
Title: Bubble Point Test for 0.2 Micron Filters

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1.0 Purpose

This procedure describes the operation for integrity testing of sterilizing membrane (0.2 micron) filters.

2.0 Scope

This procedure is applicable for use in the BOP where it is necessary to ensure that a 0.2 micron filter meets the manufacturer's specifications for sterilization of liquids or gasses. It describes procedures for wetting the filter with WFI, 70% IPA or 100% Ethanol.

3.0 Authority and Responsibility

- 3.1 The Director, Technical Operations, Late Process Science, Biopharmaceutical Development Program (BOP), has the authority to define this procedure.
- 3.2 BOP personnel are responsible for the implementation of this procedure.
- 3.3 Biopharmaceutical Quality Assurance (BQA) is responsible for quality oversight of this procedure.

4.0 Equipment and Materials

- 4.1 Micron Durapore Hydrophilic Filter (e.g., Millipak, Sterivex, etc.).
- 4.2 Micron PTFE Hydrophobic Filter (e.g. Acrodisc CR 25 mm) vent filter



- 4.3 Reinforced tubing capable of withstanding a minimum of 60 psig.
- 4.4 Adapters as required to connect air lines to filter.
- 4.5 Canula.
- 4.6 Air supply with regulator and calibrated gauge.
- 4.7 Cable ties.
- 4.8 Water for Injection (WFI), or other appropriate water source.
- 4.9 100% Ethanol, (ETOH), BDP PN 10106.
- 4.10 70% Isopropyl Alcohol (IPA), BDP PN 30129.

5.0 Procedure

NOTE: The integrity test values in this SOP apply only to 0.2 micron Durapore Membranes from Millipore. For other filters, contact the filter manufacturer for integrity test values.

5.1 Filters Wetted with WFI

5.1.1 Flush the filter with WFI for a minimum of one minute. Increase the flow rate slowly until a steady stream is obtained.

5.1.1.1 It may be necessary to soak the filter in 70% IPA or 100% Ethanol prior to the WFI flush in order to aide in the removal of surfactants, such as Tween 80, etc.

NOTE: It is important to vent any air from the filter housing during this step to ensure complete wetting of the filter element because any dry spots will allow bulk passage of air and give a false, low reading for the bubble point. Sterivex filters are self-venting, so no venting step is needed. Check that the filter housing is full of fluid.

5.1.2 Attach reinforced tubing to the regulated air supply with a calibrated pressure gauge. Secure with a cable tie.

5.1.2.1 Attach the other end of the tubing to the filter inlet. Secure with a cable tie. Attach a second piece of tubing to the filter outlet and place the downstream end into a beaker of water.

5.1.2.2 For Sterivex filters, attach the tubing to the filter using Luer-lock connector.

5.1.3 Slowly pressurize the system to 40 psig. Look for rapid, continuous bubbling at this time. If none, continue to the next step

NOTE: If rapid bubbling occurs at this step, it may be due to insufficient wetting. Flush the filter with WFI for five minutes using a higher flow rate than used in 5.1.1.

5.1.4 Increase the air pressure to 50 psig (0.2 μ Millipore Durapore hydrophilic filter or as per the manufacturer's recommendation) and observe the outlet for bubbles for 30-60 seconds. If no bubbles are observed, continue to increase the pressure slowly while observing for continuous bubbling in the beaker.

NOTE: The Sterivex filter has hydrophobic vents on the upstream side of the filter. When the integrity test is being conducted, air will escape these

vents, but continue to increase pressure until bubbles are observed downstream the filter.

- 5.1.5 When continuous bubbling occurs, record the pressure as the bubble point on the Batch Production Record. The bubble point of the filter must exceed 50 psig (or as per the manufacturer's recommendation).
- 5.2 Filters Wetted with 100% ETOH or 70% IPA.**
- 5.2.1 Flush the filter with WFI water to rinse product from the filter. Increase the flow rate slowly until a steady stream is obtained (Not applicable to air vent filters, proceed to 3.2.2.).
- NOTE:** It is important to vent any air from the filter hosing during this step to ensure complete wetting of the filter element because any dry spots will allow bulk passage of air and give a false, low reading for the bubble point. Sterivex filters are self-venting, so no venting step is needed. Check that the filter housing is full of fluid
- 5.2.2 Flush the filter with 500 mL 100% Ethanol or 70% IPA, increasing the flow rate slowly until a steady stream is obtained. Volume required will vary depending on the surface area of the filter.
- 5.2.3 Attach reinforced tubing to the regulated air supply with a calibrated pressure gauge. Secure with a clamp tie.
- 5.2.3.1 Attach the other end of the tubing to the filter inlet. Secure with a clamp tie. Attach a second piece of tubing to the filter outlet and place the downstream end into a beaker of water.
- 5.2.3.2 For Sterivex filters, attach to the filter using a Luer-lock connector.
- 5.2.4 Slowly pressurize the system to 10 psig. Look for rapid, continuous bubbling at this time. If none, continue to the next step.
- NOTE:** If rapid bubbling occurs at this step, it may be due to insufficient wetting. Flush the filter again with 100% Ethanol or 70% IPA for five minutes using a higher flow rate.
- 5.2.5 Increase the pressure to 18.5 psig for a 70% IPA wetted 0.2 μ Millipore hydrophilic filter (or as per the manufacturer's recommendation) and observe the outlet for bubbles for 30-60 seconds. If no bubbles are observed, continue to increase the pressure slowly while observing for continuous bubbling in the beaker.
- NOTE:** If the filter has been used for a virus product, stop the integrity when minimum bubble point is attained.
- The Sterivex filter has hydrophobic vents on the upstream side of the filter. When the integrity test is being conducted, air will escape these vents, but continue to increase pressure until bubbles are observed downstream the filter.
- 5.2.6 When continuous bubbling occurs, record the pressure as the bubble point on the BPR. The bubble point of the filter must exceed 18 psig for 100% Ethanol wetted filter or 18.5 psig for 70% IPA (or as per the manufacturer's recommendation).

5.3 Hydrophobic Filter

- 5.3.1 Flush the filter with 70% IPA, increasing the flow rate slowly until a steady stream is obtained. Volume required will vary depending on the surface area of the filter.
- 5.3.2 Attach reinforced tubing to the regulated air supply with the calibrated pressure gauge. Secure with a clamp tie.
- 5.3.2.1 Attach the other end of the tubing to the filter inlet. Secure with a clamp tie. Attach a second piece of tubing to the filter outlet and place the downstream end into a beaker of water.
- 5.3.2.2 For Acrodisc with PTFE membrane, attach to the filter using a Luer-lock connector.
- 5.3.3 Slowly pressurize the system to 10 psig. Look for rapid, continuous bubbling at this time. If none, continue to the next step.
- NOTE:** If rapid bubbling occurs at this step, it may be due to insufficient wetting. Flush the filter again for five minutes using a higher flow rate
- 5.3.4 Increase the pressure to 13.0 psig for a 70% IPA wetted 0.2 μ Pall hydrophobic filter (or as per the manufacturer's recommendation) and observe the outlet for bubbles for 30-60 seconds. If no bubbles are observed, continue to increase the pressure slowly while observing for continuous bubbling in the beaker.
- NOTE:** If the filter has been used for a virus product, stop the integrity when minimum bubble point is attained
- 5.3.5 When continuous bubbling occurs, record the pressure as the bubble point on the BPR. The bubble point of the filter must exceed 13.0 psig for 70% IPA (or as per the manufacturer's recommendation).