TR40 Sterilizing Filtration of Gases
A comparison with
TR26 Sterilizing Filtration of Liquids

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Sterilizing Filtration of Gases

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- Educational guide to complement TR26
- Committee
  F. Bing (Chair), S. Sundaram (Co-chair)
  B. Bardo, T. Britton, R. Conway, T. Feeser,
  H. Haughney, A. M. Jones, M. Jornitz, S. Langille
  R. Levy, R. Madsen, J. Martin, L. McBurnie
  T. Meltzer, D. Meyer, G. Morris, D. Ridealgh
  H. Schroeder, P. Stinavage, A. M. Trotter
  – 7 manufacturers, 6 users, 4 consultants, 1 FDA
Similarities

• Both technical reports are considered to be educational guides rather than mandatory or implied standards

• Both describe filter retention mechanisms, selection criteria, sterilization methods, validation of retention capabilities and integrity test methods
Differences

• The risk associated with liquid filtration is significantly greater than the risk associated with gas filtration
  – Bioburden potential is higher in liquid
  – Example suggested action levels
    • 100 cfu mL for Purified water (liquid)
    • 100 cfu/M³ for class 8 /100,000 cleanroom
      = 0.0001 cfu/mL (air)
Removal mechanisms

- Gas filters have additional retention mechanisms and will retain smaller particles.

- Size exclusion is used in both liquid and gas.

![Diagram of particle retention by size exclusion](Figure 1: Particle Retention by Size Exclusion)
Smaller particles in gas

- Diffusional interception
- Electrostatic attraction
- Inertial impaction
Most penetrating particle size

Figure 4: Effect of Various Retention Mechanisms of Particles Retained from a Gas Stream as a Function of Particle Size
Hydrophobic membranes

- Do not readily wet with water and so avoid water blockage that can occur with hydrophilic membranes

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Critical surface tension (dynes/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTFE</td>
<td>18</td>
</tr>
<tr>
<td>PVDF</td>
<td>25</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>29.5</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>32</td>
</tr>
</tbody>
</table>
Pore size ratings

• True pore size should not be confused with nominal pore rating given by the manufacturer

• Even less meaning in the ratings of gas than liquid filters

• Gas filters are best described by performance on a challenge test correlated to a filter integrity test

• Liquid rated “sterilizing grade” 0.2 µm are much more efficient in retention in dry gas streams
Filter selection criteria

- Retention capacity
- Integrity testing
- Flow rate & throughput
- Materials of construction
  - Hydrophobicity
  - Durability
  - Toxicity
  - Particle shedding
  - Compatibility
Design considerations

• Minimize water blockage
  – Orient housing to allow condensation to drain
  – Jacket or heat trace housing (3-5°C above process temperature)
  – Open vent valve
  – Coalescing prefilter

• Integrity test
  – Test considerations
  – Wetting
  – Drying (blow down)
Ideal sterile gas filter

- Retains microorganisms even under adverse conditions such as high humidity
- High thermal/mechanical resistance
- Withstand multiple steam cycles
- High gas flow at low $\Delta P$
- Hydrophobic
- Non fiber releasing
- Integrity testable – correlated to removal efficiency
- Easy to install and maintain
- Compatible with application
Most critical applications

• Gas is in contact with sterile final product or critical surfaces of the associated equipment
  – Compressed process gases for asceptic fill operations
  – Vacuum break gases for lyophilizers and critical autoclaves
  – Headspace gases used to flush vials and ampoules
  – Sterile bulk holding tank vents
  – Nitrogen blankets

• Filter should be qualified with a liquid based bacterial challenge test and have a physical integrity test correlated to retention in liquid
Moderately critical applications

• Filtered gas is not in direct contact with exposed sterile product or surfaces
  – Intermediate process steps
  – Air supplied to a fermentation process

• Filters qualified with aerosol based bacterial challenge, correlated to a physical integrity test, are appropriate
Other applications

- Applications that only require a reduction in bioburden have less stringent requirements.

- Because the retention expectation is similar to HEPA filters, dispersed oil aerosol challenges are deemed acceptable to establish the retention capability.
Special cases

• Some applications may have additional or more specific requirements
  – e.g. bacteriophage control or virus retention

• Different articles have been published regarding retention of contaminants bacteria, phages under different conditions

• Applicability of the data to the particular situation needs to be evaluated on a case by case basis
Validation of retention capabilities

• No specific standard that defines the retention requirements of a membrane filter used to sterilize gases

• Several approaches
  – Liquid challenge
  – Aerosol challenge
    • bacteria, spores, virus, dispersed oil

• Retention studies do not need to be repeated by user

• Should evaluate applicability of the retention study to the application
Liquid challenge

- Liquid bacterial challenge represents the worst-case condition since retention in liquids is lower than gases
- ASTM F838 or comparable test on discs, capsule or high area cartridge
  - *Brevundimonas diminuta* ATCC® 19146™
  - 100% of effluent must be analyzed
Aerosol challenges

- Bacterial (spore) aerosol challenges are always less rigorous than liquid challenges even though they do represent the way the filter is challenged in a dry gas process.

- Phage/viral challenges may be the least rigorous because in gas filtration, the smallest particles are not the most difficult to retain.
Aerosol bacterial challenge

- *B. diminuta* - watch conditions for viability
- *Bacillus subtilis* - spores resist drying but are larger than vegetative cells
- Nebulizer generates droplets
- Andersen Sampler can be used to assess droplet size down to 0.65 µm
- Filtered gas is analyzed using liquid impingers
- Control, without filter is run to determine the challenge level
- Lower flow rates may be worst-case scenario
Sample aerosol challenge apparatus

Figure 7: Schematic of Aerosol Challenge Test (Split Stream Approach)
Viral aerosol challenges

- No standards
- Similar apparatus
- Bacteriophage: Phi X-174, PP7, MS2, T1
- Virus sizes = 25 nm to 180 nm
- Andersen Sampler can demonstrate droplets are <650 nm
- MPPS tends to be in 200-300 nm range
- Viral aerosol challenges may be least rigorous microbial challenge
Viral aerosol challenge

- Challenge size may be larger than virus depending on drying and size cannot be precisely established
- Viral spike solution is typically prefiltered to remove aggregates (0.2-0.1 µm)
- Higher flow rates may be worst-case since they diminish diffusional interception
- Impinger fluid is analyzed for the test particle with an infectivity assay
- A presence/absence test can be performed on the remaining fluid
Integrity tests

- Retention challenges should be correlated to an integrity test
- Traditional wetted membrane tests using a low surface tension fluid
  - Bubble Point Test
  - Diffusive/Forward Flow Test
  - Pressure Hold/Decay Test
- Water Intrusion Test (WIT)
- Aerosol Integrity Test
WIT

• Water Intrusion Test does not involve wetting the membrane with solvent

• The upstream side of the filter is flooded with water, pressurized and allowed to stabilize ~10 minutes

• The flow of water vapor through the membrane is measured over time

• Useful test for new filters, filter must be dry prior to testing
Aerosol integrity test

- Historically used for detecting failures in HEPA and ULPA grade filters
- Filter is challenged with $10^7$/cm$^2$ 0.2-0.3 µm aerosol generated from highly refined mineral oil
- A downstream sensor (laser particle counter) detects oil droplets that penetrate the filter
- Can be correlated to aerosol microbial challenge
When to integrity test

• Before sterilization – right filter, correctly installed
• Post sterilization – also detects if the filter was damaged during sterilization
• Post use – confirms filter remained good throughout the critical process
Extended use applications

- Parallel filters, use one while other is being tested and prepared for use
- Redundant filters with periodic testing and change-out
- Combination of periodic testing and change-out
- Test once only, after the first sterilization
- Do not test filters and base change-out on historical data (# sterilization cycles or time on line)
User validation of critical applications

• Generic data correlating retention (bacterial or viral) to the integrity test
• Qualification data for toxicity, durability, compatibility, recommendations for integrity test parameters
• Evaluate retention data applicability to process
  – liquid-rated represents worst case
• Physical integrity test
• Compatibility and service life in use
  – May be demonstrated by integrity testing filter
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Filter user</th>
<th>Filter manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial retention/integrity test relationship data</td>
<td>(E)</td>
<td>(Q)</td>
</tr>
<tr>
<td>Integrity test</td>
<td>-</td>
<td>(Q/R/L)</td>
</tr>
<tr>
<td>Integrity test method &amp; selection</td>
<td>(E)</td>
<td>(R)</td>
</tr>
<tr>
<td>Microbial/viral retention (liquid/aerosol)</td>
<td>(E)</td>
<td>(Q/L)</td>
</tr>
<tr>
<td>Compatibility/ service life</td>
<td>(E/V)</td>
<td>(Q/R)</td>
</tr>
<tr>
<td>Toxicity testing</td>
<td>-</td>
<td>(Q)</td>
</tr>
<tr>
<td>Effects of sterilization method on filter integrity</td>
<td>(E/V)</td>
<td>(Q)</td>
</tr>
</tbody>
</table>