Trouble Shooting Guide – Integrity Testing of Hydrophilic Filters

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1. Introduction

1.1. Scope

This technical troubleshooting document is applicable for Sartorius filters Sartopore® 2, Sartopore® Platinum, Sartobran® P, Sartolon® filter elements. which all employ sterilizing-grade (0.2 or 0.1 µm) hydrophilic membranes for the filtration of liquids. Furthermore, some bioburden reduction filters such as Sartoguard PES and Sartoguard GF, Sartopore® 2 0.8/0.45 µm and Sartobran® P 0.65/0.45 µm are also part of the scope, because they can be tested for integrity.

1.2. Purpose of this document

This document is designed for trouble shooting after a filter integrity test has failed. The procedures described herein can be used for writing and improving SOPs for filter integrity tests. The document can also be used for training purposes.

1.3. Types of filter integrity tests

For hydrophilic membrane filters, two different integrity test methods are typically used to ensure filter integrity:

- Diffusion Test
- Bubble Point Test (BP)

The two integrity test methods are based on different physical phenomena. The BP is dependent on the surface tension of the test solution and the surface properties of the membrane: During the measurement the capillary force of the liquid with the filled pores of the membrane is determined, by increasing the test pressure until the largest pores are blown free.
The Diffusion is more based on the viscosity of the test solution, the solubility of the test gas and the thickness and openness of the pores of the membrane. This test method depends also on the filtration area, whereas BP does not.
The diffusion test offers usually a higher sensitivity compared to the bubble point test.

From the regulatory view both test methods can be used. There is up to now no regulatory need to perform both integrity test methods.

2. General trouble shooting

Both Diffusion and Bubble Point testing can be negatively influenced by a variety of parameters. The following addresses the common failure modes and how they can be troubleshot.

2.1. Leak-tightness of the test system

Filter integrity tests are developed to confirm the integrity of membrane filters. However, if there is air leakage somewhere within the system, the integrity test might fail, even though the filter membrane is integral. Essentially, leakage can manifest itself as an inordinately high rate of diffusional flow, because the filter integrity tester is not capable of differentiating between air leakages upstream of the membrane and air flow through the membrane itself. The following items should be checked to identify possible leakage:

- damaged seal(s) or gasket(s) within the filter, housing, and all connections
- open valve(s) that should be completely closed during integrity testing
- leak-tightness of the tubing that connects the filter integrity tester to the filter being tested
- vent valves on filter of filter housing

✓ Check the complete inlet side of the filtration system for leakages.
Additionally, inspect the tubing from the filter integrity tester to the filter housing.

Perform a pressure drop test on the Sartocheck® Filter Tester's inner pneumatics, tubing(s) and valves:
Connect the Sartocheck® outlet to the test tube. Create the following program using the following parameters (example: Sartocheck® 5 and 5 Plus Filter Tester):

- Diffusion test
- Number of samples: 1
- Advanced: no
- Volume determination: Measure
- Test pressure: acc. to the max. pressure resistance of piece to be tested, max. 6 bar
- Max. diffusion/sample: 0.5 mL/min.
- Stabilization time: 10 min. / Measurement time: 3 min.

Run the Sartocheck® program e.g. on the test tubing, housing with blind plug etc. Then try to close any identified leak.

2.2. Wrong test program or wrong filter

The test parameters must be entered correctly in the filter test program. In addition, the correct filter test program must be selected for the specific filter being tested.

Check if the correct filter test program was used?
Check if the correct filter was mounted for filtration?
Confirm if proper test parameters were used for the filter being tested.

Preventive: Use Sartocheck's® barcode scanner for confirmation of the correct filter and for selection of the corresponding filter test program. For product or filter-specific testing, a unique custom barcode can be created and linked to a specific filter test program.

2.3. Temperature influence

Typically, the integrity test limits are only valid within the range of 20 to 25°C. As all test methods and subsequent measurements are derived from pressure decay and pressure is directly influenced by temperature, the temperature of the filter system, the wetting fluids and the test gas itself must remain consistent throughout the test. Temperature shifts while performing an integrity test can have a major impact on the integrity test result. The recommendation is to keep the temperature of all contributing factors within the range of 22 ± 2°C.

Check if the ambient temperature is between 20 to 25°C?
Check if temperatures are ambient for the

- filtration system
- wetting liquid
- test gas

Check if there are other temperature sources which have an influence on the test:

- steam pipes
- direct sun light
- air conditioning systems

Keep the temperature during a re-test as stable as possible, the target is to limit the deviation within ± 2°C for Diffusion and Bubble Point testing for all components involved in the integrity test.

2.4. Membrane test solutions (wetting liquids)

For hydrophilic filters the standard wetting media is purified water (usually WFI or RO water). In case of integrity test failures caused by product residues or other contaminant on the membrane, a test solution with a lower surface tension can be used. Therefore, Sartorius provides for most filters integrity test limits for IPA/water 60/40 Vol %.

Other solutions (buffers, product solution containing the API) can be used for routine integrity testing, if properly validated. This is advisable if product residues are difficult to be flushed out with water (e.g. Polysorbate solutions, oily preparations) or if the product loss should be minimized by not using water for flushing for a pre-use integrity test.

Check specification of the wetting solution (water).
Check the specification of the test solution, if not water is used (e.g. IPA 60:40 Vol.%).

If IPA/water mixtures are used, exchange the test solution in appropriate intervals. Solvents can remove product residues from membrane filters and be contaminated after use.

Re-wet the filter, esp. if there has been too much elapsed time between the initial wetting and the test itself, depending of the volatility of the solvent used.

2.5. Proper wetting of the membrane

According to the filter manuals the standard procedure for filter wetting is flush the filter for 5 min @0.3 bar differential pressure. In certain filter set-ups it is difficult to reach these conditions:

- In single-use set-ups, if the amount of flushing solution very often is limited by the size of the waste bag
- Esp. for bigger filters if small connectors or tubes are used. As a result, the targeted differential pressure over the membrane cannot be applied

For such cases an enforced wetting procedure is advantageous:

- By toggling a valve or pinch clamp, which is on the downstream side of the filter, the wetting can be improved. The pulses can remove entrapped air from the membranes
- Pressurizing the filter with a closed valve or pinch clamp on the downstream side of the filter has a positive effect on the filter wetting. Small air bubbles can dissolve in the wetting solution and additional flushing then remove these.

For both operations the maximum allowable pressure of the filtration system must be regarded, esp. for single-use filter transfer sets.

Check flow rate / differential pressure for the filter wetting step.

- Apply, if possible, 5 min. @0.3 bar in order to wet out the filter.
- Increase the flushing volumes.
- Increase the differential pressure over the membrane by increasing the flow rate.
- Esp. for low flush volumes apply enforced wetting procedure.

2.6. Dry steaming/autoclaving of membrane filters

All hydrophilic filters except for Sartopore® Platinum should be wetted with some water prior to autoclaving/SIP. After a dry sterilization cycle the surface properties of the membranes may change and wetting gets much more difficult. Additionally, the dry steam lowers the total lifetime of some filters (Sartobran® P).

Extended drying cycles using >80°C on the filter also decreases the ability for easy wetting for the respective filter materials.

Dry steaming is needed, if in-line steaming is performed in the reverse direction. Only Sartopore® Platinum should be used in such systems. Generally, it is not recommended to steam filters in the reverse filtration direction.

If filters are prepared for autoclaving, it is sufficient to fill ones the housing completely with water, at best from the downstream side. After some seconds the membranes are soaked with water and the overrun can just be spilled off.

Check if the failed filter have been autoclaved or in-line steamed with a complete wet membrane.

If the filter was autoclaved or in-line steamed dryly, IPA/water should be used for final release testing.

If the process requires a dry membrane prior to autoclaving/SIP, Sartopore® Platinum should be used.

2.7. Product residues on filter membrane

After filtration in certain processes some ingredients or impurities from the pharmaceutical solution, can be found on the filter membrane. Sometimes it is hard to rinse these substances, in particular if detergents (e.g. Polysorbate) or even different proteins are adsorbed to the membrane.

If product residues cannot be removed by flushing with water and integrity tests fail on a constant basis, the use of product specific integrity test limits is highly recommended.

Check if critical components are in the product solution, which cause false failed integrity test results on a constant basis and consider the determination of product specific IT parameters.

1. Flush with increased volume of water
2. If applicable flush with IPA for cleaning the membrane prior to integrity testing. If IPA is not effective, use of a suitable compatible cleaning solution (e.g. to remove proteins using 0.1 m NaOH from Sartopore® filters).
3. Autoclave or SIP (cartridges only) the filter for removing product residues prior to integrity testing. Be aware this procedure causes thermal stress on the filter element.

2.8. Volume measurement

Sartocheck® filter integrity testers use the measurement of pressure decay in conjunction with the net upstream volume to derive flow rate. The net volume can either be determined automatically or entered manually; however, it is imperative that the automatic volume measurement or manual volume entry be accurate, as any inaccuracy in the volume will manifest itself as an inaccuracy in the measured diffusion rate. This also has got an impact on the bubble point test, because it is also based on pressure drop measurements.

If automated volume measurement is activated, check if the value for the determined volume is 'typical' by comparing with earlier measurements.

If the net-volume was put in manually, check the input value and if there have been any changes to the filtration system since qualification of the net volume.

If the net-volume was put in manually, measure the net volume again by using a Sartocheck®. For net volumes above 14 Litres the external reference tank must be connected.

If the safety parameters are activated the measurement of the net volume can used for identification of faulty integrity test setups. This is available only for Sartocheck® 5 Plus and Sartocheck® 4 Plus Filter Testers.

2.9. Choice of the test gas

For Bubble Point testing, the test value is independent from the test gas used, as the test gas is used only to determine the pressure at which the largest pores are evacuated.
However, different test gases can have an influence on the Diffusion test value due to the solubility and diffusivity of those gasses in conjunction with the wetting solution. Example: If Nitrogen is used instead of compressed air for water-based test solutions, the test result will be reduced by a factor of 0.82.
The factor of 0.82 is limited to water-based solutions.

To exclude the influence of a false measurement due to the test gas, check if the correct test gas was used for the Diffusion test.

Repeat the Diffusion test using the specified test gas. The standard test gas is compressed air.

2.10. Filter integrity test device

Filter integrity test instruments from manufacturers other than Sartorius can be used for the Diffusion test (Forward Flow) and Bubble Point test.

Sartocheck® 5 and Sartocheck® 5 Plus Filter Testers measure the integrity of filters by using pressure decay as the core measurement method that relies upon high-precision pressure transducers. Those pressure transducers must remain within a tight tolerance to yield accurate measurements. Out-of-tolerance excursions can result in inaccurate measurements, so annual calibration (and possible adjustment) of the pressure transducers using NIST-traceable reference pressure gauges is recommended.

To exclude the influence of an out of tolerance integrity tester, check the calibration. interval of the used test device.

Check if the pressure sensor works properly.

If available, use a different filter test device.

In the unlikely event of a pressure reading offset, during the annual calibration of the Sartocheck®, the Sartorius Service team can help you to calculate the impact on measured values.

3. Diffusion Test

3.1. Parameter settings

Hydrophilic filters can be Diffusion tested after wetting the membrane with purified water. Other wetting agents are possible, such as different buffer solutions or directly the product solution. Product specific test parameter must be validated.

Check if the filter membrane was wetted completely.
Check if the validated wetting solution was used.
Make sure that the filter housing or capsule was vented before flushing the filter.

Repeat filter flush prior to another filter test.

The temperature range during a Diffusion test must be kept stable (± 2°C) at ambient temperature (20 – 25°C).

The Diffusion test requires as input parameters a stabilization time, test time and a maximum Diffusion test limit.
The stabilization time depends on the size of the test filter. For filters of the size 9 or smaller, a minimum stabilization time of 3 minutes is recommended, and for a single 5" to 30" filter, increase that time to 5 minutes. For testing of multi-round filter setups, please contact the Sartorius Tech Support team.

For the test time of single filters, 3 minutes are sufficient. Invoking the Auto Test Time feature can truncate that test time considerably if the measured diffusion value is below the maximum limit and the measured value is stable (not erratic or trending upward toward eventual failure). The IPA/water-based Diffusion test limits can be found in the respective filter validation guides.

If the pressure drop for a passing filter consistently is higher than 100 mbar, it is recommended to use a spool piece and increase the net volume of the filter integrity test.

4. Bubble-Point Test

4.1. Parameter settings

Hydrophilic filters can be Bubble Point tested after wetting the membrane with purified water. Other wetting agents are possible, such as different buffer solutions or directly the product solution. Product specific test parameter must be validated.

Check if the filter membrane was wetted completely.
Check if the validated wetting solution was used.
Make sure that the filter housing or capsule was vented before flushing the filter.

Repeat filter flush prior to another filter test.

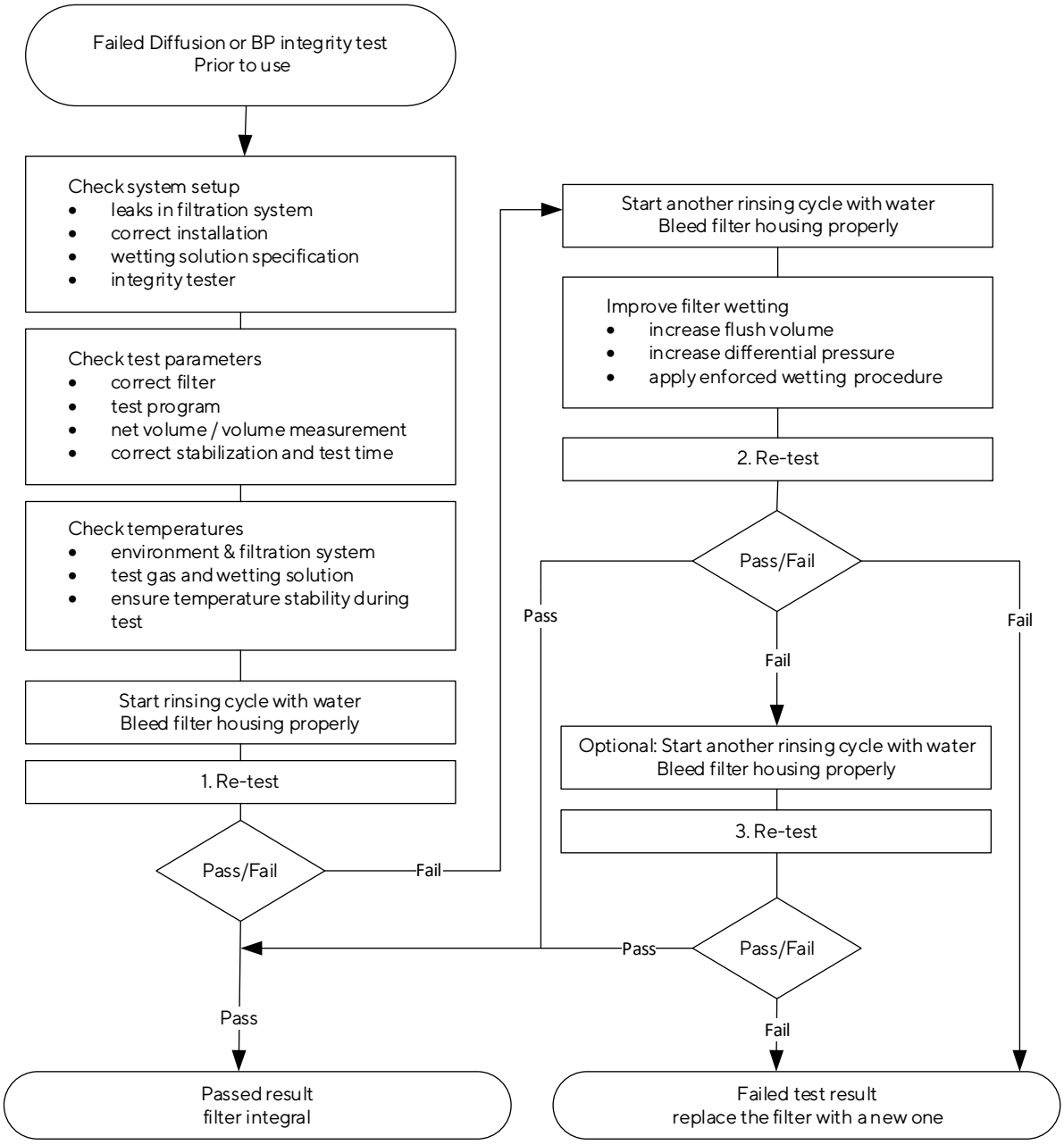
The temperature range during a Bubble Point test must be kept stable (± 2°C) at ambient temperature (20 – 25°C).

Sartocheck® 5 and Sartocheck® 5 Plus Filter Testers require for the Bubble Point test the Diffusion test limits and the input of a minimum Bubble Point. For the Sartocheck® 5 series, a maximum diffusion limit must be entered to ensure the optimal Bubble Point parameters are applied to the Bubble Point algorithm for the size filter being tested. This is synonymous with Test Class on the previous Sartocheck® models. Below is a table that relates max diffusion to test class for the different size filters.

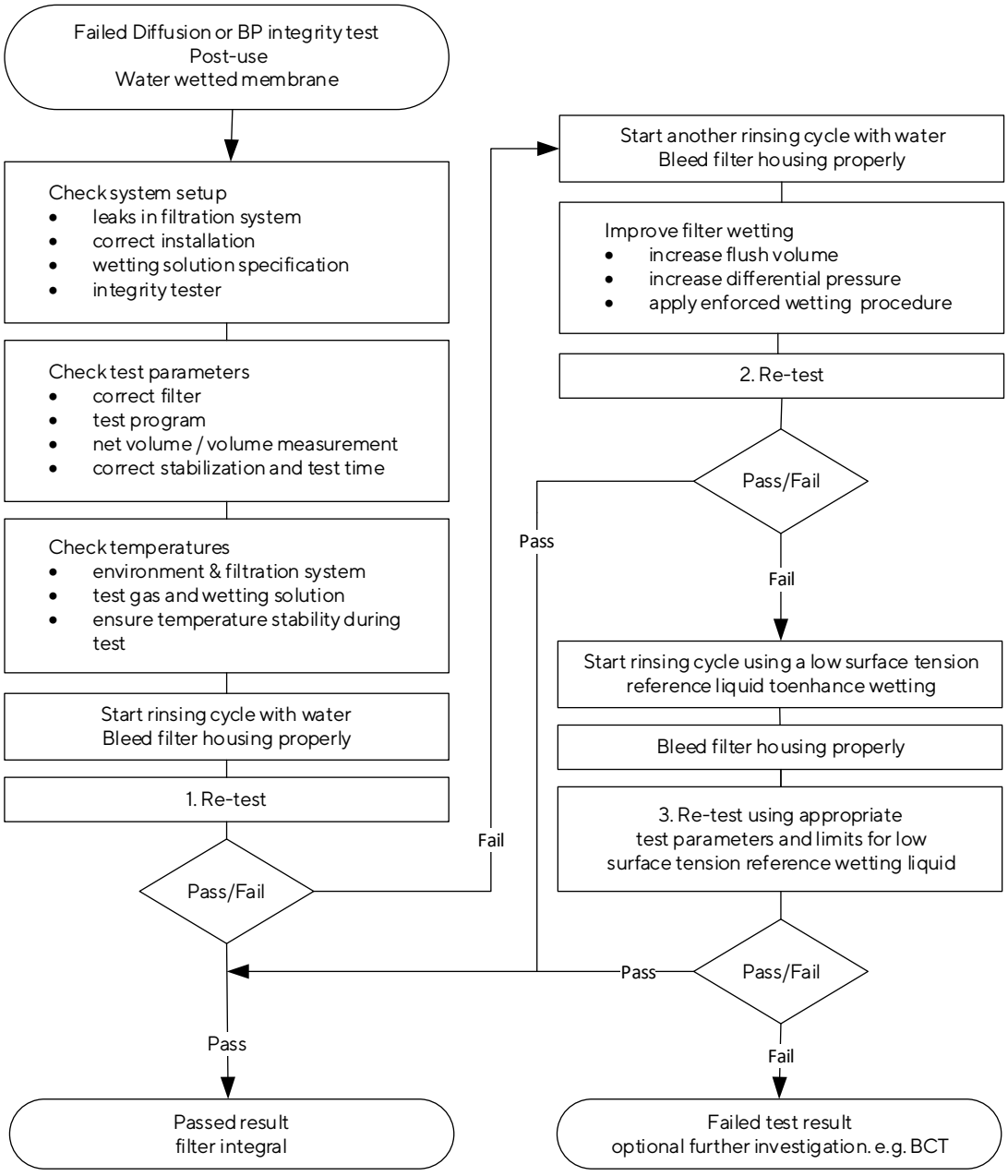
Max. Diffusion (SC5/5+)	Test Class (SC4/4+)	Over-proportionality Criterion (A1)	Bulk Flow Criterion (A2)
< 9 mL/min	Small	5	50 mL/min
> 9 and < 50 mL/min	Standard	15	150 mL/min
> 50 mL/min	Special systems (large)	30	240 mL/min

In some cases, the Sartocheck® integrity tester is not able to identify an over-proportional increase of the flow in the course of a bubble point test. Reasons can be certain membrane structures as well as influence of some wetting solution or product residues. If the Bubble Point is clearly passed, the value for the Over-proportional Criterion (A1) should be chosen smaller.

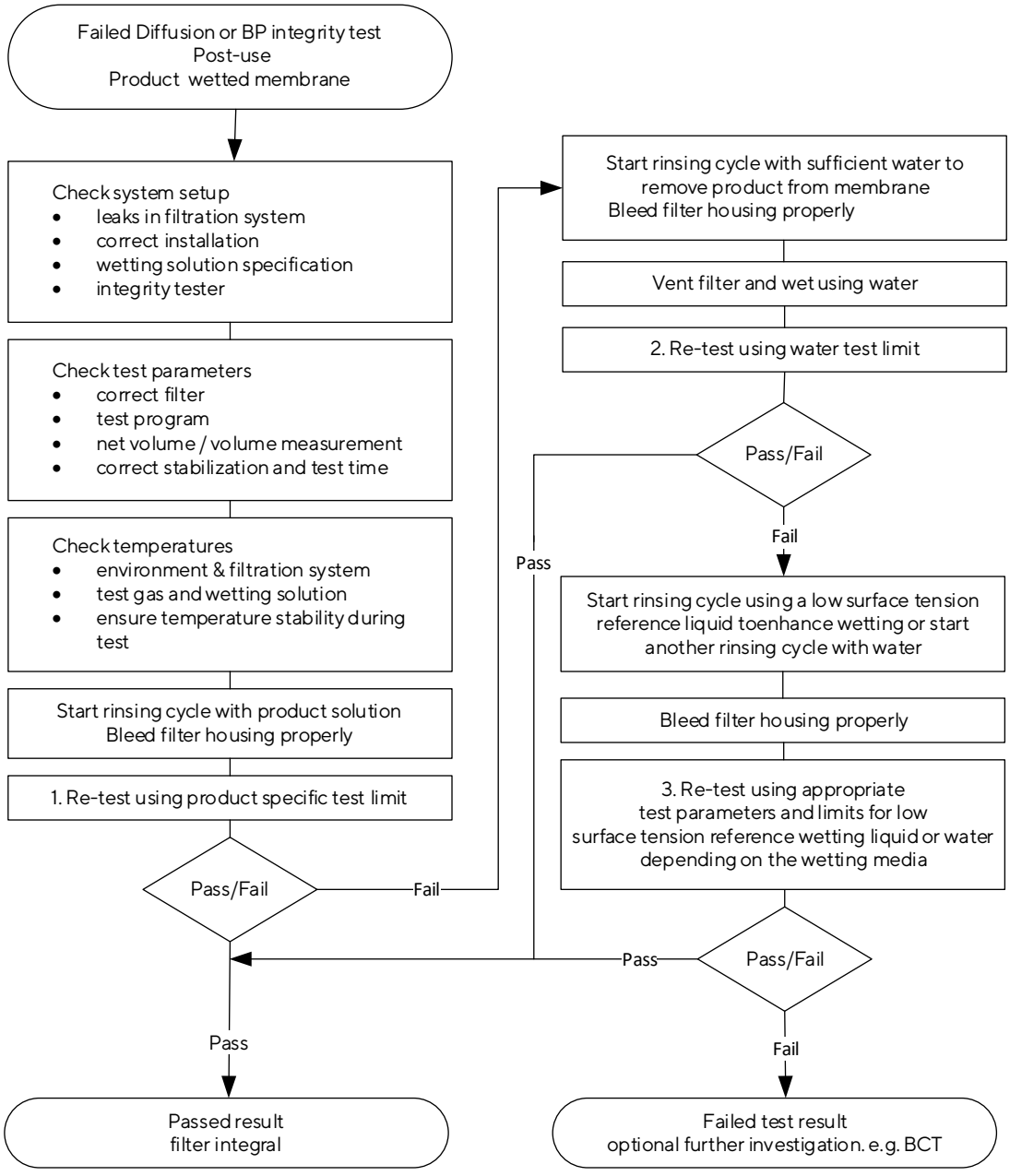
5. Flowchart for IT of a new filter pre-use



6. Flowchart for water wetted IT of a filter post-use



7. Flowchart for product wetted IT of a filter post-use



8. Avoiding false passed ITs

False passed test results in any case must be avoided. The following root causes are potentially possible:

a. A pressure drop caused by a truly non-integral filter element potentially can be masked by a temperature increase that expands the test gas during the test phase.

Don't perform integrity tests if the system or the test solution is lower than the environmental temperature (e.g. bring a filter from a cooled room to ambient temperature).

- let the system equilibrate before starting the integrity test
- choose a longer stabilization time
- integrity tests below 20°C must be validated

b. The downstream valve of a tested filter must be open during the entire test; otherwise, pressure could begin to build, reducing the differential pressure across the membrane, ultimately reducing the flow rate. If the downstream volume is big enough not to have any impact on the test result (e.g. a large volume storage tank), the downstream side valve of the tank can be closed.

Make sure that the downstream side of the tested filter is open.

- use the safety parameters of the Sartocheck® 5 Plus. A low diffusion rate and/or a wrong volume measurement can point to a closed valve

c. If a wrong test program is used, e.g. for a larger filter, the test can be prone to a false passed test result.

Make sure that the correct program is run.

- use barcode scanner for selection of the correct test program

d. Wrong parameter setting can also lead to a false pass test result.

Make sure that the test parameters are correct.

- use barcode scanner for selection of the correct test program with correct settings

e. Different test gases will have an influence on the Diffusion test value due to solubility and diffusivity. Always ensure the pass/fail diffusion limits are correct for the test gas being used.

To exclude the influence of a false measurement due to the test gas.

- check if the correct test gas was used

f. If multi-round filter housings or in parallel filter single-use setups are used, all filters are tested at the same time. A failed test result of a single flawed filter potentially could be masked by the passed results of the other filters.

Conduct a risk assessment if multi-filter installations are tested at once.

- consider using a lower Diffusion test criterium as alarm
- check if smaller filters can be used for the final step, which is to be integrity tested

More information about avoiding false passed integrity tests please refer to the "QRM Handbook - Conducting FMEA Using the Sartocheck® 5 Plus Filter Tester". For correct setup of the integrity test, the Sartorius Tech Support team can be asked for support.

9. Acronyms

API	Active Pharmaceutical Ingredient
BCT	Bacteria Challenge Test
BP	Bubble Point (integrity test)
IPA	Isopropyl alcohol (2-Propanol)
IT	Integrity Test
Max.	Maximum
PDA	Parenteral Drug Association (PDA.org)
PUPSIT	Pre-Use Post-Sterilization Integrity Test
RO	Reverse Osmosis
SC	Sartocheck® Filter Tester
SIP	Steaming In Place
Vol.	Volume
WFT	Water Flow Test

10. Literature

PDA Technical Report No. 26, (TR 26) Revised 2008, Sterilizing Filtration of Liquids

QRM Handbook - Conducting FMEA Using the Sartocheck® 5 Plus Filter Tester, updated version can be downloaded at www.sartorius.com

Sartorius Validation Guides

e.g. Validation Guide Sartopore® Platinum Family, Sterilizing Grade Filter Elements;
DIR No.: 2665259-000-00