Use of Pre-sterilized single-use disposable fluid paths in sterile manufacturing

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Components for disposable systems
Introduction

state-of-the-art?

Disposable systems in Biotech Manufacturing

Applications:

- Media preparation
- Cell cultivation
- Bioreactors
- Purification
- Filtration
- Formulation
- Product storage
- Bulk filling
Disposable path & parts

Layout of a disposable product path
Disposable path & parts

Integrated system
Introduction - Key Drivers

Reduction of Process Risk

• Cross contamination
  Microbiological, particles, product
• Toxic / leachable substances
• Cleaning solutions
Filling systems

Existing (disposable) filling systems

• Mass Flow
• Time Pressure
• Peristaltic Pump → DISPOSABLE standard
• Turning Valve Pump → DISPOSABLE available
• Rotary Piston Pump → DISPOSABLE ?
• Filling needle → DISPOSABLE ?
Filling systems: Mass flow

Pressure filling mass controlled

- Plastics, silicone, steel
- Disposable system: not available
Filling systems: Time Pressure

Pressure filling time controlled
• Stainless steel, plastics & silicone
• Disposable system: not available
Disposable Filling Pumps

Peristaltic Pump

Alternative 3 - Disposable

- Product supply → Flexboy
- Size parts → hose support → filling hoses → filling needle
- IPC
  → Teach – in
  → Tendency control

Disposable filling needle
Disposable Filling Pumps

Peristaltic Pump
Disposable Filling Pumps

Range of applications for Peristaltic Pumps

- Multi purpose filling machines
- No CIP / SIP cleaning or sterilization
- Simple hardware
- Filling speed and accuracy correlates
- Drift control required  → IPC
Disposable Filling Pumps

Range of applications for Peristaltic Pumps

- Silicone tubes need to be replaced at intervals \((8-16h \rightarrow 100h?)\)
- Shear forces might impact sensitive products
- Product contacting parts made of plastics or silicone
- Stainless steel surge tank replaceable by plastic surge bag
Diaphragma pump

- Volumetric filling
- Plastics & silicone
Disposable Filling Pumps

A disposable Rotary Piston Pump?

- Multi purpose filling machines
- Usable on all servo driven groninger rotary piston pump machines
- Well-known principal
- Well-known material
Disposable Filling Pumps

groninger Rotary Piston Pump

Still under construction, a Prototype exists
Disposable filling needle

Which material will work best?
→ Plastics?
→ Stainless steel?
→ Combination of different materials?

Easy Design - Suitable materials
Disposable filling needle

... made of PLASTICS

Attention should be paid to

- Leacheables
- Extractables
- USP Class VI - conformity
- Biocompatibility / cytotoxicity
- Particulates
- Steadyness

validation effort?
Disposable filling needle

... made of PLASTICS & METAL

Attention should be paid to:

• Leacheables  no contact to product
• Extractables  no contact to product
• USP ClassVI - conformity
• Biocompatibility / cytotoxicity
• Particulates
• Steadyness
• ...

...
Disposable filling needle

No need to combine different materials
Disposable filling needle

... made of METAL

Attention should be paid to:

- Leacheables no contact to product
- Extractables no contact to product
- USP Class VI - conformity
- Biocompatibility / cytotoxicity
- Particulates
- Steadyness

Easy Design - Easy to sterilize

Suitable material
Disposable filling needle

Additional validation effort by supplier

• Cleaning process
  a suitable and also validateable cleaning process has to be established

Suitability tests:
  Particulates
  Bio-burden
  Pyrogens
  (Cytotoxicity)
Disposable filling needle

Additional validation effort by supplier

• Sterilization process

  Possibilities
  1.) Gamma-Radiation
  2.) ETO
  3.) Steam – Sterilization
  4.) …

  Suitability test:

  check of SAL $10^{-6}$
  Bio-burden
Disposable filling needle

Dose reduction for gamma radiation through stainless steel

Linear attenuation coefficient = 0.394/cm -> 50% at 17.6mm

Nt = No*exp(-μ*t)
Disposable filling needle

Additional validation effort

• Packaging

packaging material has to protect the product both from damages during transportation and environmental influences

Suitability tests:

Transport Simulation
Real-time aging
Accelerated aging
## Disposable filling needle

<table>
<thead>
<tr>
<th>Test</th>
<th>Request</th>
<th>Correlates to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio-burden</td>
<td>&lt;100cfu/object</td>
<td>ISO 11737-1</td>
</tr>
<tr>
<td>Sterility</td>
<td>SAL 10^-6</td>
<td>ISO 11137</td>
</tr>
<tr>
<td>Pyrogens</td>
<td>&lt;0.25eu/mL</td>
<td>USP &lt;85</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Biocompatibility</td>
<td>ISO 10993-5</td>
</tr>
<tr>
<td>Cleaning process</td>
<td>Validated</td>
<td>ISO 11737-1, USP &lt;61</td>
</tr>
<tr>
<td>Particulates</td>
<td>3(&gt;25µm), ...</td>
<td>USP &lt;788</td>
</tr>
<tr>
<td>Real time aging</td>
<td></td>
<td>ISO 11607, ISTA2A, ASTM F 1980</td>
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<tr>
<td>Life period packaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport simulation</td>
<td></td>
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</tbody>
</table>
Disposable filling needle

Disposable filling needle by groninger

filling needles in 6 different sizes
Disposable filling needle

Disposable filling needle by groninger

• 6 sizes: 2, 3, 4, 5, 6, 8 mm, length 165mm
• Stainless steel 1.4435
• Raw material already Ra 0.4 (in- and outside)

The complete product path =

all product contacting parts are made of stainless steel + tubing (silicone)
Finding a suitable Packaging system

1) Needles should be withdrawable singularly
2) Easy handling through isolator gloves
3) Suitable packaging size
4) Packaging suitable for cleanroom handling
Disposable filling needle

Packaging system

1) Every needle packed singularly in a double bag
2) Easy-to-open asymmetric lash design
3) Double packs: one carton contains two needles
4) Outer box of low particle carton

Disposable filling needle
• Known material
• Real time aging will be performed
• No material toxicity - stainless steel
• Tested, validated & certificated
• Manufactured under ISO 9001
• Cleaned, packed & gamma sterilized under cGMP
• Fully validated & certified system
• Disposable filling needle
Benefits

- No more time consuming cleaning processes
- No more intricate CIP / SIP systems
- Cross-contaminations effectively eliminated
- Complete and holistic system
- Reduction of validation activities
- Reduction of qualification activities
- Time to market
Installation on filling line
Building History and Background

• Who we are and how this began:
  • 2006 – Board approval for construction of a multi-use building in Silver Spring, Maryland
  • December 2007 – Construction initiated
  • Building Statistics:
    – Height: 7 stories
    – 66,680 ft² (6,195 m²)
  • December 2009 – Occupancy permit issued

Floor 1: Lobby and Retail
Floor 2: Manufacturing, Labs & Offices
Floor 3: Manufacturing
Floor 4: Mechanical
Floors 5, 6 & 7: Offices
Our Equipment

• Fully Integrated Groninger Vial Filling Line
  – Vial Washer
  – Depyrogenation Tunnel
  – Vial Filler
  – Capper

• Skan Barrier Isolators
  – 3 Isolator System
Crossing the Barrier

• Challenges of Isolated Technologies, how to cross the sterile barrier without impacting sterility.
  1. Large Cumbersome Steel/Plastic RTP’s.
  2. Lengthy prep and setup times
  3. Increased scrutiny on sterilization techniques for assemblies.
Our Goal

• Create a system that could be used as a backbone for all sterile filled products.

• Eliminate the need to perform cleaning and sterilization validation.

• Reduce setup/breakdown times of system.

• Improve efficiency and system capability.
Further History

• No manufacturing legacies preventing implementation of new technology

• Equipment was designed to be flexible, so we needed systems that were equally as flexible.
  – Flexibility for the unknown
Why go disposable?

- Operational Flexibility
- Elimination of Cleaning Validation (CV)
- Reduction of contamination risk
- Elimination of CIP/SIP time and associated validation
- Reduced Setup times
- Improved Efficiency
- Reduced ongoing validation time and costs
My experience

- Extensive background in biologic manufacturing from CC and PP.

- Extensive knowledge of past/current disposable technologies.

- Believer in logical risk.
Designing the Guinea Pig

• There was a real lack of experience in this scope.
  – There was very little to leverage during design and conceptualization.

• OEM’s and disposable MFG’s were open to exploring the concept.

• Staged approach on our original goal would have to implemented.
Our Path

• Early 2009 sat down with disposable suppliers and OEM’s:
  – Determined what currently existed.
  – What was lacking.
  – What the path/responsibilities would be moving forward.
## What Existed, What didn’t

<table>
<thead>
<tr>
<th>What was available</th>
<th>What wasn’t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubing</td>
<td>Lack of Disposable SS Needles</td>
</tr>
<tr>
<td>Tubing connectors</td>
<td>Lack of a validation package on assemblies of this magnitude</td>
</tr>
<tr>
<td>Transfer connector bags</td>
<td>Lack of Regulatory approval using this technology in Sterile MFG</td>
</tr>
<tr>
<td>Sterile to Non-Sterile and Sterile to</td>
<td>Lack of experience with integrating assemblies with Isolated Filling lines.</td>
</tr>
<tr>
<td>Sterile Connectors</td>
<td></td>
</tr>
<tr>
<td>Disposable Surge bags</td>
<td></td>
</tr>
<tr>
<td>Experience with putting assemblies together</td>
<td></td>
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</tbody>
</table>
Planned Evolution

• Generation 1
  – Fully disposable pre-sterilized assembly from tank to end of tubing.
  – Would require purchase of disposable SS needles and having them sterilized offline.
Planned Evolution Cont’d

• Generation 2
  – Fully disposable pre-sterilized assembly from tank to needles.
• Checked/Verified fit on the filling line.

• Evaluated different pump tubing diameters to challenge filling accuracy.

• Discussed improvements before finalizing.
  – Increasing tubing length
  – Standardized “Y” connectors
  – Improved natural weak points in system.
Our Assembly

• Standard Off the Shelf Pieces
  – Millipore Lynx connectors
  – Robust Tubing at custom lengths
  – Disposable SS needles
  – LaCalhene Beta bag
Our Method

• Manual cleaning of isolator surfaces with 70% IPA.

• Sterilization of Isolators with Vaporized Hydrogen Peroxide (VHP).

• Pull in and setup of pre-sterilized disposable assembly.

• Routine Filling.

• Breakdown of system followed by disposal.
Video of Assembly Installation
## Traditional CIP/SIP vs. Disposable

<table>
<thead>
<tr>
<th>Traditional CIP/SIP System</th>
<th>Single Use Disposable System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Equipment = $300,000(^1)</td>
<td>Additional Equipment = $0</td>
</tr>
<tr>
<td>Setup = 2 hours</td>
<td>Setup = 45 minutes</td>
</tr>
<tr>
<td>CIP cycle = 40 minutes</td>
<td>Arrives Pre-cleaned</td>
</tr>
<tr>
<td>SIP cycle = 75 minutes</td>
<td>Arrives Pre-sterilized</td>
</tr>
<tr>
<td>Cool down cycle = 75 minutes</td>
<td>Ready to go</td>
</tr>
<tr>
<td>Cleanup = 1 hour</td>
<td>Cleanup = 15 minutes</td>
</tr>
<tr>
<td>Post-Use CIP = 40 minutes</td>
<td>Throw it away</td>
</tr>
<tr>
<td>Overall = ~ 7 hours and $300k(^2)</td>
<td>Overall = 1 hour, cost of assembly(^3)</td>
</tr>
</tbody>
</table>

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1. $300,000 in equipment costs, additional $200,000 in ancillary costs such as running utility supplies to perform general operation.

2. Does not include costs associated with initial and ongoing CV + Sterilization Validation, does not include utility costs.

3. Companies can stockpile assemblies. If an error occurs assemblies can be changed out rapidly with minimal processing delay.
Discussion Points for Going Disposable

• Cost
  – Additional Equipment vs. other
• Time
  – CIP/SIP Validation
• Resources available
• Maintenance
Take Away

• Companies should not be afraid of this technology.
  – We did not have the experience but we leveraged our knowledge which resulted in steering vendors to advance what was available.

• Proven Regulatory acceptance
  – FDA PAI with no deficiencies regarding single use disposable assembly.
Points to consider

• Single Use Disposable assemblies are not right for every application.

• What works for us won’t always work for Company X.

• Explore tubing options.

• Evaluate how tight your filling tolerance must be.
Challenges Ahead

• Costs
  – OEM’s and Disposable MFG’s need to do more to bring the costs down.

• Minimum order quantities
  – Disposable Assembly MFG’s are strong-arming users into high min order Qty’s.

• Acceptance by industry personnel
  – We need to embrace this technology.
Recommendations

• Do a thorough cost vs. benefit analysis
  – Capital investments
  – Validation Requirements (ongoing)
  – Labor hours required
• Don’t create more/less than what you truly need.
  – How many products do you have and what are the volume differences?
  – Evaluate whether your process requires inline filtration.
Many thanks for your attention
Any questions?

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