PALL Life Sciences

Application Note

USD3000

Successful Wetting for Filter Integrity Testing in Volume-Restricted Systems

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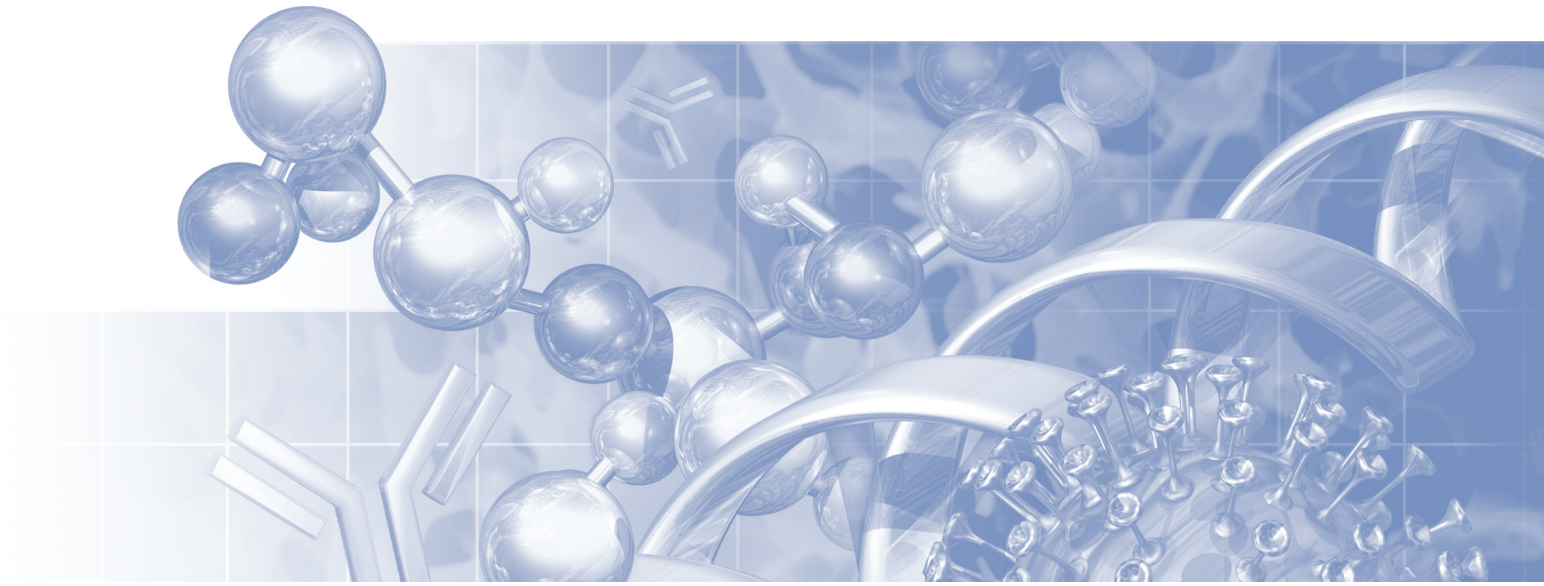

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1. Introduction

Filters with a qualified retention for bacteria, mycoplasma or viruses are commonly used in many pharmaceutical processes. In a validated GMP process, these filters must be routinely tested for integrity. For both of the most commonly used filter integrity (IT) tests, the Forward Flow Test and the Bubble Point Test, the filter membrane must be completely wetted with an appropriate wetting liquid before starting of the test.

The automated test instruments that are used for filter integrity testing have been improved during the over 40 years that filter integrity testing has been performed. The Palltronic Flowstar IV instruments and Palltronic AquaWIT IV systems represent the latest generation of best-in-class integrity test equipment. The instruments have a very sensitive measurement system and are capable of detecting almost all conditions, where external influences could jeopardize the validity of the test result. Apart from temperature fluctuations, filter wetting has become the main factor to cause false failures during the filter integrity test.

1.1 Pre-use or post-use test?

The rules and recommendations on whether filters have to be tested pre-use or post-use, are not standardized between the different authorities. FDA and EU GMP guidelines both state that a post-use integrity test must be performed. Whilst the FDA GMP guidelines only recommend the pre-use test, the EU GMP guidelines demand that filters are tested after sterilization, and before they are used. The technology to perform a post-sterilization pre-use filter integrity test is available and can be implemented without great effort in many cases. As the PDA describes in the latest release of the PDA Technical Report #26, the pre-use test is suitable to reduce a commercial risk, while the post-use test is relevant for the product safety.

1.2 Filter Wetting Liquid

The most common liquids used to wet the filter for the integrity test are (a) water, (b) a mixture of water with alcohol or (c) the product to be filtered. In many pharmaceutical processes, alcohol is not compatible with the pharmaceutical ingredient and therefore not suitable for inline tests. It is mostly used as a backup wetting liquid for offline tests.

For certain applications (e.g. virus filtration) alcohol-based solutions are suitable but must be removed thoroughly from the filter in an additional process step prior to further processing.

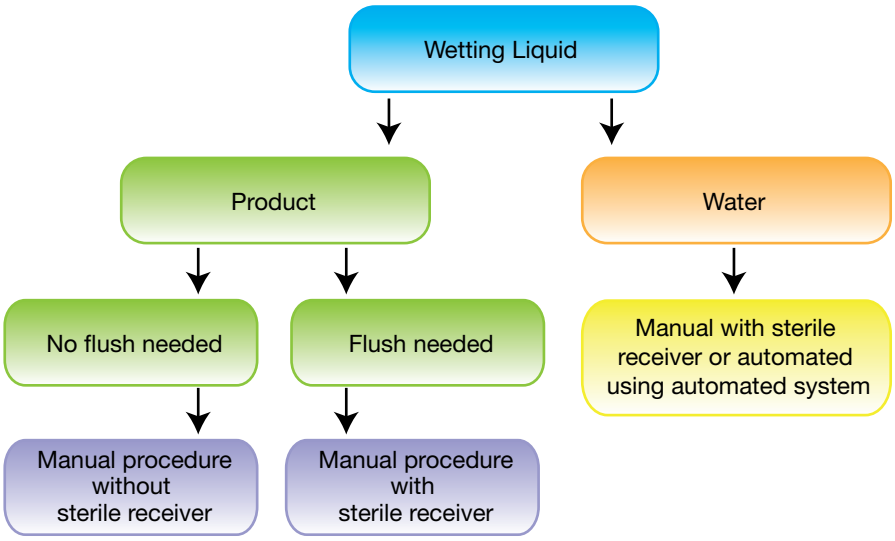
For the post-use test, the simplest wetting is carried out when the product is used as a wetting liquid. As the filter has been in contact with that liquid during the whole filtration process, it is almost always very well wetted and the filter integrity test will easily pass. If the product can be easily flushed out of the filter membrane, the filter can also be wetted with water for the post-use integrity test. In this case a decent amount of water must be flushed through the filter to reduce the product residues.

Wetting a filter for a post-use test in most cases is not too challenging. However considerations and requirements for a pre-use test are more complicated.

Where a pre-use test is required the following decisions must be taken:

- Type of wetting liquid: Product or water?
- In case of product as wetting liquid: Is a pre-flush required to reduce extractables?

Figure 1
Decision tree on wetting procedure



Both water and product can be used to wet the filter for the pre-use test. In most cases, if the filter is wetted with product before the pre-use integrity test this will not cause a product loss. Except for a comparably small amount of product that could be used to flush the filter in order to reduce the extractables and to equilibrate the filter system, the whole wetting liquid can be further used in the manufacturing process. There is only the risk of losing product if the filter fails the pre-use test. In this case the filter will have to be changed and the filter system must be cleaned and re-sterilized.

After steam sterilization, a water flush of the filter system will help to reduce the amount of extractables from the filter and to cool the filter system down to ambient temperature. The extractable concentration is usually highest in the first few liters that are flushed through the filter. As the water is flushed through the filter to the sterile side, a sterile waste receiver should be considered to drain the flushing water from the product line. In the case described above, a water-wet integrity test of the filter is convenient. An integrity test of the water wetted filter is also applicable when the filter must be sterilized in wet conditions.

When water is used as wetting liquid there are often requirements to have as little water as possible on the downstream side of the filter due to restrictions in the downstream volume of the sterile waste receiver. From a space saving point of view, the size of this receiver cannot be too large. In single-use systems the flush biocontainer should have a reasonable size compared to the filter system. In the case where the wetting liquid is directed to the product vessel or in final filling applications, dilution of the product must be kept to a minimum. The residual water in the filter or the line downstream of the filter should then either be calculated into the dilution of the product or the filter system should be flushed with an amount of product to assure the correct product concentration.

For installations where there are no volume restrictions or for post-use testing of filters inline or offline, procedures are in place and well established. Recommended procedures for are available from Pall - please contact your local Pall office to get the appropriate information for your application.

However, to address the scenarios described above and their requirements, alternative wetting procedures are needed. Pall has developed wetting procedures for water as a wetting liquid, allowing filter wetting for integrity testing with down to two liters downstream flush volume per 10-inch filter.

The procedures are different with respect to the filter type and actual filter-product combination. Where wetting a filter cartridge is known to pose no problems and water is the wetting liquid, a comparatively simple procedure with a simple setup without pressure sensors, or in case of single-use systems without the need for reinforced tubing is described in Section 2.2.

Also, this document provides guidance on wetting with low volumes of wetting liquid in cases where it is difficult to wet the filter with the respective product or standard wetting liquid. For such situations a more sophisticated procedure and setup is necessary (Section 3.1).

Where manual control is too complicated and reproducibility of the procedure applied is crucial for successful wetting, automation of the wetting process is recommended (Section 4). This applies for example, to virus filters which need special attention when it comes to wetting for pre-use and post use integrity testing (see Pall publications USTR2512 and USD2833).

The automated wetting procedure presented in this document together with the parameters given in the appendices enable the successful wetting of virus filters using water as a wetting liquid.

2. Optimized Wetting Procedure for Volume-Restricted systems – Basic Principles

Filter cartridges are installed in an 'upright' configuration with the filter outlet at the bottom. Installations with filter outlet on top should be avoided because

- Steam sterilization could be compromised with the filter installed upside down, as air can become trapped in the inner core of the filter cartridge
- Product cannot be fully recovered through the sterilizing grade filter; the complete housing volume can be lost for such an installation

The most crucial aspect of wetting a filter cartridge is to fully remove the air out of the filter to enable the wetting fluid to reach all parts of the membrane. The most critical point is the air which can be entrapped at the top end of the inner core of the filter element and which can cause problems in wetting.

In this document, three procedures primarily for wetting of sterilizing grade filters with low wetting volume are described:

I) For wetting carried out manually, a basic procedure for water wetting and products that wet the filter easily (typically low surface tension products) is described

II) An efficient wetting procedure for more challenging wetting situations as wetting of filters with products with high surface tension or gamma irradiated filters made of polyvinylidene fluoride (PVDF) is described

III) A third procedure covers the automation of the wetting steps which also allows wetting of virus filters under the given conditions

These three procedures are based on two different principles both aiming to reduce the air trapped in the filter core and the pores of the membrane.

The basic manual procedure consists of the three phases listed below.

1. Slow filling of the filter with downstream side closed
2. Allowing a certain amount of water or product to flush along the filter with open vent valve while the downstream side of the filter remains closed (for product, the minimum volume necessary must be determined during process qualification; for water please contact Pall for recommendations). If necessary this amount of wetting liquid can be collected in a sterile bag for later use
3. Pushing the wetting liquid to the downstream side while restricting the flow by partially closing the downstream valve

The second manual procedure and the automated procedure are based on the same principles and also consist of three phases differing from the phases described above.

1. Fill the filter slowly with the downstream side closed and by pushing the wetting agent into the closed system, upstream of the valve. In this phase, allow venting when a certain pressure level is reached
2. Soak the filter under pressure

3. Fast flush the filter to push the air out of the inner core

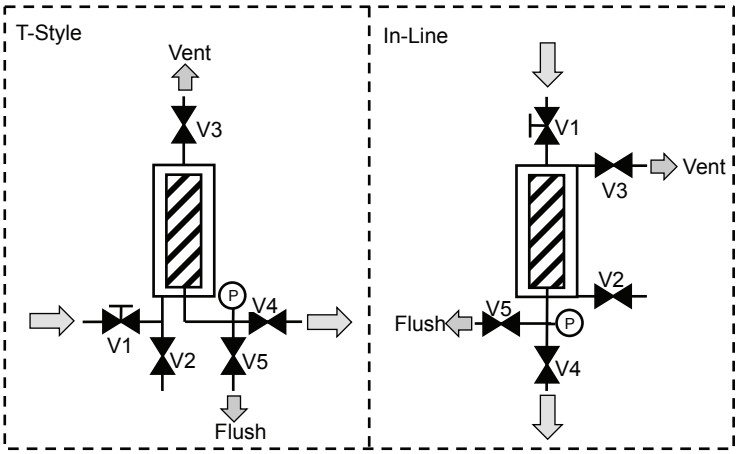
These procedures are based on experience with automatic systems where the amount of wetting fluid is limited, and on experience with single-use systems where the dimension of the flush biocontainer to collect the wetting fluid should be of reasonable size compared to the size of the filter system itself.

2.1 Setup for Low-Wetting Volume Integrity Test

Figure 2 shows a schematic setup of a filter capsule (T-Style and In-Line).

Figure 2

Schematic Setup for Filter Wetting



The filter can be wetted by filling from the inlet (V1) and vented over the vent valve (V3) of the housing (or an additional vent introduced at the top of the filter) while keeping the valve on the downstream side of the housing closed. Slow filling can either be achieved by throttling V1 or by using a pump at low speed. The downstream valves V4 and V5 remains closed during filling.

A pressure sensor downstream of the filter is recommended to control the downstream pressure during the wetting procedure and/or if the filter test is carried out with V4 and V5 closed or if the system is not open to atmosphere to control the pressure downstream of the filter.

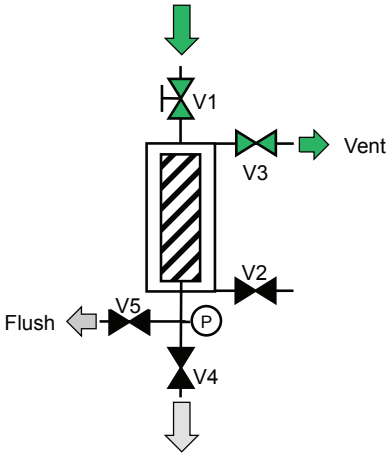
The wetting/flushing fluid can be removed via V5.

The wetting procedure can be controlled manually or by an automatic system. In the following section, the basic steps for the different procedures are described.

2.2 Step by Step Procedure for Basic Manual Wetting with Low Flush Volume (in-line configuration) for Non-Challenging Wetting Situations*

Step 1: Filling

1. Make sure the filter is in the upright position
2. The valves at the downstream side remain closed
3. Open V3 and fill filter housing slowly with wetting fluid by starting the pump at low speed or controlling the flow by throttling valve V1
4. When fluid starts to flow from the vent valve allow about 2 liters water (for 10-inch filter with water; for product, determine on a case-bycase basis) over the vent valve in order to thoroughly remove air.

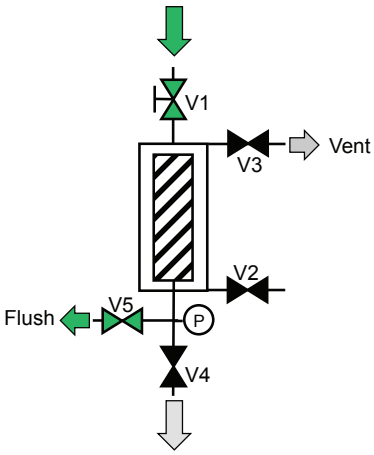


For recommended flow for filling and flushing with standard wetting fluid, see Appendix 1.*

NOTE: If the downstream system is open to a bigger tank or a vented flush bag is used, the pressure sensor can be omitted in the setup

Step 2: Flushing

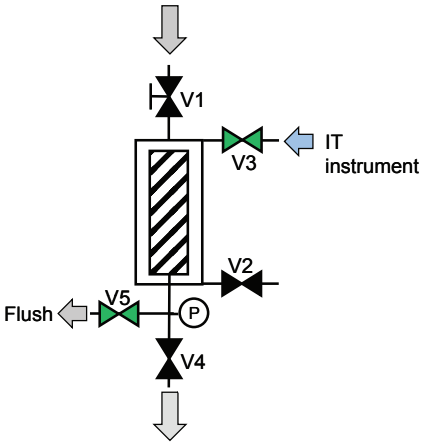
1. Close the vent valve and open V5 (fully or partially depending on filter size and flow rate)
2. Make sure the filter membrane is completely covered by wetting liquid during the wetting procedure for example by throttling the liquid passage and additional venting.
3. After passing an adequate amount of wetting liquid (for recommended volumes using the standard wetting liquid water see Appendix 1) to the downstream side into the sterile receiver (or product vessel), stop the liquid feed.
4. Drain as much wetting liquid as possible from the filter housing via V5.



Step 3: Testing

Note: The integrity test instrument must be connected to the top of the filter housing and placed above the filter. The filter should be drained at least below V3 before connection of the integrity test instrument in order to avoid contamination of the test device

1. Connect the filter integrity test instrument to the upstream side of the filter
2. Make sure the valve V3 is open to allow pressurization of the filter
3. At least one of the downstream valves (V4 or V5) should be fully open.



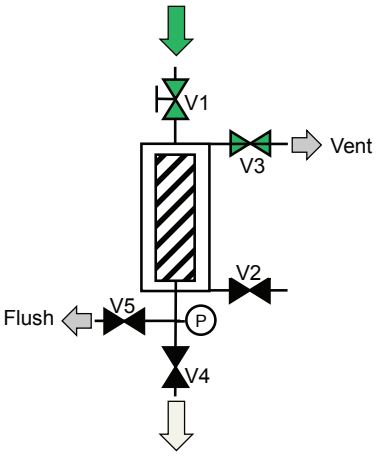
Note: If neither V4 or V5 can be opened or if a non-vented bag is connected to the open valve, the pressure downstream must be monitored especially in the initial phase of the pressurization by the integrity test instrument, in order to become aware of pressure increase due to insufficient wetting or major leaks in the membrane, for example

4. Perform an integrity test using the test limits recommended by the filter manufacturer for the corresponding filter, fluid and test gas combination. During the stabilization phase, fluid residues remaining on the upstream side of the filter will be forced through the filter and collected either in the sterile receiver or the product vessel.

Step 4: Starting filtration

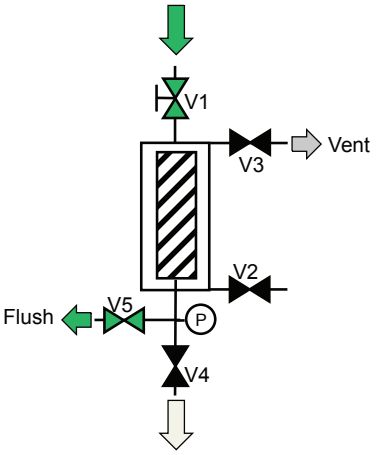
1. After completion of the test, the housing has to be filled with product by opening V1 and venting the housing via V3

If product dilution is acceptable or extensive flushing is not required, go to step 3



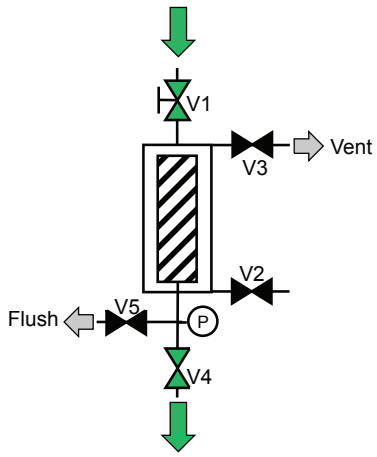
2. If dilution of the product by the remaining wetting fluid in the membrane should be avoided or further flushing is required to remove extractables/leachables, the vent valve V3 should be closed and V5 should be opened for the appropriate flushing.

After flushing with the amount of liquid necessary, close V5.



3. Open valve V4 to start filtration (V3 is closed at this point)

For filters larger than 10 inches in height, depending on the filter type and the type of installation, a more vigorous wetting procedure may be necessary. If the procedure described above is not sufficient for achieving the required 100% wetting of the filter area, the procedure described for product wet integrity test for challenging wetting situations described in Section 3.1 is recommended.



3. Product-Wet Integrity Test

For product wet integrity testing, essentially the same procedure for water wetting with slight modifications can be used to wet the filter. If a pre-use flush of the filter is required in order to reduce extractables, the sterile receiver is still needed. If no pre-flush is necessary, the sterile receiver can be omitted in the setup and the product used for wetting of the filter also directed into the product vessel. The procedure for wetting with product is the same as for water wetting with one exception: extensive filter venting after filling of the filter housing generally will be omitted with product for economic reasons.

3.1 Challenging Wetting Situations (Sterilizing Grade Filters)

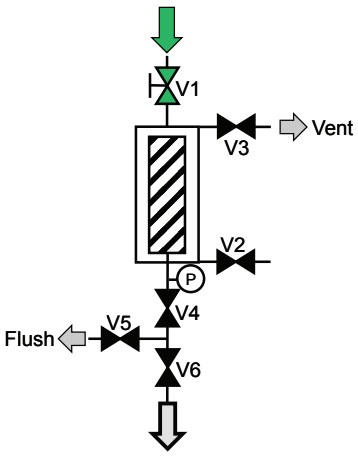
For some product-filter combinations 100% wetting can be challenging. For such situations, a more elaborate wetting procedure is suggested. The procedure follows more or less the same steps and conditions used by the filter wetting function of the Palltronic AquaWIT IV filter integrity test system (see Section 4).

The setup and procedure for more difficult pre-use wetting applications is described in the following section.

A pressure transducer must be installed either upstream or downstream of the filter (see also the procedures below).

Step 1: Filling

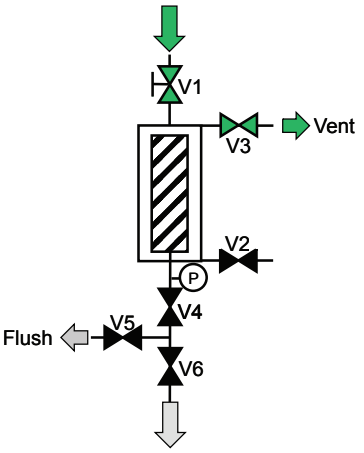
1. Make sure the filter under test is in an upright position
2. The valves at the downstream side and the vent valve V3 remain closed.
3. Fill the filter housing slowly with wetting fluid by starting the pump at low speed or controlling the flow by throttling valve V1.
4. When a pressure of 0.5-0.8 bar is reached at the pressure transducer, vent the housing via vent valve V3. As soon as the pressure returns to zero, close vent valve again and continue filling.



Proceed with filling and venting until bubble free liquid comes out of V3. Close V1 and pressurize the filled housing via V3 with compressed air or nitrogen at 0.8-2 bar for 5 minutes.

NOTE: Venting:

Vent at pressure between 0.5 and 0.8 bar



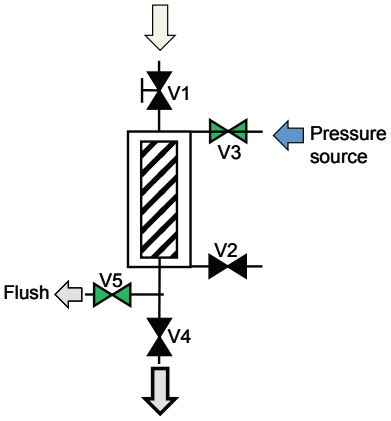
Step 2: Flushing

1. Open downstream valve and flush liquid by applying pressure via V3 into product vessel or sterile receiver.

For recommended parameters for filling, pressurizing and flushing see Appendix 2.

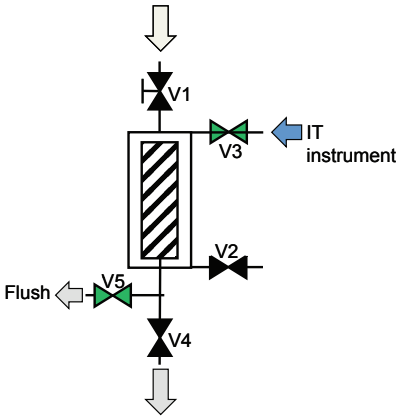
Option for even more challenging situations:

2. Leave V5 open and pressurize the emptied filter housing /capsule via V3 with integrity test pressure for 300 seconds while having V1 closed.



Step 3: Testing

Note: The integrity test instrument must be connected to the top of the filter housing and placed above the filter. The filter should be drained at least below V3 before connection of the integrity test instrument in order to avoid contamination of the test device



1. Connect the filter integrity test instrument to the upstream side of the filter
2. Make sure the valve V3 is open to allow pressurization of the filter
3. At least one of the downstream valves (V4 or V5) should be fully open.

Note: If neither V4 or V5 can be opened or if a non-vented bag is connected to the open valve the pressure downstream must be monitored especially in the initial phase of the pressurization by the integrity test instrument in order to become aware of pressure increase due to insufficient wetting or major leaks in the membrane for example.

4. Perform an integrity test using the test limits recommended by the filter manufacturer for the corresponding filter, fluid and test gas combination. During the stabilization phase, fluid residues remaining on the upstream side of the filter will be forced through the filter and collected either in the sterile receiver or the product vessel.

If one wetting cycle is not sufficient to obtain a positive test result, adapt the procedure for two cycles. Between the cycles add a 5 minute pressure hold step for the drained housing at test pressure. The downstream valve should be open during this phase, the same as for an integrity test.

Start filtration as described for standard manual wetting.

4. Automation of Filter Wetting and Testing using the Palltronic AquaWIT Filter Integrity Test System

The procedures described above allow successful filter wetting and testing, provided that the steps are followed thoroughly and in a well-controlled way. Under production conditions the control of a manual procedure is often a challenge. Therefore in the current Palltronic AquaWIT model (Pall Part Number AW04), an automated wetting function for water wet integrity testing is featured. Wetting with product is not recommended as cleaning and cleaning validation of the system would be too labor-intensive.

In a controlled automated sequence, the filter integrity test instrument fills the filter housing, vents it and allows for filter type specific flushing and soaking. The integrity test is subsequently carried out automatically by the system using the programmed test parameters. The wetting procedure is carried out with defined and controlled parameters enabling reproducible wetting of the filter membrane.

The steps described for manual wetting of the filter have been implemented in an automated cycle. The cycle allows for definition of the filling pressure, the soaking time and the drain pressure. Furthermore, for filter types known to be difficult to properly wet, e.g. virus filters, multiple wetting cycles can be applied.

In order to verify the functionality of the integrity test instrument regarding filter wetting, different filter types and wetting parameters were assessed and defined. The resulting recommended parameters are listed in Appendix 2.

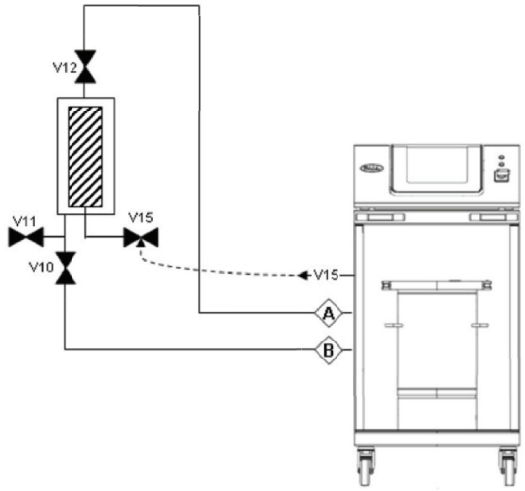
The actual volume needed for wetting of a specific filter type depends on the number of cycles needed for an efficient and reliable 100% wetting of the filter. In many cases only one cycle is needed and the resulting wetting volume is as low as one housing volume.

4.1 Wetting Function of the Palltronic AquaWIT IV Filter Integrity Test System

The wetting function of the system can be chosen as an option when carrying out a Forward Flow integrity test using a Palltronic Flowstar IV integrity test instrument integrated into a Palltronic AquaWIT IV system. The instrument carries out the wetting according to the parameters defined followed by the integrity test sequence. The parameters for the wetting are pressure for filter filling, soak time and soak pressure, as well as drain time and drain pressure and number of cycles to be carried out.

The principle of the wetting is depicted in Figure 3 showing a schematic of a standard set-up for filter wetting.

Filter Wetting - Standard Set-Up



The valve downstream of the filter is essential as during the filling and the soaking phase of the wetting cycle the water must be kept in the housing.

The system carries out the wetting by automatically filling the filter housing from the tank of the Palltronic AquaWIT system. After filling the filter housing is pressurized to the preset pressure and the pressure is kept for the soaking. After the soaking time has elapsed valve 15 is opened and the water drained either to waste or back into the tank of the Palltronic AquaWIT system. After completion of the number of wetting cycles programmed, the filter is integrity tested by the Forward Flow test.

Appendix 1

Recommended Flow Rates and Wetting Volumes for Pall Sterilizing Grade Filters (0.1 µm /0.2 µm) with the Standard Wetting Fluid Water for non-challenging wetting situations

Filter Type	Flow Rate for Filling and Flushing	Volume (Liters)*	Comments
Sterilizing-grade non-gamma irradiated: 10-inch cartridges or capsules of the following membranes: Supor® EKV; Ultipor® NF, NT; Fluorodyne® EX Grade EDF (steam sterilized pre-wetted), EX Grade EDT; Fluorodyne II Grade DFL, DJL	At least 250 mL / min up to 1 L /min	2	No backpressure
Sterilizing-grade gamma-irradiated: 10-inch cartridges or capsules of Supor EKV; Fluorodyne EX Grade EDF or EDT; Fluorodyne II Grade DFL or DJL membrane	At least 250 mL / min up to 1 L / min For Fluorodyne II, 1 L /min is mandatory	2	No backpressure
Bioburden reduction gamma and non gamma irradiated: 10-inch cartridges or capsules of: Supor EAV membrane	At least 250 mL / min up to 1 L/min	2	No backpressure
Sterilizing grade gamma irradiated: 20-inch cartridges or capsules of Fluorodyne II DFL membrane	2 L/min	10	Slight back pressure (< 400 mbar) by partially closing clamp / valve on downstream side of the filter

** Provided that about 2 L are used to flush along the filter (inlet to vent) with the downstream side closed. For filters used in single-use systems this volume may be collected in a biocontainer connected to the vent.*

Appendix 2

Recommended Wetting Parameters for Pall Sterilizing Grade Filters (0.1 µm /0.2 µm) for challenging wetting fluid / filter combinations.

Filter Size	Flow rate for filling [mL /min]	Soak filter pressure [mbar]	Soak filter time[s]	Flush filter pressure [mbar]	Pressure for optional pressurizing step [mbar]	Soak/flush cycles*
10 inch	500	800-2000	120-300	500-1500	Actual test pressure	1-3
20/30 inch	750	800-2000	120-300	500-1500	Actual test pressure	1-3

**For Fluorodyne EX Grade EDF steamed or autoclaved under dry conditions, more flush cycles may be needed as this treatment makes the filter harder to wet for IT (refer also to the product Validation Guide, Pall publication USTR 2378)*

Appendix 3

Recommended Wetting Parameters for Pall Sterilizing Grade Filters (0.1 µm /0.2 µm) with the Standard Wetting Fluid Water for automated wetting using the Palltronic AquaWIT IV Filter Integrity Test System

Filter Size	Fill filter pressure [mbar]	Fill filter time[s]	Soak filter pressure [mbar]	Soak filter time[s]	Flush filter pressure [mbar]	Flush filter time[s]	Optional additional inter cycle pressurisation pressure [mbar]	Soak/flush cycles*
10 inch	500	400	1500	120	1500	300	Actual test pressure	1-3
20/30 inch	750	400	1500	120	1500	300	Actual test pressure	1-3

**For Fluorodyne EX Grade EDF steamed or autoclaved under dry conditions, more flush cycles may be needed as this treatment makes the filter harder to wet for IT (refer also to the product Validation Guide, Pall publication USTR 2378)*

Recommended Wetting Parameters for Pall Virus Filters (Ultipor VF DV20, Pegasus™ SV4) with the Standard Wetting Fluid Water for automated wetting using the Palltronic AquaWIT IV Filter Integrity Test System

Filter Size	Wetting Fluid	Test gas	Fill filter pressure [mbar]	Fill filter time [s]	Soak filter pressure [mbar]	Soak filter time[s]	Flush filter pressure [mbar]	Flush filter time[s]	Soak/ flush cycles
10 inch	Water	Air	500	400	3000	120	3000	120	1
20/30 inch	Water	Air	750	400	3000	120	3000	120	1

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