

Filter Integrity Testing Troubleshooting Guidelines



Application
Note

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Background:

Integrity Testing is a *non-destructive* physical test to determine the presence of oversized pores or other defects that may compromise a given filter's retention capability. Performing filter integrity tests is a requirement by Regulatory Agencies (FDA, EU) when a product is labeled 'sterile'.

During the integrity test, whether manually or using an integrity test instrument like the Sartocheck 4 Plus, potential false filter integrity test failures can occur. This guide should be used as a reference to troubleshoot the integrity of the filter.

The Parenteral Drug Association (PDA), Journal of Pharmaceutical Science and Technology - Technical Report No. 26 (Sterilizing Filtration of Liquids) specifically addresses steps to take in troubleshooting filter integrity test failures.

PDA TR 26: Section 7.7 states:
Following these recommendation details a 3 strike rule. If the filter fails, repeat by re-wetting with the same wetting agent, checking all connections, program type, etc. If the 2nd test fails, wet the filter with a lower surface tension reference fluid to assess the filters wettability. If the filter fails this 3rd test, the filter fails the test. If this case happens, industry recommends contacting the filter manufacturer for further assistance in resolving the integrity failure.

Troubleshooting Points to review for each filter issue:

1. First Check - Incomplete assembly, incomplete wetting of the filter.
2. Always use reinforced tubing that can withstand high pressure (~90-100psi).
3. Have a written documented filter failure investigation and retest procedure documented.
4. Next step
 - a. Ensure the correct program number was selected for the filter tested
 - b. Check filter manufacturer's filter test parameters for actual values
 - c. Confirm which wetting fluid is being used; Water, Product, other solvent
 - i. Always use the manufacturer's recommended wetting procedure.
Example:
Rinse the filters in the direction of flow for 5minutes with a differential pressure of 4psid in order to assure that the filters have been wetted completely. The higher the differential pressure, the better the wetting of the filter polymer. Generally, hydrophilic filters are wetted with water.
 - d. Leaks (in vents, tubing). See Leak Testing recommendation step.
 - e. temperature (room temperature medium),
 - ii. high temperature increases solubility coefficient (higher diffusion) and decreases surface tension (lower BP) causing false failures
 - f. calibration (review calibration sticker),
 - g. test setup (follow manufacturer's recommendation)
5. If the integrity test failed with a value just above the test limit (diffusion test/ Intrusion test); re-wet filter (see Point 8); check connections and confirm water temperature is room temperature. Repeat test.
6. Minimize the time span between filter use and filter integrity tests to minimize the risk of drying product (residue) on the filter membrane. If filters are not tested right away, ensure the inlet and outlets are capped until testing time.

7. Ensure that the filter is adequately flushed in accordance with the *Manufacturers Directions for Use* to minimize the amount of residual product remaining in the filter.
 - a. If residual product is a concern; determine Product Wet Specific Integrity Test value.
8. Following a water integrity test failure, increase the differential pressure (*20-30psid*) and or flush time (*5-10minutes*) to minimize the amount of residual product remaining in the filter.
9. If water bubble point integrity tests continue to fail, perform an integrity testing using Isopropyl Alcohol (IPA)/RO Water.
 - a. 60% IPA minimum bubble point with a **Sartobran P** 0.2µm filter is 17 psi.
 - b. 70% IPA minimum bubble point with a **Sartobran P** 0.2µm filter is 16 psi.
 - c. 60% IPA minimum bubble point with a **Sartopore 2** 0.2µm filter is 19 psi.
 - d. 70% IPA minimum bubble point with a **Sartopore 2** 0.2µm filter is 17 psi.
10. Integrity tests with IPA alleviate most false integrity test failures; however, false failures can still occur and may require cleaning of residual product from the membrane. Contact filter manufacturer for further options.

Repeating an integrity test on a filter that has not been flushed prior to the integrity test is not recommended. It has the potential of drying the filter on repeated tries by an operator.

Leak Testing:

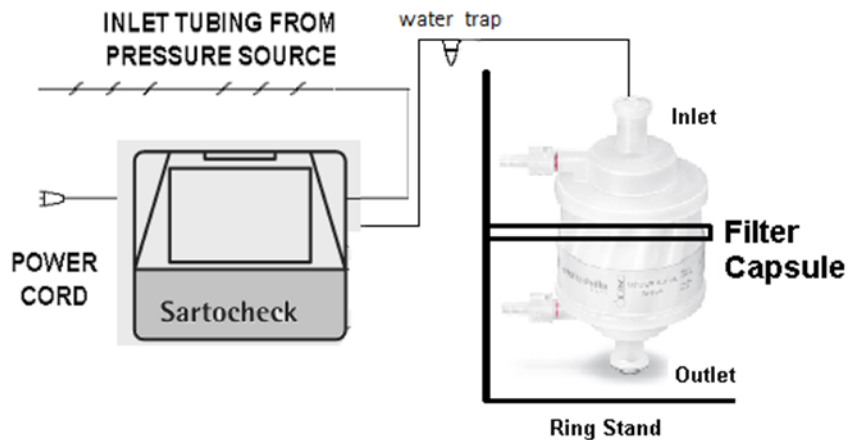
Integrity Test Instrument – check connections for potential leaks. Use a cap on the end of the Outlet tubing set and run the following program. Perform a Leak test using the following parameters:

Pressure Drop Test	
Test Pressure	45psi
Stabilization Time:	3 minutes
Test Time:.....	5 minutes
Limit:	0.05psi

If the test result is greater than 0.05psi, check for leaks in the fittings by placing the Outlet tubing set (with cap on end) in a bucket of water and repeat test. Look for bubbles and tighten fitting.

Recommended Integrity Filter Test Set-up:

The Sartocheck Outlet Tubing set to a test filter capsule (or housing) should be orientated so that the Water trap filter assembly is higher than the test filter (see diagram). This orientation prevents fluid going back into the unit.

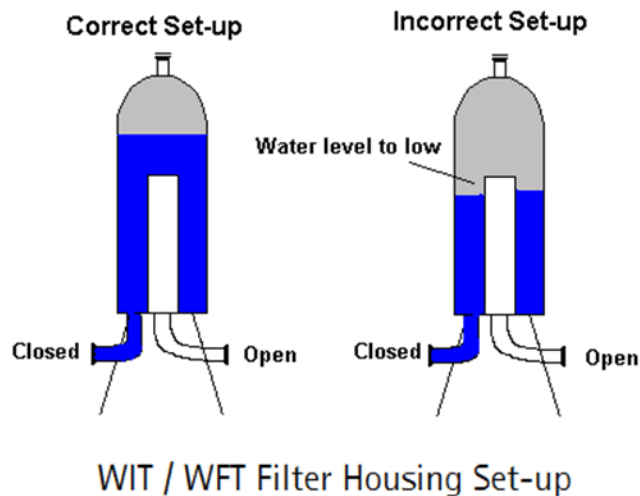


Filter Integrity Test Set-up

If an operator / technician observes liquid coming out of the vent port on the right side of the Sartocheck following any integrity test; Sartorius recommends the Sartocheck be cleaned as soon as possible. Contact the Service Center at 1.866.208.3484, ext. 7247.

Vent Filters

If performing an Intrusion Test (WIT/WFT), ensure filter has sufficient room temperature water above the cartridge. During pressurization, the water is pushed into the pleats and the level decreases from the initial start point.



Blow down of a Vent filter

If a vent filter fails the Water Intrusion Test (WIT) after long-term use, it may be attributed to the filter membrane being wetted out (saturated with water) from the condensation that's occurred over the usage period. Even though the filter has passed the Pre-Use WIT, the initial post-use WIT value exceeds the manufacturer's test limit.

Sartorius' recommendation for vent filters that exceed the WIT test limit is to blow down the filter prior to repeat testing:

Forward Air Direction (Upstream side → Downstream side)

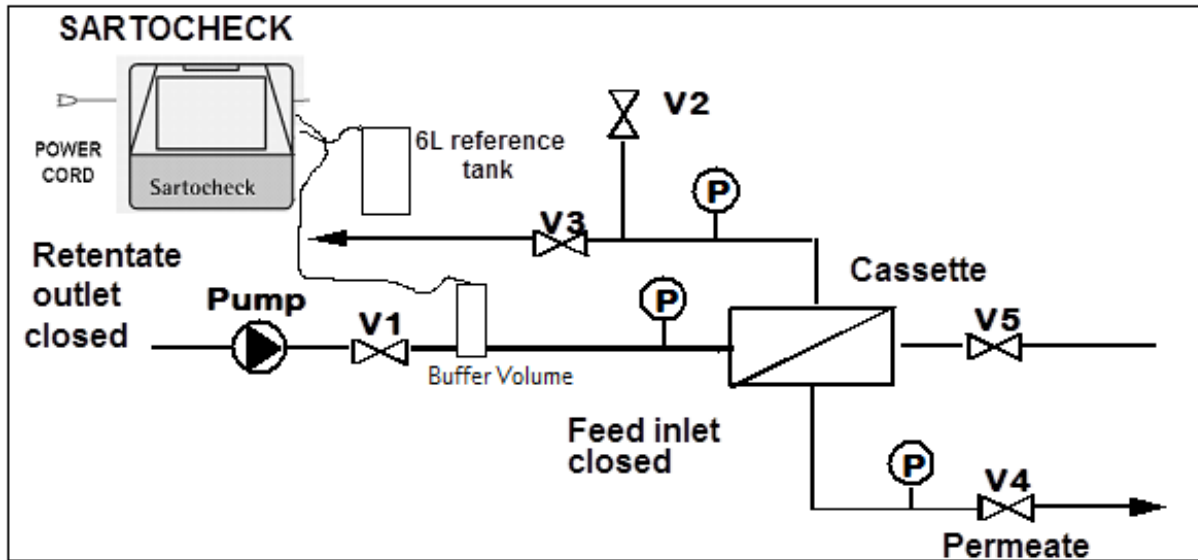
Using a pressure regulator, provide a dry air source (Nitrogen (N₂) or Compressed Air (CA)) @ ~15-20psi to the Inlet (top) of the filter housing for 25-30minutes. Slightly open the base vent drain on the housing (if applicable). This step allows excess moisture within the housing/membrane to be dispersed out the base of the housing during the blow down period. Repeat the WIT test.

Reverse Air Direction (Inner Core → Outer Core)

Using a pressure regulator, provide a dry air source (N₂ or CA) @ ~15-20psi to downstream side (Outlet) of the filter housing for 25-30 minutes. Slightly open the base vent drain on the housing. This step allows excess moisture within the housing/membrane to be dispersed out the base of the housing during blow down. Repeat the WIT.

Note: During the WIT, ensure the filter is immersed in water by adding a *spool piece* to the top of the filter housing. During the pressure increase step, the air pressure forces the water level to decrease in the test housing. The spool piece allows extra volume of water so the amount of decrease is not lower than the cartridge height.

Integrity Testing Crossflow Cassettes



1. Install the cassettes at 60 or 80Nm torque (use manufacturer's recommendation).
2. Wet the filter cassettes with water at 20-22°C with valve 2 and 3 closed. The wetting fluid will exit through valve 4 and 5 to drain. You can install several filter cassettes (be aware of that low diffusion cassettes can mask high diffusion cassettes). The cassette holding device and Sartocheck should be at the above-mentioned temperature.
2. Keep Valve 2 & 3 on the Sartocheck test holding device closed during the integrity test. Afterwards, close the isolating valves. In addition, water is forced through the permeate outlet during the stabilization phase of Sartocheck (make sure you have you low pint drain on the permeate side open to drain the liquid).
3. If you are testing more than 10 cassettes at a time with an upstream volume less than 4L you have to use a reference tank connected to the Sartocheck unit and a buffer tank of approx. 20L. If just a few cassettes, you can by-pass the buffer tank.
4. Test Program

<u>Diffusion Test</u>	
Test Pressure	15psi
Stabilization Time:	3 minutes
Test Time:	5 minutes
Maximum air diffusion:	Check manufacturer's recommendation for specific cassette

5. Once the self-test has been run, the integrity measurement will automatically start. Following a successful measurement, the Sartocheck automatically generates a printout.

Definitions:

1. **Bubble Point Test** - the pressure at which a given liquid in the wetted pores of a membrane is forcibly removed. The removal of the liquid allows free flow of air through the membrane.
2. **Diffusion Test** is the flow of compressed gas (e.g. air or nitrogen) per time through the wetting liquid within the pore system of a membrane at a defined test pressure (70–80 % of Bubble Point)
3. **Diffusion & Bubble Point Test** – Combination of Diffusion and Bubble Point test.
4. **Intrusion Test** is an in-situ integrity test for hydrophobic filters. The WIT measures the decay rate of a pressure level imposed upon a hydrophobic membrane enveloped in water. Two Options:
 - a. **Water Intrusion Test – performed on Sartorius filters**
 - i. The WIT test option reports test results as a downstream flow measurement.
 - a. **Water Flow Test – performed on non-Sartorius filters**
 - i. The WF test option measures flow on the *upstream side* with the values expressed in terms of water flow measurement.
5. **Pressure Drop Test** is the pressure decay on the upstream side of a membrane filter system on the basis of diffusion of gas molecules out of the constant volume of the upstream side

Reference:

1. PDA Technical Report No. 26 – (Rev 2008), Volume 62 – No. S-5 2008
2. FDA – Aseptic Guideline (page 33)
3. EC Guide to GMP, Revision to Annex 1, Feb 2008 (Annex 1 – Number 113)
4. Filtration in the Biopharmaceutical Industry (Theodore H. Meltzer, Maik W. Jornitz)



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