
<tr>
<td>2. Package integrity</td>
<td>2. 100% Package inspection</td>
</tr>
<tr>
<td>4. Sterility</td>
<td></td>
</tr>
<tr>
<td><strong>IRRADIATION PERFORMANCE QUALIFICATION</strong></td>
<td><strong>GAMMA IRRADIATION PROCESS CONSISTENCY</strong></td>
</tr>
<tr>
<td>1. Dose mapping and limit setting</td>
<td>1. Product density</td>
</tr>
<tr>
<td>2. Density range and limit setting</td>
<td>2. Min and max irradiation dose</td>
</tr>
</tbody>
</table>

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*ISO 11137: Sterilization of Medical Devices*
# 2 - Points to Consider

## Quality Controls

<table>
<thead>
<tr>
<th>Monitoring tests</th>
<th>Lot release tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxins test USP&lt;85&gt; and E.P. 2.6.14</td>
<td>100% visual testing of bag and seal</td>
</tr>
<tr>
<td>USP&lt;788&gt; and E.P. 2.9.19 : Particulate</td>
<td>100% air pressure leak test</td>
</tr>
<tr>
<td>ISO 11737: Bioburden</td>
<td>Technical drawing compliance</td>
</tr>
<tr>
<td>ISO 11137: Sterilization of Medical Devices</td>
<td>Dimensional check</td>
</tr>
<tr>
<td>ISO 14644: Cleanrooms environmental controls</td>
<td>Packaging and labelling inspection</td>
</tr>
<tr>
<td></td>
<td>Gamma sterilization</td>
</tr>
</tbody>
</table>
2 - Points to Consider

Quality Controls

Pressure Decay Integrity Test for Large Volume 3D Bag Chambers < 200l

- The integrity test is performed on folded bags
  - Tested volume is small for increased test sensitivity
  - No bag refolding / handling required after testing
- Porous layers on bag faces and gussets
  - Prevent blocking of pinhole on the plate or in gusset
2 - Points to Consider
Extractable Data

<table>
<thead>
<tr>
<th>Solution</th>
<th>Compounds</th>
<th>Extraction times</th>
<th>Compounds</th>
<th>Extraction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFI + HCl (pH &lt; 2.5)</td>
<td>Volatile, semi-volatile</td>
<td>1d, 1w, 1m, 4m</td>
<td>Non volatile</td>
<td>4m</td>
</tr>
<tr>
<td>WFI</td>
<td>Volatile, semi-volatile</td>
<td>1d, 1w, 1m, 4m</td>
<td>Non volatile</td>
<td>4m</td>
</tr>
<tr>
<td>WFI + NaOH (pH &gt; 11)</td>
<td>Volatile, semi-volatile</td>
<td>1d, 1w, 1m, 4m</td>
<td>Non volatile</td>
<td>4m</td>
</tr>
<tr>
<td>100% ethanol</td>
<td>NA</td>
<td>NA</td>
<td>Non volatile</td>
<td>4m</td>
</tr>
<tr>
<td>WFI + HCl (pH &lt; 2.5)</td>
<td>NA</td>
<td>NA</td>
<td>Metal Analysis</td>
<td>4m</td>
</tr>
</tbody>
</table>

- **TOC quantification**
  - **METAL analysis** 20 – 500 ppb
- VOLATILE leachables or compound (VOC)
  - GC/MS: Identification and ½ quantification, 5 – 50 ppb
  - ½ VOLATILE leachables (SVOC)
    - GC/MS Identification and ½ quantification, 50 ppb
- NON VOLATILE leachables (NVOC)
  - LC/MS. Identification and full quantification, 1-5 ppb
2 - Points to Consider

Costs & Environmental Impact

- **Carbon Footprint**: 25.5% reduction
- **Utility Requirements**: 87% less water
- **Materials**: 95% reduced CIP material
- **Labor**: 21% less
- **Space**: 38% less
- **Steelwork**: 62% less
- **Electricity**: 39% less

### 2 - Points to Consider
Validation Master Plan for Aseptic Processing

<table>
<thead>
<tr>
<th>Traditional Aseptic Processing</th>
<th>Single Use Aseptic Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steam sterilization</td>
<td>Gamma irradiation sterilization</td>
</tr>
<tr>
<td>Filter retention validation</td>
<td>Filter retention validation</td>
</tr>
<tr>
<td>Filter extractable</td>
<td>Single Use system leachables</td>
</tr>
<tr>
<td>Integrity testing</td>
<td>Bacterial ingress testing</td>
</tr>
<tr>
<td>Filter compatibility</td>
<td>Single Use system compatibility</td>
</tr>
<tr>
<td>Media fills</td>
<td>Media fills</td>
</tr>
<tr>
<td>Fills accuracy</td>
<td>Fills accuracy</td>
</tr>
<tr>
<td>Bioburden &amp; sterility testing</td>
<td>Bioburden &amp; sterility testing</td>
</tr>
<tr>
<td>Stability testing</td>
<td>Stability testing</td>
</tr>
<tr>
<td>Others, CIP, rising...</td>
<td>Elimination by incineration</td>
</tr>
</tbody>
</table>
3 – Technologies

1 – Bags Systems
2 – Mixing Systems
3 – Containers
4 – Filters
5 – Connectors
6 – Transfer Systems
7 – Filling systems
3 - Technologies

Bag Systems

- **Bag design**
  - **3D for Cubic tanks**
    - 50 – 3000L
  - **3D for Drums**
    - 50 – 1000L
  - **2D bags**
    - 50ml – 50L
3 - Technologies

Bag Systems

- Volumes: 50 mL up to 3500 L
- 2D and 3D Bags
- Contact layer PE or EVA
- Smaller bags (≤ 10L) hanging installation
- Low level of leachables
- High clarity and flexibility
- Gamma sterile
- Level control e.g. with scale
3 - Technologies Mixing Systems

- Stirring
  - Top Impeller
  - Bottom impeller
  - Paddle
  - Wand
- Shaking
  - Orbital shaking
  - Rocking motion
- Recirculation
- Vibration
  - Vibromixer
3 - Technologies
Containers

Storage
In-Process Handling
Shipping
Mixing & Weighing
3 – Technologies
Single Use Filters

Single Use Filters

• Millipore OptiCap

• Pall Kleenpak

• Sartorius-Stedim Sartopore

Features

• Gamma sterilizable up to 50 kgy

• In line and T line

• PVFD or PESU membranes
3 – Technologies
Single Use Connectors & Disconnectors

Main Suppliers
- Colder
- Millipore, Pall, Sartorius
- Wave, Terumo
- Others

Non sterile
- All size of tubing 1/8” to 1”

Sterile
- ¼” and ½”

Clipster
- Sizes : up to 3/4” OD

Biwelder
- Thermal weld of TPE Tubing
- Sizes : up to 3/4” OD

Biosealer
- Thermal seal of TPE Tubing
- Sizes : up to 3/4” OD
3 - Technologies
Single-Use Aseptic Transfer Systems:

Rotative System
- Re-usable & disposable Bags
- Multiple connections

Magnetic System (safe & easy docking)
- Biosafe® Bags
- Single-use technology

Liquid Transfer
- SART connector
3 - Technologies
Disposable filling systems

Main suppliers
- Millipore (Acerta)
- Flexicon (PD12I)
- Bosch (Prevas)

Fill volumes
- Acerta: 0.2 - 10 ml @ +/- 0.5% accuracy
- PD12I: 0.5 - 250 ml @ +/- 0.5% accuracy
1 to 16 heads
3 - Technologies
Disposable filling systems

- tubing to product tank of customer
- intermediate tank as a bag
- manifold
- filling needle
- RDP

PreVAS
Disappearing Dosage Systems
BOSCH
4 - Summary

Single-use Systems bear multiple advantages and well address the needs for small batch complexity

- Reduced cleaning & sterilization requirements & validation
- Lower capital investment
- Faster qualification & implementation
- Increased production capacity utilization by reducing multiple change over times associated to small batches
- Higher flexibility for varying production volumes or process needs
- Lower costs & environmental impact

Product robustness and security of supply become the most important critical success factors for the implementation of single use processes
Thank You For Your Attention!