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Technical Brief

Best Practices for Integrity Testing of Viresolve® Pro Devices

Background

Virus filtration is a common step in the production of many biologics and, dependent on the pore size of the filter, can remove both large and small viral contaminants. Integrity testing (IT) confirms the retention performance of the filter. Pre-use IT confirms the filter was not damaged during shipment and that the filtration system is set up correctly. Post-use testing confirms fluid processing was performed on an integral filtration device. When performed correctly, an integrity test is a fast, simple, and reliable way to assure retention performance of the filter. Following the correct test procedure minimizes the risk of an integral filter failing integrity testing.

Prefilters such as Viresolve® Pro Shield and Viresolve® Pro Shield H should not be integrity tested as these filters do not have virus retention claims.

The goal of this document is to describe critical elements of integrity testing Viresolve® Pro Devices (viral retentive filters) using automated testers and follow-up actions in the event a filter does not pass. This information supplements the Viresolve® Pro Solution User Guide[1] and is intended to minimize your risk of an unsuccessful integrity test.

Measuring Filter Integrity

For Viresolve® Pro Devices, integrity is assessed by measuring the diffusional flow rate of air through water-wetted membrane at a pressure below the membrane bubble point. If air flow is below the Viresolve® Pro Device specification, the filter is integral, and the membrane will meet virus retention performance expectations. If air flow is above this specification, the Viresolve® Pro Device may not deliver the expected virus retention performance and follow-up actions are required.

The maximum air diffusion specifications for Viresolve® Pro Devices are summarized in Table 1. These specifications are valid for wetting with water for injection (WFI), air (~80% nitrogen, ~20% oxygen), at a test temperature of 25° C.

Viresolve® Pro Devices should not be wet with alcohol solutions before air diffusion testing as the membrane chemistry is not compatible with alcohol.

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Table 1. Viresolve® Pro Device Air Diffusion Specifications

Unit	Air Water Diffusion Flow Rate at 50 psi (3.4 bar) in water at 25 °C (cc/min)
Viresolve® Pro Modus 1.1 Device	≤0.7
Viresolve® Pro Modus 1.2 Device	≤2.7
Viresolve® Pro Modus 1.3 Device	≤8.8
Viresolve® Pro Magnus 2.1 Device	≤20
Viresolve® Pro Magnus 2.2 Device	≤60

Note: A stack containing multiple devices can be tested as a single unit and the diffusion rate specification is the sum of diffusion rates for each component device.

Considerations for Confirming Device Integrity with Automated Testers

Integrity testing can be performed manually or with automated integrity testers; procedures are described in the Viresolve® Pro Solution User Guide[1]. This section highlights important considerations for integrity testing using automated integrity testers. Before testing, the Viresolve® Pro Device should be separated or isolated from prefilters.

Device Wetting

Complete filter wetting is a prerequisite for accurate integrity testing. Before testing, Viresolve® Pro Devices should be wet out with WFI to a minimum of 50 L/m² at 2.1 - 4.1 bar (30-60 psi). When wet out completely, the normal water permeability (NWP) of the Viresolve® Pro Device should be within the specification range of 131-363 LMH/bar (9-25 LMH/psi) and stable over 3 sequential measurements. If end-users have setups that prevent wetting at 2.1 bar (30 psi), filters should be wet with at least 50 L/m² or until NWP is 131-363 LMH/bar (9-25 LMH/psi). **Insufficient wetting may result in integrity test failure or reduced permeability.**

When performing pre-use IT, it is critical to confirm the Viresolve® Pro Device is fully wet before processing, by re-venting and re-wetting with a minimum of 50 L/m² at 2.1 - 4.1 bar (30-60 psi) until NWP is within the range of 131-363 LMH/bar (9-25 LMH/psi).

Connecting and Programming Automated Testers

Connecting automated testers to Viresolve® Pro Device installations depends on the orientation of filters in the stack and the configuration of sanitary connections.

Before integrity testing, isolate the Viresolve® Pro Device by preferably capping or closing the valve on the inlet and downstream vent (1 ½ inch connections). The automated tester should be connected to the upstream vent (3/4-inch connection), Figure 1. Outlet 2 on the base plate should be open and not connected to the automated tester.

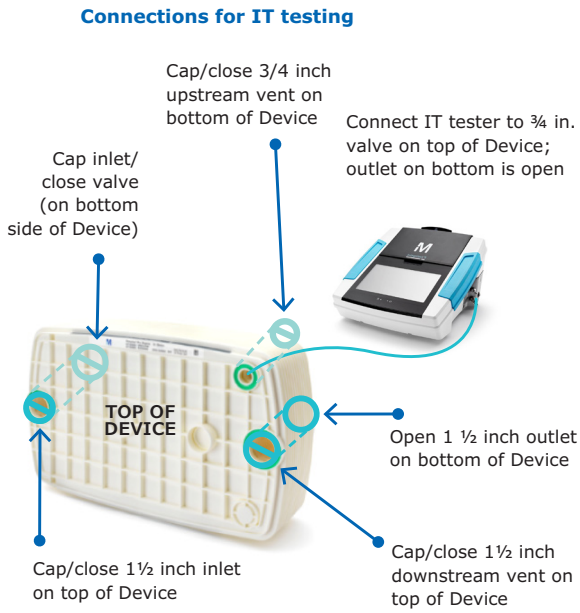

Figure 1. Schematic showing connections to Viresolve Pro® Magnus Device during integrity testing.

The same procedures on automated testers are performed for both pre- and post-use integrity tests. After wetting and firmware checking, the liquid held up in the filter is cleared before a pre-pressurization period to ensure that liquid downstream of the filter is removed.

Insufficient pre-pressurization could result in a diffusion flow rate higher than the specification and false test failure.

- Pre-pressurization with Integritest® 4 and Integritest® 5 instruments involves pressurizing the filter to 55 psi for 15 minutes, depressurizing to 0 psi for 3 minutes, then re-pressurizing to 55 psi for an additional 10 minutes.
- Pre-pressurization with other automated integrity testers includes a single pre-pressurization period of 30 minutes at 50 psi.

Most automated testers can accommodate either single or multiple Viresolve® Pro Devices in a filter stack. If more than one Viresolve® Pro Device is tested, the diffusion specification for the stack is the sum of the diffusion specifications for each component device.

For example, a stack of two Magnus 2.2 Devices and two Magnus 2.1 Devices would have an expected diffusion rate of less than or equal to 160 cc/min: (2 x 60) + (2 x 20).

Incorrect calculation of the Viresolve® Pro Device stack air diffusion flow rate could result in a false test pass or a false test failure.

Integrity Test Failures: Root Cause

In the event of an IT failure, troubleshooting and retesting should be conducted to determine if the root cause is due to factors which caused a false test failure or, if the failure is a true failure indicating a non-integral device. Establishing the true root cause of a failed integrity test allows corrective actions to be implemented and reduces the likelihood of future test failures.

For some end-users, air diffusion values may meet filter specifications, but are outside the typical range for their process, and may prompt an investigation of the filtration operation and integrity test. Table 2 highlights potential reasons Viresolve® Pro Devices might fail an air diffusion integrity test.

Table 2. Possible Integrity Test Failure Modes for Viresolve® Pro Devices

Diffusion flow rate higher than specification	
Possible Cause	**Remedy**
Insufficient filter wetting	Check permeability measurements Confirm permeability in range: 131-363 LMH/bar (9-25 LMH/psi) Rewet for additional 50 L/m², verify permeability is in range
Wetting performed at low pressure (< 30 psi).	Flush filter to >50 L/m² or until permeability is 131-363 LMH/bar (9-25 LMH/psi)
System/fitting leaks; valves not fully open/closed	Check valve positions and status, correct valve position and retest If system fails again replace closed valves with caps and retest
Insufficient compression or incomplete sealing of gaskets	Confirm Viresolve® Pro Devices correctly installed and compressed between the top and bottom plates of the holder (holder gauge reads 76 ± 13.8 bar (1100 psi ± 200)) Adjust and retest
Membrane damage (tear, poor bond, transient pressure excursion during operation, reverse pressure damage)	Filter damage, contact supplier
Device damage (poor bond, damage due to mishandling, gasket O-ring damage)	Filter damage, contact supplier

Diffusion flow rate meets specification, but outside typical process range	
Possible Cause	**Remedy**
Incorrect IT cycle on automated tester (insufficient stabilization); operator error	Confirm the correct IT parameters in the automated tester: test temperature, pressure and stabilization/pre-pressurization. Retest using correct program.
Incorrect specification for stack installation	Recalculate diffusion specification based on Viresolve® Pro Devices in stack.
Wrong test gas/wetting fluid	Retest filter with air
Retest filter with air	Retest filter with a different automated tester
Valve at filter outlet closed	Check installation Open filter outlet valve, retest
Post-use flow rates lower than expected: possible membrane fouling	Check prefilter and filter-sizing calculations

Path to Investigation

Check Setup & Wetting

The first step in troubleshooting a failed test is to confirm the integrity test setup and execution. This should be performed irrespective if the air diffusion value is close to the filter specification or very different to the specification. Air diffusion tests may be performed multiple times if there is a rationale for repeat testing.

The most common cause of a failed integrity test is incomplete filter wetting. NWP should be in the range of 131-363 LMH/bar (9-25 LMH/psi) for three sequential measurements.

- For pre-use tests, wetting beyond 50 L/m² might be necessary to achieve NWP in the recommended range.
- For post-use testing, filters should be flushed with more than 50 L/m² WFI as NWP may be lower than the pre-use NWP value due to filter fouling.

Considerations for Filter Stacks

If a filter stack fails a pre-use or post-use test, the stack installation and setup and the Viresolve® Pro Device stack air diffusion specification calculation should be carefully checked. If the stack fails a second post-use test, assessing the integrity of individual filters might identify the root cause of failure. The stack can be disassembled, individual filters should be labeled and position in the stack recorded, then individual filters retested.

Pressure records may help identify abnormal events from the processing run that result in filter failure. If all individual filters pass the repeat test, poor sealing of the devices within a stack may be a potential root case for integrity test failure. **If the filter stack fails the second test, the filter supplier should be contacted.**

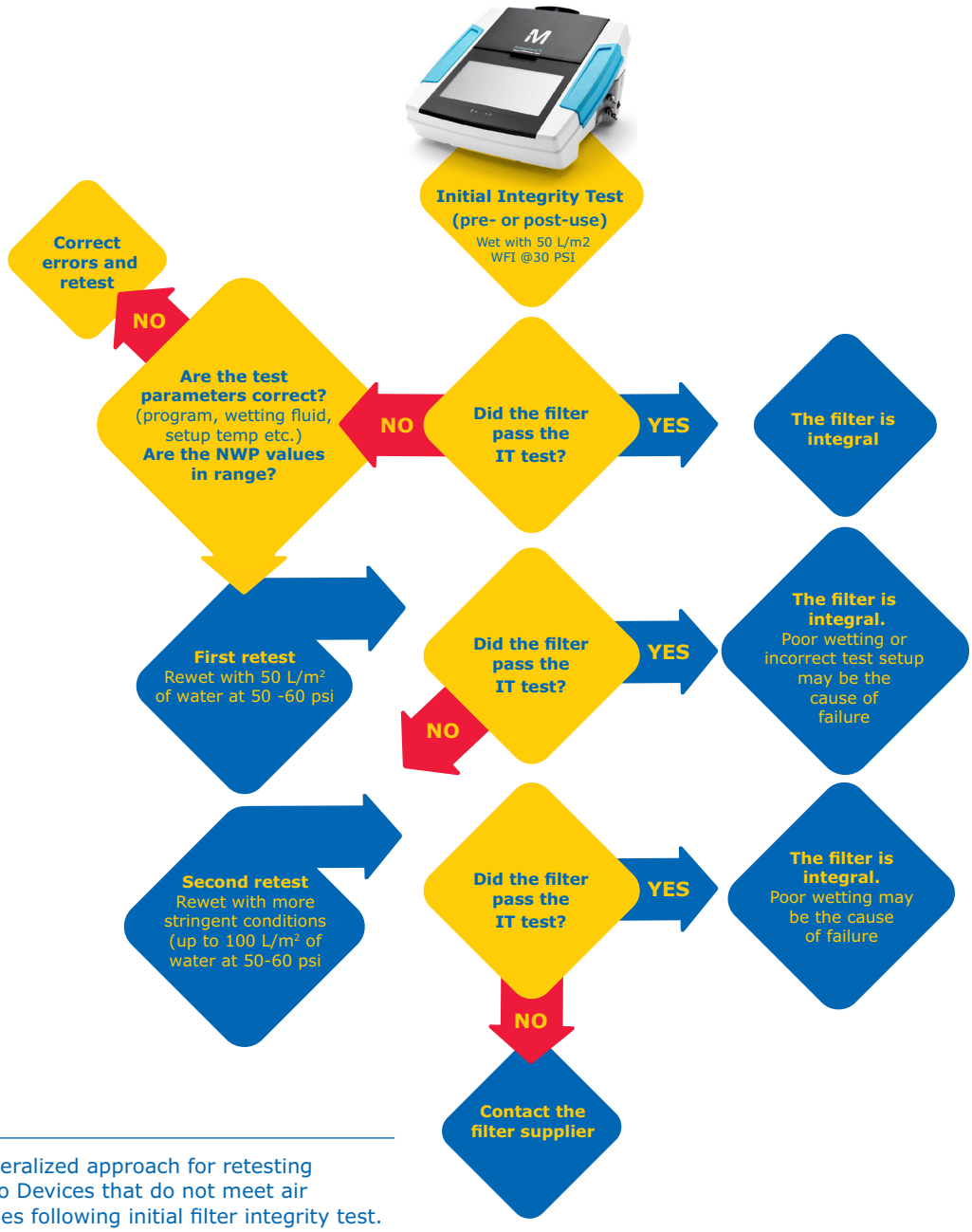

Figure 2. Generalized approach for retesting Viresolve® Pro Devices that do not meet air diffusion values following initial filter integrity test.

Summary

Air diffusion testing provides a simple, reliable method to quickly assess filter integrity and confirm retention performance of Viresolve® Pro Devices. If a filter or filter stack does not meet the air diffusion specification, test setup and execution should be carefully reviewed before retesting is performed. It is critical to determine if the root cause of failure is due to incorrect setup and execution or if the failure is an indicator of a non-integral device.

It is highly recommended that each manufacturer has a detailed process for investigating both pre- and post-use integrity test failures that is appropriate for their process conditions. If additional support is needed, contact your filter supplier.

References

(1) Viresolve® Pro Solution User Guide
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