Technological and Engineering Innovations around sterile Medicinal product filtration

National GMP & Validation Forum
Hosted by Pharmout
Melbourne, August 6, 2018

Michael Payne
Principal Technical Consultant
Merck
1 Sterile medicinal product overview
2 Steps in filtration process
3 Some improvements and considerations
4 Cautionary tale
5 Conclusion
Balance Change and Control and Risk
Keep Key Regulatory Concerns in Mind

<table>
<thead>
<tr>
<th>Efficacy / Strength</th>
<th>Does the change in the validated production process result in a product / residues that interfere with drug product strength or efficacy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity &amp; Purity</td>
<td>Does the change to the validated production process result in a product / residues that interfere with drug product purity?</td>
</tr>
<tr>
<td>Safety</td>
<td>Does the change to the validated production process result in a product / residues that are toxic to the patient?</td>
</tr>
</tbody>
</table>

US FDA Vision – MUST involve change!
“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
8 Elements of Sterile Filtration Qualification
Represent “worst case” process conditions, process fluid, filter performance & microbiological challenge

Prove the filter’s bacterial retention capabilities with a non-destructive test.

Prove the filter removes bacteria from the stream compliant with ASTM and relevant regulations.

Prove the stream does not adversely impact the filter duty or process stream.

Prove the filter meets all performance & duty requirements within product & process conditions.

Prove the sterilization method is effective and does not compromise the filter.

Identify, quantify, and assess impact of compounds that migrate from filter to process stream.
Focus on Formulation / Filling Suite

Circled filters are critical

The filter directly affects product quality

Where process fluids “are in direct contact with sterile final product or critical surfaces of the associated equipment.” (PDA TR40)

Part of Direct Impact System - equipment or system that will have focused and immediate impact on product quality (ISPE Commissioning & Qualification Baseline Guide (2001))

No purification step after sterilizing filtration
1 Sterile medicinal product overview
2 Steps in filtration process
   Some improvements and considerations
3 Cautionary tale
4 Conclusion
**Product Adsorption**

**Examples of Change of Approach – Location and Chemistry**

*Adage – look for the filter with the lowest adsorption.*

*Need information on saturation curve*

**Considerations:**

- **Adsorption of What**
  - Drug substance / preservative / excipient /
- **Critical Filter Location**
  - Tank to tank
  - Point of Use
- **Effect of Intermittent Flowrate**
  - Bounce-back
- **Impact to total cost of production**
Filter Sizing
Examples of Change of Approach – Location and Performance

Adage – Perform Filter Sizing Focusing on Capacity

Need information or testing

Consider Filter Location
Tank to tank – capacity is important
Point of Use – flowrate is important

Nomograph for Sizing
Using pressure, permeability, test library
Extractables & Leachables (E&L): PDA Definitions

**Extractables**

“Any chemical component that is removed from a material by the application of an artificial or exaggerated force (e.g., solvent, temperature or time).”

Determined under “worst-case” conditions following the Model Stream approach.

**Leachables**

“A chemical component that migrates from a contact surface into a drug product or process fluid during storage or normal use conditions.”

Determined with the product under normal processing/storage conditions.

**Extractables Study:**
To identify and quantify as many compounds as possible that have the potential to become leachables.

**Leachables Study:**
To identify and quantify as many compounds as possible that migrate from the filtration process or storage systems into the actual drug product.

*PDA® Technical report N°26, 2008*
*PDA® Technical report N°66, 2014*
Filter Extractables & Leachables
Examples of Change of Approach – Increased Scrutiny and Risk Reduction

Historical Approaches
• Overlook influence
• Use extractables information
• Flush filter before sterilization
• Flush filter before use
• Use vendor TOC curves

Current Approaches
• Check Toxicity Concerns
• Extractables information
• Patient dosage
• Check toxicity (Threshold of Toxicity Concern – TTC)
• Implement mitigation tactics
• Determine individual components
• Check toxicity
• TTC for genotoxic impurities (ICH M7):

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>≤ 1 month</th>
<th>&gt;1-12 months</th>
<th>&gt;1-10 years</th>
<th>&gt;10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Impurity</td>
<td>120 µg</td>
<td>20 µg</td>
<td>10 µg</td>
<td>1.5 µg</td>
</tr>
<tr>
<td>Multiple Impurities</td>
<td>120 µg</td>
<td>60 µg</td>
<td>30 µg</td>
<td>5 µg</td>
</tr>
</tbody>
</table>
Filter Integrity Testing – Aim for First Time Every Time
Example of Change of Approach – Review Total Test Time

Optimise Filter Flushing

Pre-use
Air removal from filter
Reference fluid vs. product based FIT
Adequate pressure vs filter permeability

Post-use
Flushing vs. product based FIT

Review Automatic Testing Information

Check tester history
Establish baseline of efficiency
Number of “tests” per filter / location

Trend and track
Look for changes in raw material / process influence

Convert to OEE metric
Total cost of retesting
Automated Filter Integrity Testing
Example of Change of Approach – Reduction in Human Error

Well designed GUI – combining text and graphics
  • Aids correct filter integrity test
  • Speeds operator training

Standard off-the-shelf bar code reader
  • Speeds data entry
  • Decreases operator error
  • Reduces human / documentation driven deviations

Insert data automatically into fields
  – Batch number, Lot number, Serial number
Adaptation to Regulatory Fears
Example of Change of Approach – System Design

Meets EU regulatory and guidance

Meets US guideline
Overall Economics – Product Recovery from Expendables
Example of Change of Approach – Device Design

Filter Housing / Capsule Design

Holdup volume after 400 kPa blow-down

Stacked disk filters
- 500 cm²  4.5
- 1000 cm²  8.3

Pleated capsule products
- 900 cm²  29
- 1800 cm²  44
- 3500 cm²  75

Gas / Liquid Filter Device Design

Consider use when downstream volume is a large yield loss
Overall Economics – Product Recovery from Hardware
Examples of Change of Approach – Special vs Standard Housing

~100 ml
Level inlet vs. standard T-line

~60 ml
Recessed adapter & narrow base vs. wire harness in standard low cost housing

10 -20 ml
Hold-up volume trapped between base and lowest cartridge window

Special may imply cost and delivery impact

Use annual increased yield calculations to select for expensive drug product
Single-use or Multi-use
Examples of Change of Approach – SUS for Final Filling

Desired Outcomes – Reduction in;
• CIP/SIP cleaning.
• WFI water use.
• Filling room space requirements by 75%.
• Filling labour by 60%.
• Risk of sterility breach
• Exposure to operators / environment
• Turnaround time.
• Reporting and documentation.

SUS is not a panacea but can be a very useful tool
1 Sterile medicinal product overview

2 Steps in filtration process
   Some improvements and considerations

3 Cautionary tale

4 Conclusion
Cautionary Tale - “Like for Like” Sterilizing Final Filling Filter Change

Situation
Dual sourcing policy started. Risk assessment - only one supplier for the sterilizing filter for POU final filling process.

Activities
Procurement asks filter suppliers for the “same” filter [12.5cm long, sterilizing grade, same materials of construction (silicone, PES, PP)] operating the same conditions [temperature, flowrate, pressure, pH, compatibility, etc.]. Regulatory confirms this will meet marketing manufacturing authorizations. Quality, technical service, production, engineering, on decision making team

Result
Lower cost vendor chosen. Met all requirements as specified. Within 1 week, filling yield dropped by 2%. Investigation showed alternative filter had more rejects due to lower assays

Cause
Membrane polymer identical, but hydrophilization method (used on all PES membrane) different resulting in higher binding, longer time for saturation

Preventative Actions
Know your process, use SMEs with line knowledge, take a “big picture” approach, break down the organization silos, provide more information to filter vendor

NB – replacement filter uses more product to achieve acceptable concentration
Conclusion & Summary

✓ In formulation and filling systems, innovations and improvements are small but can be extremely tangible

✓ Multidisciplinary groups should be used to build a true picture of filter needs

✓ Filter vendor partnership is very important

✓ Include learnings from annual product review and CAPA resolutions

✓ Total product economics is important

✓ Filtration is a small but can be a significant impact on compliance
Thank You for your Attention!

May we be of Further Assistance?

michael.payne@merckgroup.com