PALL Life Sciences

Validation Guide: Addendum

USTR 2341

Pall Ultipor® VF Grade DV20 AB Style Virus Removal Filter Cartridges

Validation of Forward Flow integrity test parameters for water-wet filter cartridges

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CONTENTS

1. Introduction

The purpose of this addendum is to provide a user-friendly pre- and post-use integrity test option for AB style **Ultipor** VF grade DV20 filter cartridges based on the Forward Flow test done on water-wet filter cartridges.

This document is an addendum to (and should be read in conjunction with) the existing Pall publication 'VG-DV20: Validation Guide for Pall ULTIPOR VF Grade DV20 AB Style Virus Removal Filter Cartridges'.

The extensive validation work undertaken by Pall on the **Ultipor** VF grade DV20 membrane and on the filter cartridges ensures that the finished product performs to the claimed specifications in terms of flow characteristics and viral retention. The assurance that these performances are maintained on currently manufactured membrane and cartridges relies on a series of in-process QC tests including the individual integrity test done on the finished filter cartridges. The 100% integrity test is performed on filter cartridges wet in 30% IPA and is correlated to the retention of PP7 and PR772 bacteriophages as demonstrated in Pall publication VG-DV20.

The pressure used for this integrity test has been set at 5.86 bar (85 psi), in order to be as close as possible to the bubble point of the membrane, yet not exceeding the maximum recommended differential pressure (during integrity testing) for this filter, that is 6.2 bar (90 psi). The 30% IPA has been chosen as the test fluid because of its low surface tension, which increases the test sensitivity. By selecting this wetting fluid and this integrity test pressure for the individual manufacturing release integrity test of DV20 filter cartridges, Pall has taken the approach of maximizing the sensitivity of this integrity test. This approach is consistent with the current PDA Technical Report # 41 on Virus Filtration, which states in pages 28 – 29:

"The selection of test pressure for forward/diffusive flow testing of virus filters is critical in determining the test sensitivity. The higher the test pressure, the more sensitive the test. Generally, the test pressure selected for any Forward/Diffusive Flow Test should satisfy the following criteria: It should be below the putative bubble point of the filter but not exceed the differential pressure rating of the filter. This varies depending on the filter, but is usually never greater than 5.5 – 7.6 bar (80 – 110 psi).

The integrity test fluid should be carefully selected. Generally speaking, the lower the surface tension of the integrity test fluid, the more sensitive the test. A water-wet test at low test pressure is only capable of confirming proper installation of virus filter and absence of gross damage."

As mentioned above, the purpose of this addendum is to provide filter users with a user-friendly alcohol-free pre- and post-use test option for **Ultipor** VF grade DV20 filter cartridges. This test option is based on the Forward Flow integrity test done on water-wet filter cartridges and correlated to virus retention. This approach is consistent with the recommendations of PDA Technical Report # 41 on Virus Filtration, as all released filter cartridges are pre-tested on a 100 % basis with the more sensitive and stringent virus retention-correlated alcohol-wet Forward Flow test method during filter manufacture.

Filter cartridge identification control ensures that the filter cartridges used are perfectly traced to the filter cartridge manufacturer's process validation and release qualification. Virus retention-correlated integrity tests done before and/or after use ensure that the filter cartridges installed in the user's process are properly installed and undamaged, either by mishandling or by the process conditions.

As stated in PDA Technical Report # 41, the sensitivity of this test is a function of the applied test pressure and the surface tension of the wetting fluid. The water-wet integrity test parameters proposed by Pall allow performing an integrity test with a non-alcoholic fluid for customer convenience. The proposed test pressure of 5.86 bar (85 psi) is the same as the one chosen for the critical alcohol-wet IT. It is the highest feasible test pressure in order to provide as much sensitivity as possible for this test.

The determination of the water-wet Forward Flow limit value has been carried out during the **Ultipor** VF grade DV20 filter cartridges validation study, described in Pall publication VG-DV20. The limit value has then been chosen so that it is consistent with a viral retention in conformance to product specification. The specific data relative to the water-wet construction integrity test validation is described below.

2. Parameters Determination

Based on viral challenge and forward flow integrity tests conducted on production-quality AB style **Ultipor** VF grade DV20 filter cartridges, it was determined that a Forward Flow integrity test air pressure of 5.86 bar (85 psi) is suitable for integrity testing the AB style **Ultipor** VF grade DV20 filter cartridges when the filter cartridges are wet with water. Under these test conditions, the maximum allowable Forward Flow value for one 254 mm (10 inch) filter cartridge predictive of viral retention claims, was determined to be 8.5 mL of air per minute.

In order to validate the use of 5.86 bar (85 psi) air pressure and the maximum allowable flow of 8.5 mL/minute (for water), filter cartridges were sampled from multiple production lots and tested as described below.

3. Integrity Testing and Viral Challenge Validation Procedure

See Pall publication VG-DV20, Section I, page 3 and Appendix A, pages 13 to 19. For alternative procedures for integrity testing by filter users, please contact Pall Corporation.

4. Results

The data from the viral retention versus water-wet forward flow study are listed in Table 1 and plotted on Figure 1. AB style **Ultipor** VF grade DV20 254 mm (10 inch) filter cartridges with Forward Flow values from 5.6 mL/min to 14.1 mL/min – when wet with DI water and tested at 5.86 bar (85 psi) air pressure – gave titer reductions for bacteriophage PR772 and PP7 of greater than or equal to 6 logs and 3 logs respectively, under the same test conditions. The test conditions included challenge with bacteriophage viruses at concentrations of greater than or equal to 10^6 pfu/mL in an isotonic protein solution (phosphate buffered saline + 10 mg/mL bovine serum albumin) with an applied differential operating pressure of 2 bar (30 psi) differential, and effluent was sampled and analyzed post-filtration after 1 L challenge throughput volume.

5. Conclusion

Per this additional study, the Forward Flow integrity test performed at 5.86 bar (85 psi) in DI water establishes that AB style **Ultipor** VF grade DV20 filter cartridges with Forward Flow values of up to 8.5 mL/min have retained, in the specified test conditions, bacteriophages PR772 and PP7 with titer reduction of $\geq$ 6 logs and $\geq$ 3 logs respectively. Filter cartridges with Forward Flow values between 9.1 and 14.1 mL/min have also proved to be virus retentive to the product specification for AB style **Ultipor** VF grade DV20 filter cartridges, indicating a safety margin above the limit value.

Table 1: Water-wet Forward Flow Values of AB1DV20 Filter Cartridges and Retention of Bacteriophages PP7 and PR772

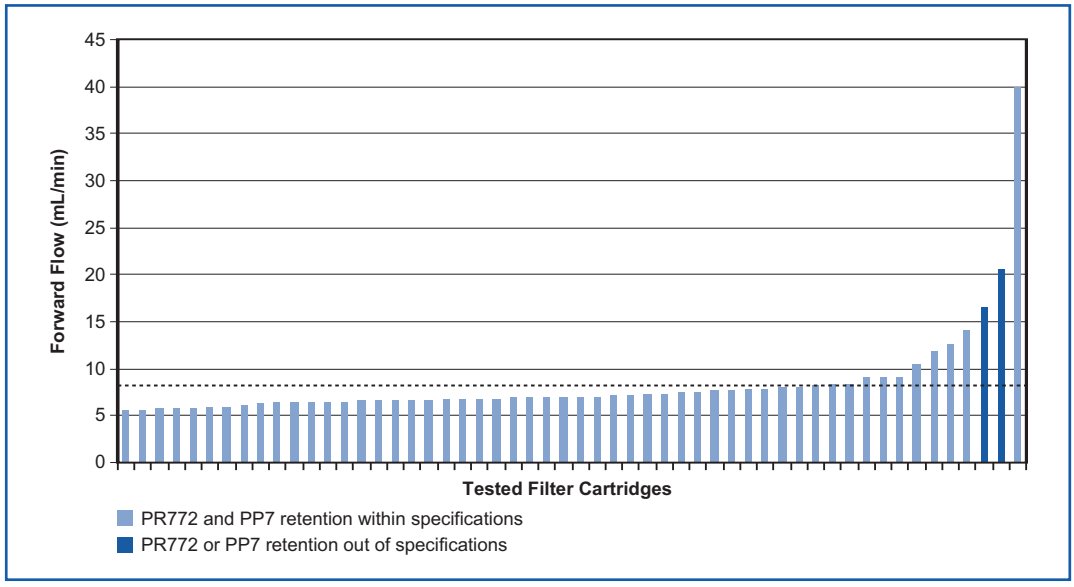
Filter Cartridge Serial Number	Forward Flow mL/min at 5.86 bar, DI water	T_R for PR772	T_R for PP7
EL0430017	5.6	> 1.0×10^6	1.2×10^5
EK0260006	5.6	> 1.0×10^6	6.7×10^4
EL0430006	5.7	> 1.0×10^6	3.3×10^5
EL0430007	5.8	> 1.0×10^6	2.9×10^5
EK0260011	5.8	> 1.0×10^6	6.2×10^4
EK0300042	6.0	> 1.0×10^6	3.1×10^4
EK0260028	6.0	> 1.0×10^6	6.1×10^4
EK0410091	6.1	> 1.0×10^6	2.0×10^4
EK0260120	6.2	> 1.0×10^6	8.2×10^5
EK0300046	6.4	> 1.0×10^6	5.0×10^5
EK0300009	6.4	> 1.0×10^6	1.1×10^5
EK0260039	6.4	> 1.0×10^6	1.2×10^5
EK0260020	6.4	> 1.0×10^6	4.0×10^5
EK0410122	6.5	> 1.0×10^6	1.9×10^5
EK0260032	6.6	> 1.0×10^6	1.8×10^5
EK0260061	6.7	> 1.0×10^6	2.0×10^5
EK0300066	6.7	> 1.0×10^6	3.1×10^5
EL0510109	6.7	> 1.0×10^6	4.5×10^3
EK0300013	6.7	> 1.0×10^6	9.5×10^3
EL0430029	6.8	> 1.0×10^6	1.8×10^5
EL0510098	6.8	> 1.0×10^6	2.7×10^3
EL0580026	6.8	> 1.0×10^6	7.9×10^4
EK0300052	6.8	> 1.0×10^6	5.4×10^5
EK0300017	6.9	> 1.0×10^6	8.0×10^4
EK0300061	7.0	> 1.0×10^6	9.0×10^4
EK0300063	7.0	> 1.0×10^6	1.3×10^5
EK0300022	7.0	> 1.0×10^6	1.6×10^5
EK0300068	7.0	> 1.0×10^6	1.7×10^5
EL0510185	7.0	> 1.0×10^6	3.2×10^3
EK0470001	7.2	> 1.0×10^6	1.0×10^5
EK0300035	7.2	> 1.0×10^6	8.4×10^4
EK0410014	7.3	> 1.0×10^6	1.7×10^4
EK0260077	7.3	> 1.0×10^6	1.4×10^5

Table 1 (Continued)

Filter Cartridge Serial Number	Forward Flow mL/min at 5.86 bar, DI water	T_R for PR772	T_R for PP7
EK0260025	7.5	> 1.0×10^6	5.2×10^4
EK0260085	7.5	> 1.0×10^6	2.3×10^5
EK0300038	7.6	> 1.0×10^6	6.8×10^4
EL0510137	7.7	> 1.0×10^6	2.3×10^4
EK0470013	7.8	> 1.0×10^6	5.2×10^5
EL0510012	7.8	> 1.0×10^6	2.9×10^4
EL0510022	8.0	> 1.0×10^6	2.4×10^4
EL0510107	8.1	> 1.0×10^6	3.1×10^3
EL0510143	8.2	> 1.0×10^6	1.6×10^4
EK0470042	8.3	> 1.0×10^6	2.9×10^4
EL0510202	8.4	> 1.0×10^6	1.3×10^4
EL0510088	9.1	> 1.0×10^6	1.2×10^4
EK0410084	9.1	> 1.0×10^6	1.5×10^3
EK0260040	9.1	> 1.0×10^6	8.3×10^4
EK0470040	10.4	> 1.0×10^6	1.1×10^4
EK0410006	11.9	> 1.0×10^6	2.8×10^4
EK0260030	12.6	> 1.0×10^6	3.8×10^4
EK0410085	14.1	> 1.0×10^6	3.0×10^3
EK0410093[1]	16.6	> 1.0×10^6	8.7×10^2
EK0260003[1]	20.5	< 1.0×10^4	7.4×10^3
EK0410034	> 40	> 1.0×10^6	3.3×10^4

[1] Filter cartridges with less than stated log reduction claim, i.e. < 6 logs for bacteriophage PR772 and/or < 3 logs for bacteriophage PP7.

Figure 1: Water-wet Forward Flow (mL/min) for AB1DV20P7H4 Filter Cartridges



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