PDA TR #26 Update
Sterilizing Filtration of Liquids
Meeting Validation Requirements

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Presentation Overview

- Scope of the new edition TR#26
- Content overview
- Key revisions
- How to meet TR#26 recommendations
Scope of TR26 New Edition

- Original TR26 is almost 10 years old
  - Key recommendations provided, but some topics not fully addressed and others not covered
- Original TR26 oriented to Pharma final filt’n only
- Biotech applications and new approaches needed
  - Larger filtration systems
  - Process validation in biotech applications
  - Redundant filtration
  - Single use systems

Need for an expanded/updated TR was recognized
TR26 Re-Write Task Force

- Pharma/Biotech filter users
- Filter manufacturers
- Regulatory representatives
- Independent consultants

Important initiative came from the biotech industry
Overview of Changes by Chapter

1.0  Introduction → Small changes

2.0  Pharmaceutical filtration, Historical Highlights
    → Glossary implementation

3.0  How filters work → Small changes

4.0  Filter selection and characterization → New edition

5.0  Filters use, handling and design considerations → New edition

6.0  Sterile filter validation/bacterial retention → Small changes

7.0  Integrity testing → More comprehensive

8.0  Filter sterilization → Small changes

9.0  Single use disposable systems → New section
Chapter 4 - Filter Selection and Characterization

- Expanded listing of characteristics
- Includes validation as part of filter selection and characterization
  - Defines the responsibilities of the filter validation
  - Summary actions table previously in Appendix
### Table 4.4-1 Qual’n and Valid’n Recommendations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Filter User</th>
<th>Filter Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device</td>
<td>Membrane Disc</td>
</tr>
<tr>
<td>Bacteria retention in water, saline lactose broth (SLB) with integrity test correlation in water or solvent</td>
<td>-</td>
<td>Q, L</td>
</tr>
<tr>
<td>Bacteria retention in product</td>
<td>V*</td>
<td>-</td>
</tr>
<tr>
<td>Chemical compatibility, effects on filter integrity</td>
<td>V</td>
<td>Q</td>
</tr>
<tr>
<td>Extractables</td>
<td>V</td>
<td>Q</td>
</tr>
<tr>
<td>Leachables</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Sterilization method, effects on filter integrity</td>
<td>V</td>
<td>Q</td>
</tr>
<tr>
<td>Integrity test (water or solvent)</td>
<td>V</td>
<td>Q, L</td>
</tr>
<tr>
<td>Integrity test method selection (product)</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>Toxicity testing - USP Class VI</td>
<td>-</td>
<td>Q</td>
</tr>
<tr>
<td>USP bacterial endotoxin</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>USP particulate matter</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>USP non fiber release</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>TOC and conductivity- USP Purified Water</td>
<td>E</td>
<td>-</td>
</tr>
</tbody>
</table>

L = Filter manufacturer’s lot release criteria  
V = Process specific validation testing  
E = Evaluate the need for testing  
Q = Filter manufacturer’s qualification  
V* = Can be performed in disc or device format
Chapter 4 – Added Sections

- Revalidation
  - Based on proper change control
  - Based on a risk assessment
  - To be agreed by all relevant stakeholders

- Animal derived materials
  - Filters may contain animal derived products
    - Bovine stearates from tallow in polypropylene resins
    - Stearate/Resin mfrg processes destructive for prions
    - Sourced from certified BSE-free countries
  - Filter manufacturers can provide further info
Chapter 4 – Extractables and Leachables

- Extractables: expanded discussion
  - Filter manufacturer should...
    - be able to provide extractables information (water)
    - provide quantitative information

- Leachables: mainly critical for final fill
  - Process contaminants may not be removed during purification steps = leachables

- Potential sources for extractables/leachables and influencing factors discussed
Chapter 4 – Extractables and Leachables (cont.)

- Methods for extractables discussed
  - Should be performed with the actual used filter style
  - Should mimic the worst case scenario
  - Soak tests are possible approach
  - Model solvent approach is applicable
  - Analysis should be qualitative and quantitative

- Filter should be rinsed before use
  - Water or product
Chapter 5 – Filter Use, Handling and Design Considerations

- More educational
- Shows factors affecting flow rate and throughput
### Table 5.1-1 Factors Affecting Flow Rate

<table>
<thead>
<tr>
<th>Higher Flow Rate</th>
<th>Lower Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High porosity / greater voids</td>
<td>Low porosity / fewer voids</td>
</tr>
<tr>
<td>Larger pore size</td>
<td>Smaller pore size</td>
</tr>
<tr>
<td>Thinner membrane (less hydrodynamic resistance)</td>
<td>Thicker membrane (more hydrodynamic resistance)</td>
</tr>
<tr>
<td>High effective filtration area</td>
<td>Low effective filtration area</td>
</tr>
<tr>
<td>High differential pressure</td>
<td>Low differential pressure</td>
</tr>
<tr>
<td>Straight flow path</td>
<td>Tortuous flow path</td>
</tr>
<tr>
<td>Low viscosity</td>
<td>High viscosity</td>
</tr>
<tr>
<td>High temperature</td>
<td>Low temperature</td>
</tr>
</tbody>
</table>

**Smaller pore size**

**Low porosity / fewer voids**

**High porosity / greater voids**

**Lower Flow Rate**

**High effective filtration area**

**High differential pressure**

**Straight flow path**

**Low viscosity**

**High temperature**

**High Flow Rate**

**Larger pore size**

**Thinner membrane**

**Thicker membrane**

**Tortuous flow path**

**High viscosity**

**Low temperature**

**Low differential pressure**

**Low effective filtration area**
### Table 5.1-2 Factors Affecting Throughput

<table>
<thead>
<tr>
<th>Higher Throughput</th>
<th>Lower Throughput</th>
</tr>
</thead>
<tbody>
<tr>
<td>High porosity / greater voids</td>
<td>Low porosity / fewer voids</td>
</tr>
<tr>
<td>Larger pore size</td>
<td>Smaller pore size</td>
</tr>
<tr>
<td>Low non-specific adsorption</td>
<td>High non-specific adsorption</td>
</tr>
<tr>
<td>Asymmetric pore shape</td>
<td>Isotropic</td>
</tr>
<tr>
<td>High effective filtration area</td>
<td>Low effective filtration area</td>
</tr>
<tr>
<td>Low contaminant load</td>
<td>High contaminant load</td>
</tr>
<tr>
<td>Non-deformable, hard contaminant</td>
<td>Deformable, soft contaminant</td>
</tr>
</tbody>
</table>
Chapter 5 – Filter Use, Handling and Design Considerations

- Scale-up considerations added
  - Filter discs should be used for screening tests
  - Perform full scale (10”) for larger sizing

- Other areas covered include
  - Cartridge, capsule and system design
  - Operating conditions
    - Inlet and differential pressures
    - Process temperature and filtration exposure time
    - Flushing conditions
Chapter 6 – Sterile Filter Validation / Bacterial Retention

- Basic approach remains the same:
  - Bacterial retention in process fluid (where possible)
  - Three different membrane lots should be used
    - One of the three membranes should be “worst case”
    - Physical integrity test value at or near the filter manufacturer's production limit (e.g. min Bubble Pt)

- Challenge organism selection is based on a bioburden analysis
Chapter 6 – Sterile Filter Validation / Bacterial Retention

New to TR26:

- Harmonize with FDA recommendations
- “Worst case” membrane defined as within 10% above minimum specification
- Grouping of product families is applicable
- Re-use of filters is not recommended
- Risk assessment concept is shown
<table>
<thead>
<tr>
<th>Higher Risk</th>
<th>Factor</th>
<th>Lower Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher levels, diminutive organisms</td>
<td>Bioburden</td>
<td>Lower levels, large organisms</td>
</tr>
<tr>
<td>Higher</td>
<td>Differential pressure</td>
<td>Lower</td>
</tr>
<tr>
<td>Higher</td>
<td>Flow rate</td>
<td>Lower</td>
</tr>
<tr>
<td>Growth promoting</td>
<td>Product</td>
<td>Bactericidal or preserved</td>
</tr>
<tr>
<td>Ambient and high</td>
<td>Temperatures</td>
<td>Refrigerated</td>
</tr>
<tr>
<td>Longer</td>
<td>Time</td>
<td>Shorter</td>
</tr>
</tbody>
</table>
Chapter 6 – Sterile Filter Validation / Bacterial Retention

Serial / Redundant Filtration:

- Filters in series can be used...
  - To achieve a sterile filtrate
    - Both filters have to pass the integrity test
  - In a redundant setup for maximum safety
    - Only one filter has to pass the IT-Test
  - The influent bioburden to the final filter should not exceed a max. bioburden level of 10 cfu/100ml
Chapter 7 – Integrity Testing

- Better structured
- Integrity test is key for entire process safety
  - Test alone is not sufficient
  - Continuous control in the filter manufacturing
  - Validation studies necessary
  - Process control is critical (Bioburden Level, etc.)
- New section on test devices
Chapter 7 – Integrity Testing: Test Devices

- Automated devices should be used for
  - Higher sensitivity
  - Minimize operator influence
  - Consistent results / automated record

- Devices should be qualified
  - DQ → At the manufacturer following GAMP guidelines
  - IQ → Instrument specific
  - OQ → Based on risk assessment: cover key functions
  - Calibrate against international standards (pressure, flow)
Chapter 7 – Integrity Testing
When Should a Filter be Tested?

- Recommends pre- and post-use

- Pre-use
  - Pre-sterilization or post-sterilization
  - Regional variations
  - More relevant to economy than process safety

- Post-use
  - Should be done as soon as possible right after use
  - If water-wet test, remaining product should first be removed from the filter (flushing)
  - If product-wet test, parameters should be qualified
Chapter 7 – Integrity Testing
When Should a Filter be Tested?

- **Serial Installations**
  - If a double filtrate setup is chosen –
    - Both filters are needed to reach sterility
    - Both filters have to be tested
  - If a redundant setup is chosen -
    - Single filter for sterility, second filter is back-up only
    - Only one filter has to pass the integrity test
Chapter 7 – Integrity Testing
Integrity Testing of Multiple Filter Installations

- IT > 3 x 10” modules increases risk of false pass
- Bubble Point
  - False pass risk due to masking effect of one marginal IT failure module with several good modules
- Forward/Diffusive Flow
  - False pass risk due to masking effect also possible
- Various test approaches provided by filter mfr’s, e.g. non-linear multipliers for Forward/Diffusive Flow limit
  - All approaches should be scientifically evaluated
Integrity Testing Failure Analysis Decision Tree

- System Parameter Checks
- Integrity Test Parameter Checks
  - Rewet Filter and Repeat IT
    - Pass / Fail
      - Pass
      - Fail
        - Aggressive Filter Wetting (Stage 1)
Integrity Testing Failure Analysis Decision Tree

Record Pass
Filter is Integral

Pass

Pass / Fail
Pass

Filter Wetting with Low ST Fluid (Stage 2)

Fail

Pass / Fail
Pass

Record Failure
Filter Fails the Test
Chapter 8 – Filter Sterilization

- Steam Sterilization
  - Autoclave Sterilization
  - Sterilize-in-Place
- Irradiation Sterilization
- Gas Sterilization

Chapter 9 – Disposable Systems

- Discusses advantages of disposable systems
- A proper URS is basis for a good disposable system evaluation
- Describes possible tests for the system qualification

A new task force on disposables has been formed
Application of User’s Process Information to Sterilizing Filtration Validation following PDA TR26
Validation of Sterilizing Filters

- User-specific studies based on process fluid parameters
- Physical Properties
- Extractables Studies
- Microbial Retention / FF Test Correlation
- Biocompatibility
  - USP <88> Biological Reactivity

Core Validation Data Published in Validation Guides

Drug/Biologics Master File (DMF/BMF) at FDA

Biological Safety baseline studies
Parametric Validation - Aim

- Determine any effect of the fluid on the filter
  - Compatibility testing
  - Product-wet integrity test
- Determine any effect of the fluid on retention of a suitable challenge bacteria
  - Bacterial viability and retention testing
- Determine any effect of the filter on the product
  - Extractables testing
  - Adsorption testing
  - Stability testing
Pall’s Parametric Validation - Strategy

- Product attributes
  - Chemical, Physical, Microbial, etc.
- Process parameters
- Worst-case conditions
- Use of actual products wherever possible
- Scientific rationale
Product and Process Questionnaire

- Overview of user’s fluid & process
  - Used to establish fluid / process-specific test protocols
  - Sections request all information needed to conduct proper validation and report
- Ensures fluid maintained under correct conditions
- Ensures fluid and test parameters are representative of that used by customer
## Considerations for “Worst-Case” Testing

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Composition</th>
<th>pH</th>
<th>Ionic Strength</th>
<th>Viscosity</th>
<th>Osmolarity</th>
<th>Surface Tension</th>
<th>Filter Throughput</th>
<th>Time</th>
<th>Flow Rate</th>
<th>ΔP</th>
<th>Temp</th>
<th>Sterilization Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viability</td>
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</tr>
</tbody>
</table>

- **Pink**: Considered for “worst-case”
- **Light Blue**: Evaluated for information only
Pall Validation Services

- Typical validation study includes:
  - Bacterial viability tests
  - Bacterial retention tests
  - Filter compatibility tests
  - Filter extractables tests
  - Customer fluid-wet Integrity Test values

- Final report provides
  - Test protocols and rationales
  - Summary of test data
  - Results and Conclusions
Pall Global Service and Support Facilities

Multiple facilities with good geographic spread can ensure rapid and effective support.
Validation of Sterilizing Filtration

Filter Validation Guide

Successful Sterilizing Filtration

User Process Validation

GMP and Filter Mfrg Quality

Filter Validation Report