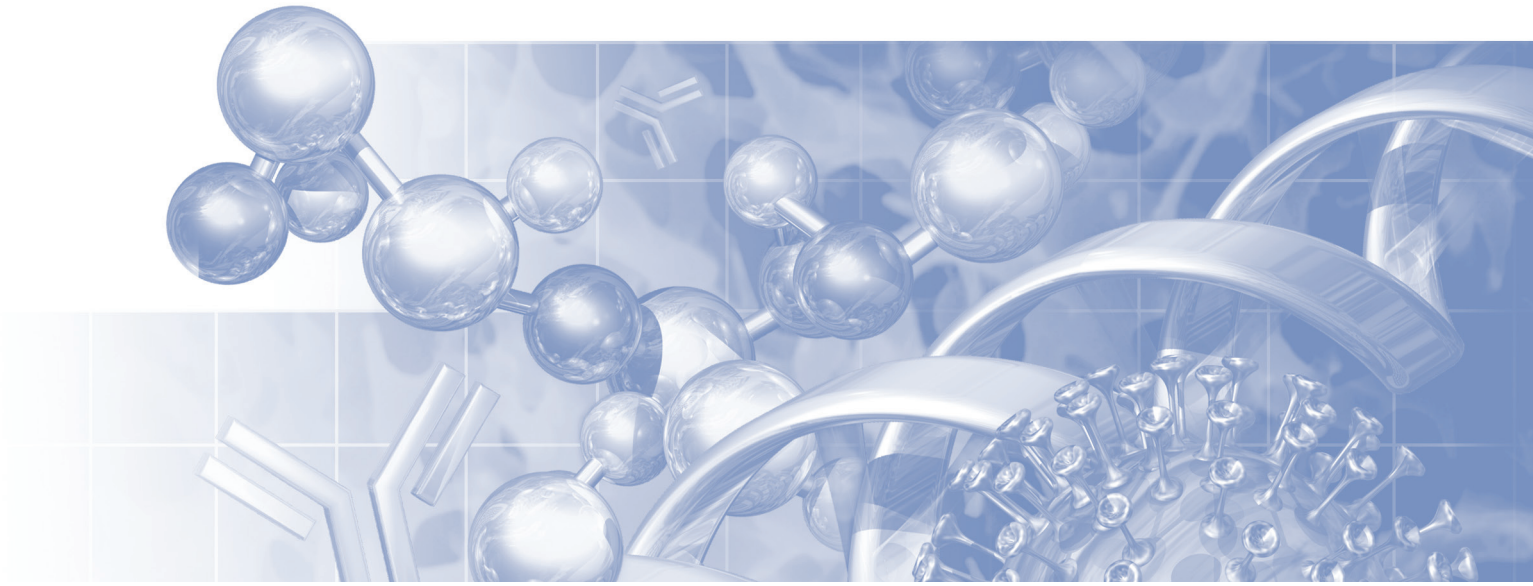
PALL Biotech

Validation Guide

USTR3143b

Pegasus™ Prime Virus Removal Filter Cartridges and Kleenpak™ Nova Filter Capsules with Pegasus Prime Virus Removal Filter Membrane



*Filtration. Separation. Solution.*SM

Table of Contents

1. Overview

1.1 Introduction

This validation guide contains qualification data applicable to Pegasus Prime virus removal filters employing both 25.4 mm (1 in.), 127 mm (5 in.), and 254 mm (10 in.) modules. The document is intended to provide complementary data to the user's qualification studies and does not replace the performance qualification that the user will need to perform as a part of process validation.

The risk of viral contamination is a feature of all biotechnology products derived from cell lines or other biological sources. The safety of these products can only be reasonably assured by ensuring the absence of contaminating viruses from media components and other raw materials as well as by implementing a robust virus removal or inactivation and testing program in the manufacturing process. The confidence in the absence of virus contamination in the product, in most instances, is derived mainly from the ability to demonstrate the virus clearance ability of the manufacturing process rather than the testing of the product. This, in addition to addressing risk associated with known viruses, also provides a measure of confidence that any unknown unsuspected harmful viruses may have been removed. Thus the evaluation and characterization of virus removal procedures occupies a central position in the overall risk mitigation strategy[1,2].

Virus filtration using specifically designed virus filters is an established and effective means of removing potentially hazardous virus particles from pharmaceutical products.

Pegasus Prime virus removal filters are designed for highly efficient clearance of large and small enveloped and non-enveloped viruses, from biological solutions. They combine robust, high viral clearance with high flow rates for biological fluids providing an economical solution. The validation data presented in this document have demonstrated robust > 4 log titer reduction for ~ 25 nm PP7 bacteriophage which is a model for parvovirus, as recommended in PDA Technical Report 413. The product design is embedded in automated system concept and is offered as a sterile product.

Pegasus Prime filters are made from modified hydrophilic polyethersulfone (PES) filter membrane, polyester support and drainage layers, and polypropylene molded components. Filter cartridges are intended for installation in suitable stainless steel or disposable filter housing assemblies.

The qualification of the filters was conducted in accordance with the recommendations outlined in Parenteral Drug Association (PDA) Technical Report 41, PDA Technical Report 26 and USP <1050>[1,3,4]. The data was generated using either filter cartridges or representative capsules by employing compendia methods applicable for the qualification of virus filters. Two types of filter devices that are identical in the construction of filter module and media pack were used. Where applicable the device type representing worst-case conditions was selected for the tests. The tests that were performed to qualify the performance under a range of test conditions included the following:

- Determination of water flow characteristics
- Viral (bacteriophage) retention tests correlated with Forward Flow integrity test
- Sanitization / sterilization
- Water extractables test
- Biological reactivity tests on the materials of construction
- Structural robustness
- Chemical compatibility

Pegasus Prime virus removal filters are manufactured in accordance with an ISO 9001 certified Quality Management System.

Pegasus Prime virus removal filters employing the 25.4 mm (1 in.), 127mm (5 in.) or 254 mm (10 in.) module may be used in conformance with current Good Manufacturing Practices (cGMP) in Manufacturing, Processing, Packing or Holding of Drugs per Title 21 of the U.S. Code of Federal Regulations (21 CFR Part 210) and cGMP for Finished Pharmaceuticals (21 CFR Part 211).

The letter "P" in the part numbering code indicates that these filters are intended for pharmaceutical service, that they are manufactured in controlled environments that meets the air quality standards of an ISO Class 8 room with respect to viable and nonviable particulate and positive pressure, and that they are subject to stringent quality control including in-process controls and testing of the filter elements as follows:

(1) 100% Fabrication integrity tested – correlated to PP7 bacteriophage removal

(2) Viral titer reduction tested with PP7 bacteriophage

(3) 100% fabrication water flow test

(4) Effluent quality testing comprising cleanliness, TOC and conductivity, pH and endotoxins

This guide may be complemented by other documentation for Pegasus Prime virus removal filters namely:

- Datasheet (USD 3157)
- Application Notes (USTR 3159 and USTR 3160)
- Certificate of Test for Pegasus Prime virus removal filters (included in each filter cartridge packaging)

This comprehensive package substantiates the product specification and quality control standards applied to Pegasus Prime filters.

NOTE: The units of pressure quoted in this document are "bar" and "pounds force per square inch (psi)". The following figures can be used to convert these units of pressure to Pascal (Pa):

- 1 bar = 1 x 10^5 Pa
- 1 psi = 6.89476 x 10^3 Pa

1.2 Summary of Validation/Qualification Tests

1.2.1 Determination of Water Flow Characteristics

Pressure drops at set water flow rates have been determined and can be used to assist users in sizing filter systems employing Pegasus Prime filters. The typical clean water flow rate at 20 °C is shown in Table 1.

Table 1
Clean water flow

Filter Part Numbers	Typical Water Flow Rate at 2.1 bard (30 psid), 20 °C (L/min)
NP1LUPRMP1S	0.66 - 0.95
NP5LUPRMP1S	3.8 - 4.1
AB1UPRM7PH4S / NP6LUPRMP1S	5.7 - 8.9

1.2.2 Viral (Bacteriophage) Clearance

Pegasus Prime filters were tested using viral (bacteriophage) challenge tests with bacteriophage PP7 (~ 25 nm). The results demonstrated a > 4 log titer reduction for bacteriophage PP7.

1.2.3 Integrity Test

The Forward Flow integrity test was shown to be a suitable non-destructive integrity test for Pegasus Prime filters. Test parameters have been set as shown in Table 2.

Table 2

Forward flow integrity test parameters for Pegasus Prime virus removal filter cartridges

	NP1LUPRMP1S	NP5LUPRMP1S	AB1UPRM7PH4S NP6LUPRMP1S
Test pressure	4.150 bar (60 psi)	4.150 bar (60 psi)	4.150 bar (60 psi)
Wetting liquid	Water	Water	Water
Temperature	20 °C ± 5 °C	20 °C ± 5 °C	20 °C ± 5 °C
Test gas	Air	Air	Air
Maximum allowable Forward Flow limit*	3.6 mL/min	17.6 mL/min	35.0 mL/min

**During the test period the temperature of the filter assembly should not vary more than 1 °C.*

1.2.4 Sanitization and Sterilization

Chemical Sanitization: Pegasus Prime filters can be sanitized using Minncare◆ cold sterilant (4 - 6% peracetic acid, 8 -10% acetic acid and 20 - 24% hydrogen peroxide). The data presented in this report support that sanitization using Minncare or an equivalent sterilant does not affect filter performance in terms of virus removal.

Gamma Irradiation: Pegasus Prime filters are provided gamma sterilized in accordance with standards described in ISO 11137 Sterilization of Healthcare Products and ISO 11737-2 Sterilization of medical devices[5,6,7].

Pegasus Prime filters must not be autoclaved or steamed for sterilization.

1.2.5 Extractables (Water Extraction)

The typical amount of non-volatile residue (NVR) extracted from Pegasus Prime filters with water has been determined after a 2 x 24 hours extraction time at 40 ºC after a pre-flush with water (see table below).

Table 3

Non-volatile residue data for Pegasus Prime virus removal filter modules

	NP1LUPRMP1S	NP5LUPRMP1S	AB1UPRM7PH4S NP6LUPRMP1S
Test pressure	4.150 bar (60 psi)	4.150 bar (60 psi)	4.150 bar (60 psi)
Pre-flush liquid	Water	Water	Water
Pre-flush volume required	10 L	20 L	30 L
Temperature	40 °C ± 5 °C	40 °C ± 5 °C	40 °C ± 5 °C
NVR, First extraction (Mean ± SD)	14.7 ± 3.3 mg	54.2 ± 5.1 mg	91.1 ± 13.5 mg
NVR, Second extraction (Mean ± SD)	6.1 ± 1.1 mg	32.6 ± 2.9 mg	61.3 ± 4.4 mg

The FTIR spectra of all extracts indicate the presence of compounds typical for the materials of construction, i.e. the PVA-PVA co-polymer used to render the membrane hydrophilic and polyester compounds from the non-woven support and drainage layers. Water extractables of polypropylene hardware components are extremely low and were therefore not detected in this test.

1.2.6 Biological Reactivity Tests on the Materials of Construction

All of the materials used in Pegasus Prime filters meet the requirements for biological reactivity, *in vivo*, under United States Pharmacopoeia (USP) <88> (for Class VI–121 °C plastics) and *in vitro*, under USP <87>. *In vivo* tests included the Systemic Toxicity Test, the Intracutaneous Tests, and the Implantation Test. *In vitro* testing performed was the Minimum Essential Medium (MEM) Elution Cytotoxicity Test. Copies of the test reports can be obtained by contacting Pall Corporation[8,9].

1.2.7 Robustness Tests

Structural Robustness Test: Continuous exposure to forward pressure for 25 hours at 4.1 bard (60 psid) and 40 °C as well as at 5.2 bard (75 psid) at 25 °C did not compromise filter integrity as demonstrated by a passing Forward Flow integrity test.

1.2.8 Chemical Compatibility

General chemical compatibility information based on the material of construction can be provided by Pall on request. A process-specific confirmation of the compatibility of Pall Pegasus Prime virus removal filters at the conditions of use and with process fluid is recommended.

2. Determination of Water Flow Characteristics

2.1 Introduction

The objective of these tests was to determine the typical differential pressure across Pegasus Prime virus removal filters at set water flow rates.

2.2 Summary of Methods

The tests were performed on six (6) NP1LUPRMP1S filters, six (6) NP5LUPRMP1S filters and twelve (12) Pegasus Prime filters, part numbers AB1UPRM7PH4S and NP6UPRM7H4S, from three different cartridge batches. Filter manufacturing and sampling considered possible variation in the filter manufacturing conditions.

Prior to water flow measurement the filters were wetted with water and integrity tested using the Forward Flow method and the procedure described under section 3.2. For water flow measurements, pre-filtered deionized water was pumped through the filters in the normal flow ('out to in') direction. Pressure readings from transducers on the upstream and downstream sides of the test assembly were monitored to calculate the differential pressure at set water flow rates. Water flow at 2.1 bard (30 psid) was measured for a minimum of 2 minutes. The results were corrected for viscosity variation at different temperatures in order to normalize performance to a standard temperature of 20 °C (68 °F).

2.3 Results

Figure 1 shows the mean clean water flow rates of six Pegasus Prime NP1 filters. Figure 2 shows the mean clean water flow rates for six Pegasus Prime NP5 filters. Figure 3 shows the mean clean water flow rates of twelve AB1/NP6 Pegasus Prime filters from three different batches. From these experiments a water flow value at a set pressure of 2.1 bard (30 psid) was determined (Table 3).

Figure 1

Clean water flow for Pegasus Prime virus removal filters: Differential pressure versus water flow for part number NP1LUPRMP1S (n=6)

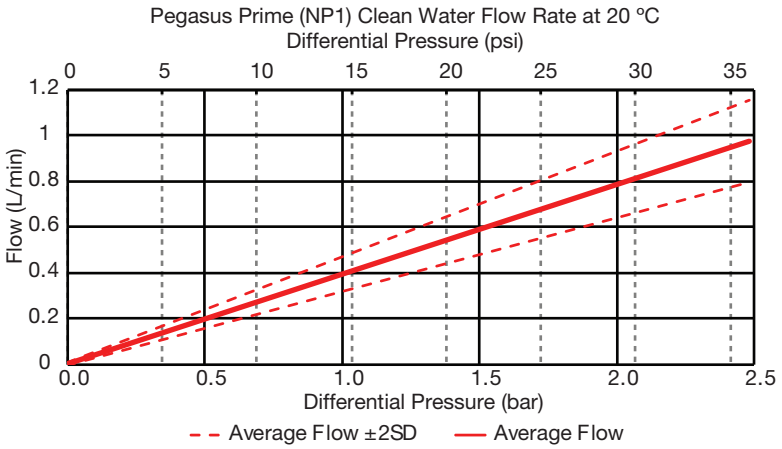


Figure 2

Clean water flow for Pegasus Prime virus removal filters: Differential pressure versus water flow for part NP5LUPRMP1S (n=6)

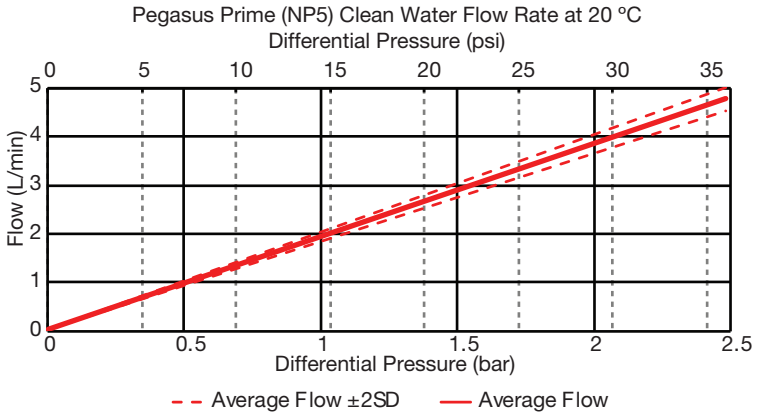
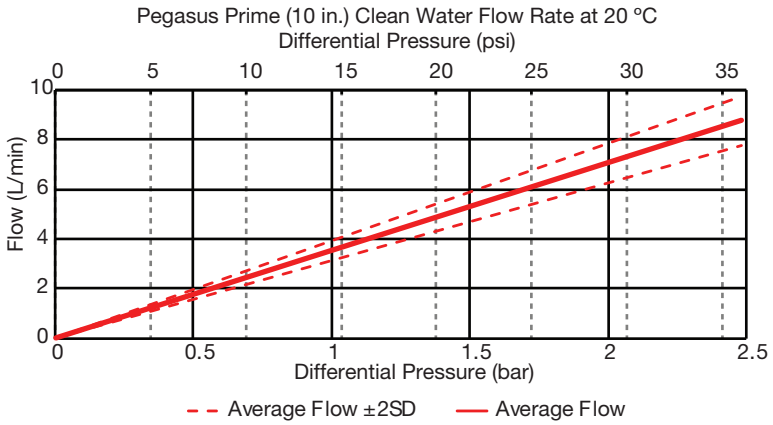


Figure 3

Clean water flow for Pegasus Prime virus removal filters: Differential pressure versus water flow for part numbers AB1UPRM7PH4S in Pall Advanta™ filter housing and NP6LUPRMP1S (n=12)



2.4 Conclusions

Water flow rates at set differential pressures have been determined. The results support that the typical clean water flow rate for Pegasus Prime virus removal filters at 2.1 bar (30 psi) pressure drop and 20 °C is 0.66 – 0.95 L/min for part number NP1LUPRMP1S (25.4 mm, 1 in.), 3.8 – 4.1 L/min for part number NP5LUPRMP1S (127 mm, 5 in.), and 5.7 – 8.9 L/min for part numbers AB1UPRM7PH4S and NP6LUPRMP1S (254 mm, 10 in.). These data can be used to assist users in sizing filter systems employing Pegasus Prime filter devices.

Table 4

Clean water flow at 2.1 bard (30 psid)

Filter Part Numbers	Typical Water Flow Rate at 2.1 bard (30 psid), 20 °C (L/min)
NP1LUPRMP1S	0.66 - 0.95
NP5LUPRMP1S	3.8 - 4.1
AB1UPRM7PH4S, NP6LUPRMP1S	5.7 - 8.9

3. Virus (Bacteriophage) Clearance Tests

3.1 Introduction

A wide range of pharmaceutical products of biological origin are produced with cell-culture techniques including vaccines, monoclonal antibodies, recombinant therapeutic proteins and hormones. In addition, there are numerous plasma derived products such as fibrinogen, immunoglobulins and clotting factors. The risk of virus contamination is ever-present in such products. Potential sources of virus contamination of biotechnology products include viruses associated with the cell lines (endogenous viruses), virus used in the creation of cell lines or hybridomas, or viruses introduced into the bioreactor from culture medium or during the production processes (adventitious viruses). With plasma derivatives viruses could potentially be present in donor plasma.

The incorporation of robust virus inactivation or removal steps into the production process is key to the strategy for preventing viral contamination of the final product.

Virus filtration by size exclusion represents a robust removal method that demonstrates high efficacy for virus removal, and has become a well-accepted orthogonal method for the clearance of infectious viruses from biological API (Active Pharmaceutical Ingredient) and drug products. It is considered as alternative or complementary viral removal technology, and therefore broadens the portfolio of adequate virus contamination-control strategies mandated by regulatory agencies. Filtration is attractive for enhanced virus safety as it has little if any effect on the biological activity of the product, does not require the use of additives (or their subsequent removal), and can typically be readily included into the manufacturing process.

The application of filtration for critical process steps requires demonstration and documentation of the filter's performance through a physical test. The PDA Technical Report No 41 "Virus Filtration" states: "These physical tests enable confirmation of filter integrity by the manufacturer prior to shipment and confirmation of performance by the end user"[3].

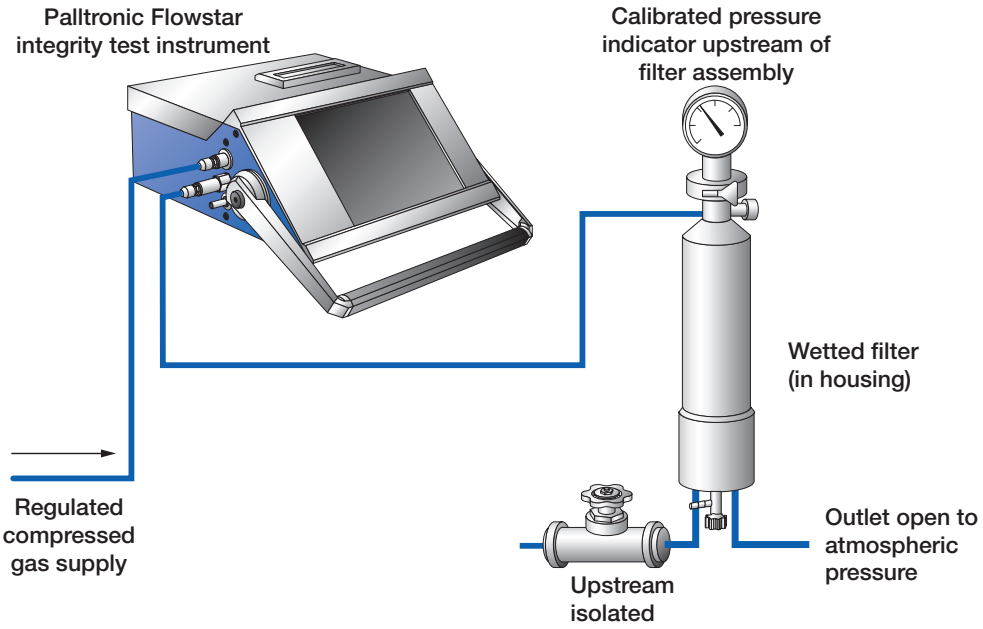
The correlation between viral retention and a non-destructive integrity test is an important aspect of the validation of filters for virus contamination control. The Forward Flow test was the integrity test used during this study. This test is also employed by Pall for the non-destructive integrity testing of each virus removal membrane filter element during manufacturing as part of routine quality control testing.

3.2 The Forward Flow Integrity Test

In the Forward Flow test, a filter is wetted with an appropriate test liquid and a pre-determined gas pressure is applied to the upstream side of the filter assembly. After a stabilization period, the gas flow through the wetted membrane can be measured on the upstream side using sensitive flow measurement equipment such as the Palltronic® Flowstar filter integrity test instrument. A schematic representation of a Palltronic Flowstar integrity test instrument connected to a filter to be tested is shown in Figure 4.

Figure 4

The automated integrity test



The objective of the Viral (Bacteriophage) Clearance test described below was to determine the removal efficiency of typical Pegasus Prime virus removal filters for bacteriophage PP7 (sized at 25 nm) and to document the correlation of the integrity test parameters to the bacteriophage removal efficiency.

3.3 Summary of Methods

Pegasus Prime virus removal filters (part numbers NP1LUPRMP1S, NP5LUPRMP1S, AB1UPRM7PH4S and NP6LUPRMP1S) were tested using the following procedure:
The filters were drawn from three manufacturing lots for each size.

a) Filter installation:

Filter installation steps for part number AB1UPRM7PH4S are described below

1. Open the plastic bag taking care not to damage the filter cartridge inside.
2. To prevent accidental contamination, whenever practical wear gloves and retain the open plastic bag around the filter cartridge when fitting into the filter housing. Remove the bag before closing the filter housing.
3. Certain filter cartridges are supplied with ‘bomb fin’ protective caps; these must be removed before use.
4. Ensure that o-rings are undamaged and correctly positioned in the grooves.
5. Check that the sealing surface on the filter housing is clean and undamaged.
6. To assist ease of fitting, it is strongly recommended that the o-rings are lubricated by dipping the open end of the filter cartridge in a suitable liquid which is compatible with the fluid to be filtered. Water with the same quality as used for final rinsing of the installation is a satisfactory lubricant in many cases.
7. Grip the outside of the filter cartridge as closely as possible to the open end.
8. Insert the filter cartridge with a gentle twisting motion to assist wetting of the surfaces. Gently ease into place. Do not attempt to force the cartridge into position.
9. For filter cartridges with bayonet lock fitting, finally twist the filter cartridge clockwise to engage the retaining lugs within the filter head.

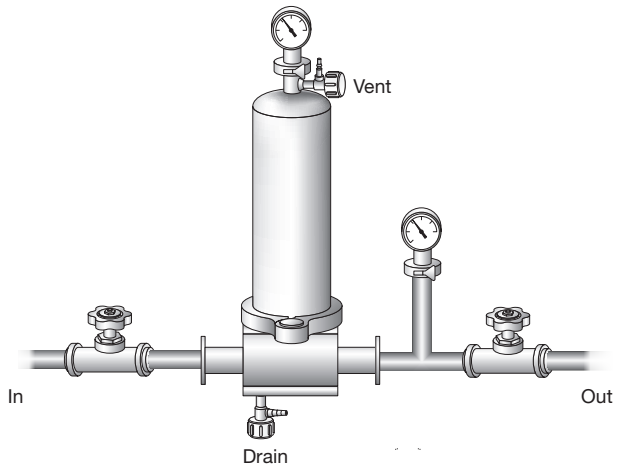
b) Filter Wetting Pre-Use

The first contact of the filter with wetting liquid was carefully controlled to ensure even and complete wetting. The filling was implemented from bottom to top on a filter being held in a vertical position and bubble free, in a time not faster than 1 minute for a 25.4 mm (1 in.) filter, not faster than 1.5 minutes for a 127 mm (5 in.) filter, and not faster than 2 minutes for a 254 mm (10 in.) filter. The wetting was performed in accordance with Pall Publication USD 3132, "Instruction for Use: Pegasus Prime Virus Removal Filter Cartridges and Kleenpak Nova Filter Capsules with Pegasus Prime Virus Removal Filter Membrane". The steps are briefly described below.

1. Install the filter into the filter housing and orientate the filter housing as shown below.
2. Connect filter housing to a pre-filtered de-ionized (DI) water supply.
3. Ensure that the vent valve and downstream valves are OPEN and SLOWLY open the upstream valve to fill the filter housing with pre-filtered DI.
4. Ensure that all air is purged from the filter housing using the appropriate vent valve, then close the vent valve.
5. Slowly open the upstream valve to generate an inlet pressure of 2.1 barg (30 psig).
6. When the pressure is stable, carefully close the downstream valve to apply back-pressure.
7. Adjust the back-pressure until the inlet pressure and back-pressure are approximately 3.1 barg (45 psig) and 1.0 barg (15 psig) respectively.
8. Flush the filter with at least 30 L of water per 254 mm (10 in.) element (approximately 4-6 minutes) adjusting upstream and downstream valves to maintain the inlet and outlet pressure.
9. After flushing open the back-pressure valve and wait for the outlet pressure to decay to ~0 mbar (0 psig).
10. Slowly close the upstream valve until the inlet pressure reads 0 mbar (0 psig).
11. Drain the excess fluid from the upstream side of the filter housing.

Figure 5

Filter orientation for wetting



c) Integrity Testing (Pre-Use)
Forward Flow integrity testing was performed on the water wetted filters using a Palltronic Flowstar integrity test instrument at a test pressure of 4.150 bar (60 psi) employing a test time of 10 minutes (600 sec).

d) Liquid Bacteriophage Challenge
A schematic representation of the bacteriophage challenge test equipment is shown in Figure 6. The filters were challenged with PP7 or PR772 bacteriophage in a carrier fluid at ambient temperature, containing 0.1% bovine serum albumin (BSA) in phosphate buffered saline (PBS). The bacteriophage spikes were adjusted to contain a final concentration of at least 1.0×10^7 plaque forming units (pfu)/mL for PP7 and 1.0×10^6 pfu/mL for PR772. Samples were taken from the spiked challenge fluid prior and after the challenge to confirm the actual phage challenge concentration for the respective challenge test and analyzed as described below under step 'h'. The test pressure was set at 2.1 bard (30 psid).

For 25.4 mm (1 in.) size filters and capsules, 50 mL filtrate samples were collected, respectively, after 0.126, 0.630 and 1.260 liters had passed through the test filter. For 127mm (5 in.) size filters, 50 mL filtrate samples were collected, respectively, after 0.614, 3.070 and 6.140 liters of challenge fluid had passed through the filter. Filtrate samples of 50 mL were collected, respectively, after 1.215, 6.075 and 12.15 liters of challenge fluid had passed through the test filter for 254 mm (10 in.) size filters and capsules. The filtrate samples were analyzed as described in section 'h'.

e) Chemical Sanitization
Filter cartridges were sanitized by soaking in 1% sodium hypochlorite for a minimum of 30 minutes and not exceeding 16 hours. It is important to note that the sanitization methods described in this step is not to be used in routine operation. The procedure was used to ensure decontamination for the laboratory operation post challenge testing.

f) Post Challenge/Sanitization Flushing
The 1% sodium hypochlorite solution was drained from the filter. The filter was installed into filter housing (where applicable) and flushed with 0.1 µm deionized water for at least 10 minutes at a differential pressure of 2.1 bard (30 psid) following the procedure described in section 'b'.

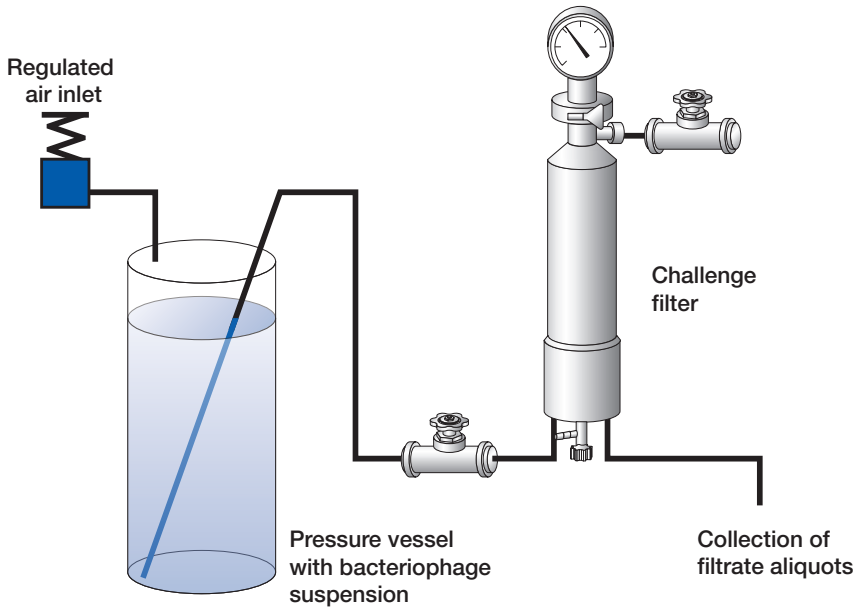
g) Integrity Testing (Post Challenge)
Forward Flow integrity testing was performed on the water wetted filters using a Palltronic Flowstar integrity test instrument at a test pressure of 4.150 bar (60 psi) employing a test time of 10 minutes (600 sec).

h) Bacteriophage Assay
All samples were assayed for bacteriophage content using the agar overlay method. For the input challenge fluid of PP7 one (1) mL samples of 10-fold serial dilutions were assayed. For the effluent samples of PP7 one (1) mL samples of 10-fold serial dilutions and also of the undiluted effluent were assayed. The plaque assay plates were incubated at 37 °C ± 2 °C overnight, plaques were counted and the viral (bacteriophage) removal efficiency or Titer Reduction (TR) of the filter was calculated as follows, using the lowest input challenge concentration determined and the titer determined for the 12th liter filtrate sample.

$$TR = \frac{\text{Concentration of challenge bacteriophage in influent (pfu/mL)}}{\text{Concentration of challenge bacteriophage in effluent (pfu/mL)}}$$

Figure 6

Bacteriophage challenge apparatus



3.4 Results

The data from the viral (bacteriophage) retention versus Forward Flow integrity test for part number NP1LUPRMP1S (25.4 mm, 1 in. size) is listed in Table 5. The data from the viral (bacteriophage) retention versus Forward Flow integrity for part number NP5LUPRMP1S (127mm, 5 in. size) is listed in Table 6. The data from the viral (bacteriophage) retention versus Forward Flow integrity test for part numbers AB1UPRM7PH4S / NP6LUPRMP1S (254 mm, 10 in. size) is listed in Table 7. The higher of the two Forward Flow values measured (pre-use and post-use) is presented and the data are arranged in order of increasing Forward Flow value.

Pegasus Prime virus removal filter, part number NP1LUPRMP1S (25.4 mm, 1 in. size) with Forward Flow values from 2.74 mL/min to 6.14 mL/min – when wet with water and tested at 4.150 barg (60 psi) – gave titer reductions for bacteriophage PP7 (sized at 25 nm) of > 4 log under the test conditions. The mean titer reduction for PP7 was 7.5 ± 0.5 log. The mean titer reduction for PR772 was 6.6 ± 0.3 log (results not shown).

Pegasus Prime virus removal filter, part number NP5LUPRMP1S (127 mm, 5 in. size) with Forward Flow values from 12.5 mL/min to 16.9 mL/min – when wet with water and tested at 4.150 barg (60 psi) – gave titer reductions for bacteriophage PP7 (sized at 25 nm) of > 4 log under the test conditions. The mean titer reduction for PP7 was 6.91±0.11 log. The mean titer reduction for PR772 was 7.04±0.65 log (results not shown).

Pegasus Prime virus removal filters, part numbers AB1UPRM7PH4S / NP6LUPRMP1S (254 mm, 10 in. size) with Forward Flow values from 23.4 mL/min to 52 mL/min – when wet with water and tested at 4.150 barg (60 psi) – gave titer reductions for bacteriophage PP7 (sized at 25 nm) of > 4 log under the test conditions (see section 3.2). The mean titer reduction was 7.4 ± 0.6 log. With PR772 challenge titer reduction of 6.7 ± 0.3 log was obtained for all test samples (results not shown).

Table 5

Forward Flow values and bacteriophage PP7 (sized at 25 nm) retention for Pegasus Prime virus removal filters, part number NP1LUPRMP1S (25.4mm, 1 in.).

Test Unit	Forward Flow* at 4.150 bard (60 psid) (mL/min)	Titer Reduction for Bacteriophage PP7 (~ 25 nm)
1	2.74	4.70×10^{7}
2	2.76	4.70×10^{7}
3	2.83	7.40×10^{7}
4	2.83	5.10×10^{7}
5	2.88	3.80×10^{7}
6	2.89	5.25×10^{5}
7	2.90	3.80×10^{7}
8	2.91	3.80×10^{7}
9	2.92	3.80×10^{7}
10	2.93	3.80×10^{7}
11	2.96	3.33×10^{7}
12	2.98	6.65×10^{7}
13	2.98	4.95×10^{7}
14	3.00	6.65×10^{7}
15	3.02	3.80×10^{7}
16	3.07	4.20×10^{7}
17	3.09	9.33×10^{6}
18	3.11	1.98×10^{7}
19	3.25	1.65×10^{7}
20	3.31	5.30×10^{7}
21	5.45	7.40×10^{7}
22	5.56	7.40×10^{7}
23	6.14	1.87×10^{4}
24	55.8	1.22×10^{3}

Table 6

Forward Flow values and bacteriophage PP7 (sized at 25 nm) retention for Pegasus Prime virus removal filters, part number NP5LUPRMP1S (127mm, 5 in.).

Test Unit	Forward Flow* at 4.150 bard (60 psid) (mL/min)	Titer Reduction for Bacteriophage PP7 (~ 25 nm)
1	12.5	3.63×10^{7}
2	13.2	2.82×10^{6}
3	13.3	4.02×10^{5}
4	13.4	4.40×10^{7}
5	13.4	2.30×10^{7}
6	13.4	4.00×10^{7}

Table 6 (*continued*)

Test Unit	Forward Flow* at 4.150 bard (60 psid) (mL/min)	Titer Reduction for Bacteriophage PP7 (~ 25 nm)
7	13.5	1.07×10^6
8	13.5	5.45×10^7
9	13.6	5.59×10^6
10	13.7	9.26×10^5
11	13.8	9.43×10^6
12	13.8	2.30×10^7
13	13.8	6.06×10^6
14	13.9	6.79×10^6
15	13.9	2.93×10^7
16	13.9	4.00×10^7
17	14.0	4.40×10^7
18	14.3	4.43×10^6
19	14.5	2.50×10^7
20	14.7	2.30×10^7
21	15.1	2.30×10^7
22	15.2	4.00×10^7
23	15.3	2.50×10^7
24	16.9	6.14×10^5

Table 7

Forward Flow values and bacteriophage PP7 (sized at 25 nm) retention for 254 mm (10 in.) Pegasus Prime virus removal filters, part numbers AB1UPRM7PH4S and NP6LUPRMP1S.

Test Unit	Forward Flow* at 4.150 bar (60 psi) (mL/min)	Titer Reduction for Bacteriophage PP7 (~ 25 nm)
1	23.4	$>1.12 \times 10^8$
2	24.7	$>1.85 \times 10^8$
3	25.8	8.45×10^6
4	26.5	2.47×10^7
5	26.7	$>1.26 \times 10^8$
6	26.9	$>1.07 \times 10^8$
7	27.0	9.70×10^5
8	27.0	1.77×10^7
9	27.0	5.60×10^7
10	27.1	$>1.41 \times 10^8$
11	27.2	9.30×10^7
12	27.4	$>6.10 \times 10^7$
13	27.4	2.45×10^7
14	27.4	1.15×10^8
15	27.5	2.45×10^7
16	27.6	9.55×10^7
17	27.6	1.33×10^7
18	27.8	4.07×10^7
19	27.8	$>3.70 \times 10^7$
20	27.8	3.00×10^7

Table 7 (*continued*)

Test Unit	Forward Flow* at 4.150 bar (60 psi) (mL/min)	Titer Reduction for Bacteriophage PP7 (~ 25 nm)
21	27.9	6.38×10^{6}
22	27.9	$>7.90 \times 10^{7}$
23	28.1	$>2.45 \times 10^{7}$
24	28.1	$>3.70 \times 10^{7}$
25	28.1	$>3.70 \times 10^{7}$
26	28.2	1.68×10^{7}
27	28.2	7.20×10^{6}
28	28.3	3.72×10^{7}
29	28.3	3.82×10^{5}
30	28.4	1.74×10^{7}
31	28.4	$>9.30 \times 10^{7}$
32	28.5	$>1.15 \times 10^{8}$
33	28.7	9.25×10^{7}
34	28.8	$>1.01 \times 10^{8}$
35	28.9	$>7.90 \times 10^{7}$
36	28.9	1.36×10^{7}
37	29.1	7.69×10^{6}
38	29.2	1.53×10^{7}
39	29.3	1.60×10^{7}
40	29.3	1.42×10^{7}
41	29.5	$>7.05 \times 10^{7}$
42	29.5	$>3.00 \times 10^{7}$
43	29.6	2.45×10^{7}
44	29.6	$>6.10 \times 10^{7}$
45	29.8	2.27×10^{6}
46	30.1	1.12×10^{8}
47	30.1	1.15×10^{7}
48	30.2	7.90×10^{7}
49	30.3	7.05×10^{7}
50	30.3	1.06×10^{7}
51	30.5	$>1.26 \times 10^{8}$
52	31.3	$>9.55 \times 10^{7}$
53	31.4	1.86×10^{7}
54	31.5	7.90×10^{7}
55	31.7	5.00×10^{7}
56	32.3	$>1.26 \times 10^{8}$
57	32.9	3.93×10^{6}
58	34.9	$>2.35 \times 10^{7}$
59	35.2	4.15×10^{6}
60	37	6.17×10^{7}
61	52	2.89×10^{4}

** Forward Flow values wet with water, at 20 °C ± 5 °C.*

3.5 Conclusions

The Forward Flow integrity test performed at 4.150 bar (60 psi) in water demonstrates that all Pegasus Prime virus removal filters tested, which displayed Forward Flow values between 2.74 mL/min and 6.14 mL/min for part number NP1LUPRMP1S (25.4 mm, 1 in. size), between 12.5 mL/min to 16.9 mL/min for part number NP5LUPRMP1S (127 mm, 5 in. size), and between 23.4 mL/min and 52 mL/min for part numbers AB1UPRM7PH4S / NP6LUPRMP1S (254 mm, 10 in. size), were retentive for bacteriophage PP7 (sized at 25 nm) with a titer reduction of > 4 log under the test conditions.

A user Forward Flow limit of 3.6 mL/min at 4.150 bar (60 psi) test pressure when wetted with water was set for part number NP1LUPRMP1S. A user Forward Flow limit of 17.6 mL/min at 4.150 bar (60 psi) test pressure when wetted with water was set for part number NP5LUPRMP1S. A user Forward Flow limit of 35.0 mL/min at 4.150 bar (60 psi) test pressure when wetted with water was set for Pegasus filters part number AB1UPRM7PH4S and NP6LUPRMP1S. These limits were based on the above results of the bacteriophage challenge tests and additional considerations and parameters.

Table 8

Forward Flow integrity test parameters for Pegasus Prime virus removal filters, part numbers AB1UPRM7PH4S / NP6LUPRMP1S and NP1LUPRMP1S

	NP1LUPRMP1S	NP5LUPRMP1S	AB1UPRM7PH4S NP6LUPRMP1S
Test pressure	4.150 bar (60 psi)	4.150 bar (60 psi)	4.150 bar (60 psi)
Wetting liquid	Water	Water	Water
Temperature	20 °C ± 5 °C	20 °C ± 5 °C	20 °C ± 5 °C
Test gas	Air	Air	Air
Maximum allowable forward flow	3.6 mL/min	17.6 mL/min	35.0 mL/min

* *See section 2.2 for test procedure.*

** *During the test period the temperature of the filter assembly should not vary more than ±1 °C.*

4. Sanitization/Sterilization

4.1 Introduction

Cleanliness of virus filtration assembly is an important factor in a successful virus filtration strategy. Pegasus Prime virus removal filters are gamma irradiated and provided sterile. The gamma irradiation is carried out following guidance stated in ISO11137 and sterility assured following ISO11737 guidelines[6,7,11].

The ability to sanitize a filtration device at point of use, for instance after a pre-use filter integrity test, adds to the flexibility of filter assembly and the filtration process. It is important to demonstrate that a given sanitization method does not negatively affect the performance of the filter as a results of a chemical or physical damage to the membrane during the sanitization process.

4.2 Summary of Methods

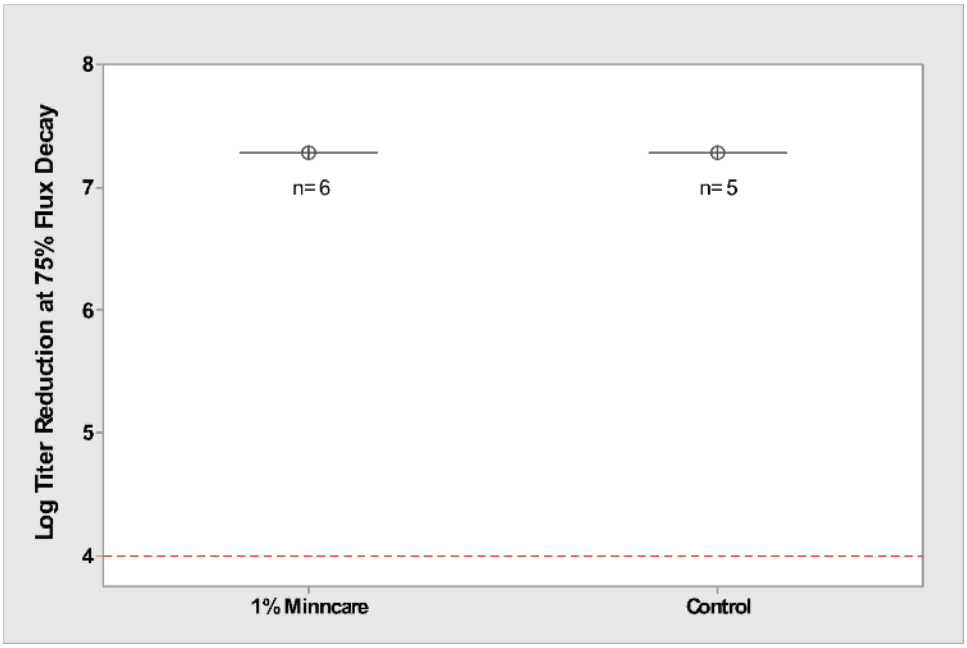
Six Pegasus Prime Microdisc capsules from two production batches were flushed with water followed by buffer (0.5 M sodium acetate pH 4). Filters then were sanitized using 1% solution of Minncare cold sterilant (4.5% peracetic acid, 22% hydrogen peroxide) by flushing for 1 hour at 0.69 bar (10 psi). At the end of the sanitization filters were flushed with buffer until all traces of Minncare solution were removed as indicated by the residual Minncare test strips and pH measurements. The buffer flux at 2.1 bard (30 psid) before and after sanitization was used for comparison. Mixed bacteriophage challenge test was then preformed in 0.0125% (0.125 g/L) human immunoglobulin G (IgG) solution as a challenge fluid using PP7 and PR772 bacteriophages. Filter capacity was determined by evaluating throughput at the point where a flux decay of 75% was observed when compared to initial flux.

4.3 Results

The mean buffer flux at 2.1 bard (30 psid) before and after sanitization was 446.9 and 462.3 L/m^2/hr. When the filter capacities of post sanitization filters were compared to controls by evaluating the throughput at 75% flux decay point, the capacities were found to be comparable. In both cases throughputs greater than 420 L/m^2 were obtained. The bacteriophage (PP7) removal studies also showed a >7 log titer reduction for both test groups (Figure 7).

Figure 7

Virus (bateriophpage) removal using Pegasus Prime Microdisc capsules sanitized with 1% Minncare solution.



4.4 Conclusion

The filter flux, capacity and virus removal data described above demonstrate that a 1% Minncare solution or a comparable alternative does not affect the performance of Pegasus Prime virus removal filters and therefore may be used for the chemical sanitization of these filters.

5. Water Extractables Test

5.1 Introduction

The objective of these series of tests was to quantify and characterize the material that can be extracted from Pegasus Prime filters using water. Pegasus Prime filter cartridges are constructed from modified hydrophilic polyethersulfone (PES) filter membrane, polyester support and drainage layers, and polypropylene molded components.

5.2 Summary of Methods

Six (6) Pegasus Prime filters from both part numbers NP1LUPRMP1S (mean effective filter area: 0.1 m^2, 1.1 ft^2) and NP5LUPRMP1S (mean effective filter area: 0.5m^2, 5.4 ft^2), as well as six (6) Pegasus Prime filters from both part numbers AB1UPRM7PH4S and NP6LUPRMP1S (mean effective filter area: 1 m^2, 10.7 ft^2) from three different batches, were used for testing. Filter manufacture and sampling considered possible variation in the filter manufacturing process.

Water Extraction for the Determination of Non-Volatile Residue (NVR)

Gamma irradiated Pegasus Prime filters were first flushed as per the methods for bacteriophage clearance testing in Section 3.3 (b). Extraction tests were then performed in a known volume of water at ambient temperature. The AB style filter cartridges were immersed in the extraction fluid in a clean measuring cylinder, as shown in Figure 8.

For 24 hours the filter was gently moved up and down. This movement created flow through the filter membrane as a result of the pressure head that was created each time the element was partially lifted out of the liquid. The extraction of the Kleenpak Nova style Pegasus Prime capsules was performed by recirculating water through the filter for the extraction time of 24 hours, to ensure that the product wetted parts of the capsule filter were extracted.

The filter cartridges and capsules were submitted to a second (consecutive) dynamic extraction cycle under the same extraction conditions as described above. Blank samples were treated the same way as appropriate for method and result controls.

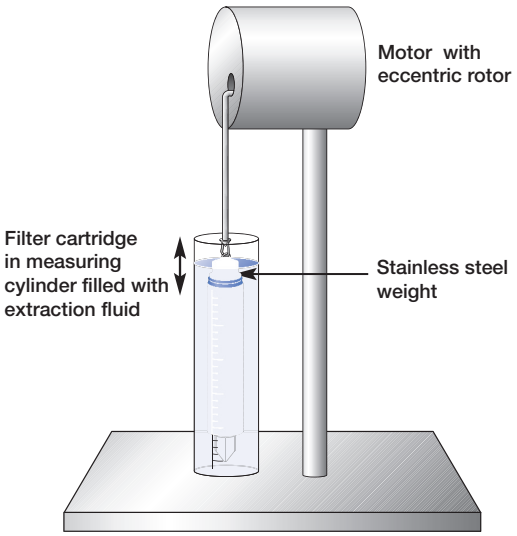
Following the extraction period, a measured volume of the extraction liquid was evaporated to dryness and the non-volatile residue (NVR) was determined gravimetrically. A correction was made to the NVR value to account for the total extraction volume used.

Analysis by Fourier Transform Infra-Red Spectroscopy (FTIR)

The dry NVR of some filter cartridges was analyzed by Fourier Transform Infra-Red Spectroscopy (FTIR) to provide information on the nature of its organic compounds. The analysis included first and the second (consecutive) extracts.

Figure 8

Filter extraction apparatus (cartridge only)



5.3 Results of NVR and FTIR

Table 9 shows the levels of aqueous extractable obtained from the six Pegasus Prime virus removal filters part numbers NP1LUPRMP1S that were tested. Table 10 shows the levels of aqueous extractable obtained from six Pegasus Prime virus removal filters part number NP5LUPRMP1S. Table 11 shows the levels of aqueous extractable obtained from the twelve Pegasus Prime virus removal filters part numbers AB1UPRM7PH4S and NP6LUPRMP1S that were tested. The mean total NVR for NP1LUPRMP1S was 20.9 mg per filter (Table 9), the mean total NVR for NP5LUPRMP1S was 86.8 mg per filter (Table 10) and the mean total NVR for AB1UPRM7PH4S / NP6LUPRMP1S was 151 mg per filter (Table 11).

Table 9

Non-volatile aqueous extractables of Pegasus Prime filters. The effective filtration area (EFA) is 0.1 m^2.

Test Unit	Filter Part Number	NVR (mg) 1st Extraction	NVR (mg) 2nd Extraction	Total NVR (mg/Cartridge)	Total NVR (mg/m^2 EFA)
1	NP1LUPRMP1S	13.4	6.0	19.4	194
2	NP1LUPRMP1S	12.2	5.5	17.7	177
3	NP1LUPRMP1S	12.0	4.8	16.8	168
4	NP1LUPRMP1S	13.6	6.1	19.7	197
5	NP1LUPRMP1S	16.8	6.7	23.5	235
6	NP1LUPRMP1S	20.4	7.8	28.2	282
	Mean ± StDev.	14.7 ± 3.3	6.1 ± 1.1	20.9 ± 4.3	208 ± 43

The typical infrared spectra of the aqueous NVR from Pegasus Prime filters (part number NP1LUPRMP1S) are shown in Figure 9 and Figure 10. Figure 9 shows the Infrared spectrum of the NVR from a first extraction of a filter cartridge. Figure 10 shows the infrared spectrum of the NVR from the second (consecutive) extraction of the same cartridge.

Table 10

Non-volatile aqueous extractables of Pegasus Prime filters. The effective filtration area (EFA) is 0.5 m^2.

Test Unit	Filter Part Number	NVR (mg) 1st Extraction	NVR (mg) 2nd Extraction	Total NVR (mg/Cartridge)	Total NVR (mg/m^2 EFA)
1	NP5LUPRMP1S	56.6	33.3	89.9	179.8
2	NP5LUPRMP1S	61.9	31.0	92.9	185.8
3	NP5LUPRMP1S	52.7	30.7	83.4	166.8
4	NP5LUPRMP1S	46.9	30.0	76.9	153.8
5	NP5LUPRMP1S	51.5	32.6	84.1	168.2
6	NP5LUPRMP1S	55.7	37.9	93.6	187.2
	Mean ± StDev.	54.2 ± 5.1	32.6 ± 2.9	86.8 ± 6.5	173.6 ± 13.0

The typical infrared spectra of the aqueous NVR from Pegasus Prime filters (part number NP5LUPRMP1S) are shown in Figure 11 and Figure 12. Figure 11 shows the Infrared spectrum of the NVR from a first extraction of a filter cartridge. Figure 12 shows the infrared spectrum of the NVR from the second (consecutive) extraction of the same cartridge.

Table 11

Non-volatile aqueous extractables of Pegasus Prime filters. The effective filtration area (EFA) is 1 m^2.

Test Unit	Filter Part Number	NVR (mg) 1st Extraction	NVR (mg) 2nd Extraction	Total NVR (mg/Cartridge)	Total NVR (mg/m^2 EFA)
1	AB1UPRM7PH4S	92.9	62.0	154.9	154.9
2	AB1UPRM7PH4S	100	64.9	164.9	164.9
3	AB1UPRM7PH4S	106.6	60.0	166.6	166.6
4	AB1UPRM7PH4S	95.3	57.4	152.7	152.7
5	AB1UPRM7PH4S	104.6	68.3	172.9	172.9
6	AB1UPRM7PH4S	92.1	62.9	155.0	155.0
7	NP6LUPRMP1S	70.0	67.8	137.8	137.8
8	NP6LUPRMP1S	63.6	59.7	123.3	123.3
9	NP6LUPRMP1S	85.5	56.7	142.2	142.2
10	NP6LUPRMP1S	89.2	59.6	148.8	148.8
11	NP6LUPRMP1S	106.9	–	–	–
12	NP6LUPRMP1S	86.9	54.8	141.7	141.7
	Mean ± StDev.	91.1 ± 13.6	61.3 ± 4.4	151.0 ± 14.0	151.0 ± 14.4

The typical infrared spectra of the aqueous NVR from Pegasus Prime filters (part numbers AB1UPRM7PH4S and NP6LUPRMP1S) are shown in Figure 13 and Figure 14. Figure 13 shows the Infrared spectrum of the NVR from a first extraction of a filter cartridge. Figure 14 shows the infrared spectrum of the NVR from the second (consecutive) extraction of the same cartridge.

Figure 9

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter (NP1LUPRMP1S) cartridges from the first extraction

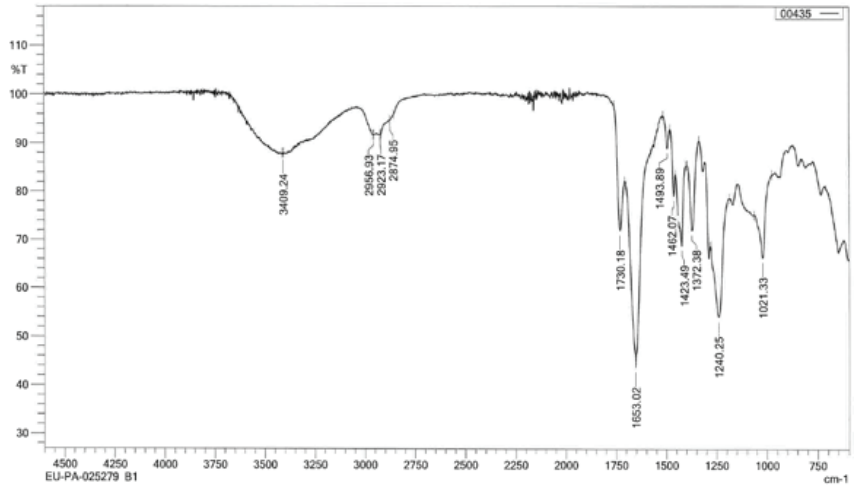


Figure 10

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter (NP1LUPRMP1S) cartridges from the second extraction

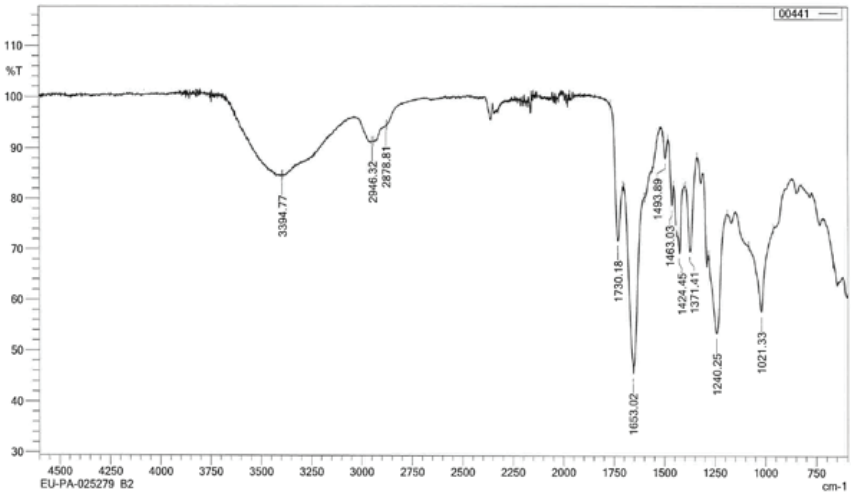


Figure 11

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter (NP5LUPRMP1S) cartridges from the second extraction

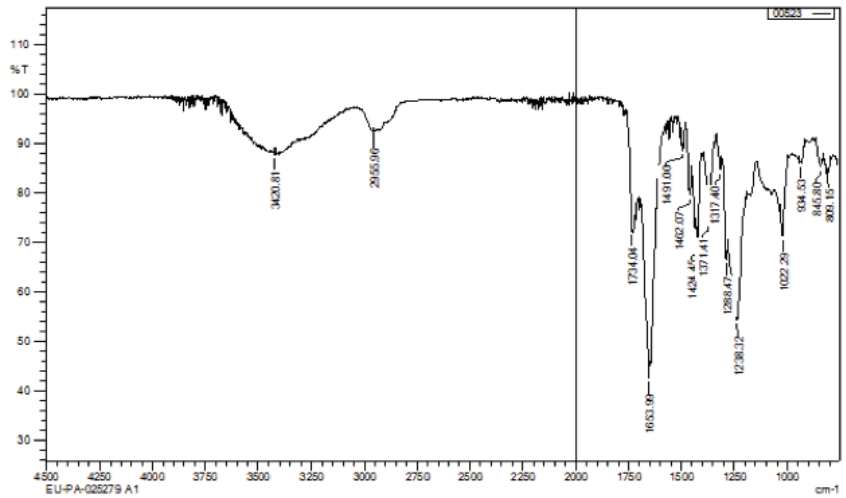


Figure 12

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter (NP5LUPRMP1S) cartridges from the second extraction

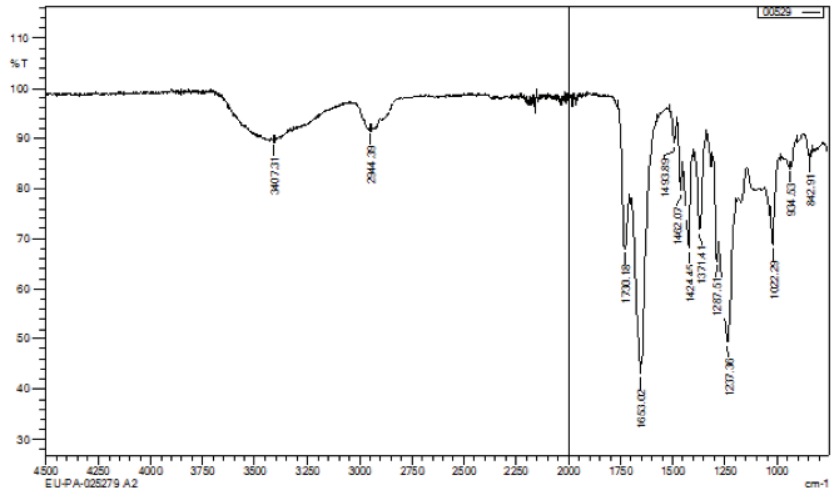


Figure 13

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter cartridges (AB1UPRM7PH4S) from the first extraction

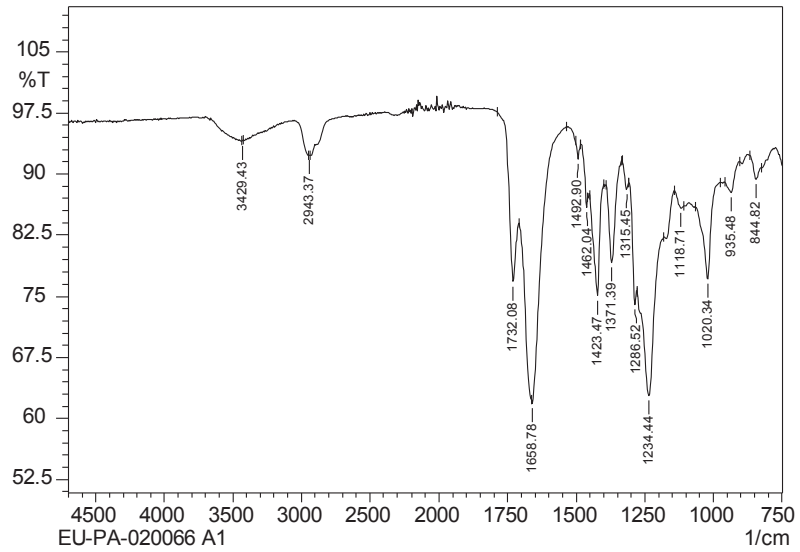
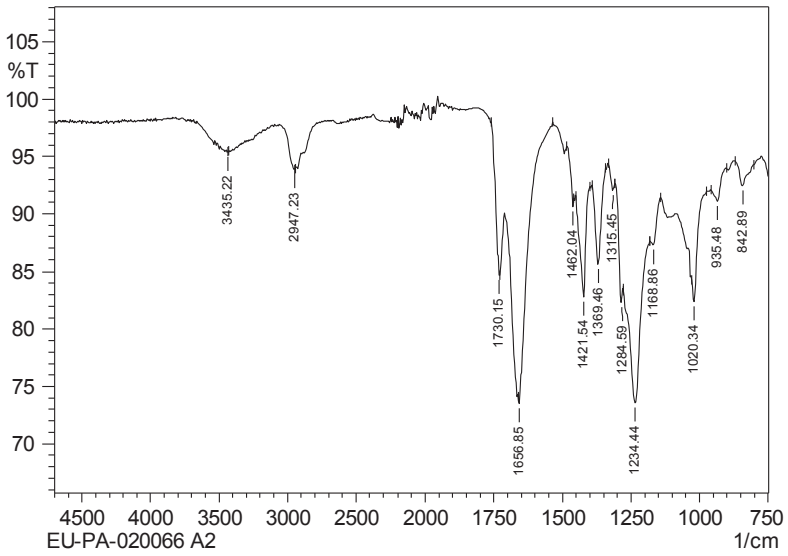


Figure 14

Typical infra-red spectrum of the aqueous NVR from Pegasus Prime virus removal filter cartridges (AB1UPRM7PH4S) from the second extraction



5.4 Conclusions

The typical amount of non-volatile residues (NVR) extracted from Pegasus Prime virus removal filers has been determined using water as the extraction fluid.

For the 25.4 mm (1 in.) filters tested (part number NP1LUPRMP1S), the aqueous extractable values ranged from 12.0 mg to 20.4 mg in the first extraction (mean ± standard deviation: 14.7 ± 3.3 mg) and from 4.8 mg to 7.8 mg in the second (consecutive) extraction (mean ± standard deviation: 6.1 ± 1.1 mg). The total NVR value per cartridge was between 16.8 and 28.2 mg (mean ± standard deviation: 20.9 ± 4.3 mg) and per unit area between 168 and 282 mg/m^2 (mean ± standard deviation: 208 ± 43 mg/m^2).

For the 127 mm (5 in.) filters tested (part number NP5LUPRMP1S), the aqueous extractable values ranged from 46.9 mg to 61.9 mg in the first extraction (mean ± standard deviation: 54.2 ± 5.1 mg) and from 30.0 mg to 37.9 mg in the second (consecutive) extraction (mean ± standard deviation: 32.6 ± 2.9 mg). The total NVR value per cartridge was between 76.9 and 93.6 mg (mean ± standard deviation: 86.8 ± 6.5 mg) and per unit area between 153.8 and 187.2 mg/m^2 (mean ± standard deviation: 173.6 ± 13.0 mg/m^2).

For the 254 mm (10 in.) filters tested (part numbers AB1UPRM7PH4S and NP6LUPRMP1S), the aqueous extractable values ranged from 63.6 mg to 106.9 mg in the first extraction (mean ± standard deviation: 91.1 ± 13.6 mg) and from 54.8 mg to 68.3 mg in the second (consecutive) extraction (mean ± standard deviation: 61.3 ± 4.4 mg). The total NVR value per cartridge as well as per 1 m^2 of effective filtration area was between 123.3 mg and 166.6 mg (mean ± standard deviation: 151.0 ± 14.4 mg).

The FTIR spectra of all extracts indicate the presence of compounds typical for the materials of construction. These are the PVP-PVA co-polymer used to render the membrane hydrophilic and polyester compounds from the non-woven support and drainage layers. Water ‘extractables’ of polypropylene hardware components are extremely low and were therefore not detected in this test. Strong peaks typical for compounds from the polyethersulfone membrane were also not detected.

Actual service will impose different conditions, such as different steaming conditions, exposure times, temperature, liquid type, etc. Evaluation under process conditions is therefore also recommended.

6. Biological Reactivity Tests on the Materials of Construction

6.1 Introduction

The aim of this study was to evaluate the biological suitability of the materials of construction of Pegasus Prime filter cartridges in AB-style. The materials of construction of the filters are as follows:

Table 12

Material of construction for Pegasus Prime virus removal filters with part numbers AB1UPRM7PH4S / NP6LUPRMP1S and NP1LUPRMP1S

Membrane	Hydrophilic modified polyethersulfone
Membrane support and drainage layers	Polyester
Core and end caps	Polypropylene
Adapter	Polypropylene with internal reinforcing ring
Filter cage	Polypropylene with titanium dioxide
O-rings	Silicone elastomer for 'H4' option

6.2 Summary of Methods

The tests on the respective material of construction were performed in accordance with the USP <88> Biological Reactivity Tests (*in vivo*) for Class VI Plastics (121 °C) as described in the current United States Pharmacopeia (USP).[9]

The testing procedures described in the United States Pharmacopeia include:

- Injection of extracts of plastic materials
- Implantation of the solid material into animal tissue

The four extracting media listed in the United States Pharmacopeia simulate parenteral solutions and body fluids. These include:

- Sodium Chloride Injection
- 1:20 Solution of Alcohol in Sodium Chloride Injection
- Polyethylene Glycol 400
- Vegetable Oil (sesame or cottonseed oil)

The United States Pharmacopeia <88> states that extracts may be prepared at one of three standard conditions: 50 °C (122 °F) for 72 hours, 70 °C (158 °F) for 24 hours or 121 °C (250 °F) for 1 hour. The most stringent condition not resulting in physical changes in the plastic is recommended, therefore the filter materials were extracted at 121 °C (250 °F) for 1 hour.

Acute Systemic Injection Tests

An Acute Systemic Injection Test was performed to evaluate the potential of a single injection of an extract to produce systemic toxicity. Sodium chloride injection and 1 in 20 solution of alcohol in sodium chloride Injection were injected intravenously. Vegetable oil extract and polyethylene glycol 400 extract were injected intraperitoneally.

Intracutaneous Tests

An Intracutaneous Test was performed to evaluate the potential of a single injection of an extract to produce tissue irritation. All four of the extracts listed above were used for these tests.

Implantation Tests

Implantation tests were also performed, in order to subject the materials of construction to the most stringent conditions included in the United States Pharmacopoeia. Each of the materials of the Pegasus Prime filter cartridges was implanted separately.

Under USP <87>, several procedures are defined[8]. An Elution Test was carried out to determine the biological reactivity of mammalian cell cultures following contact with extracts of the polymeric materials of construction.

6.3 Results

No unacceptable biological response was observed in any of the tests performed and therefore the materials used in Pegasus Prime filter cartridges passed all of the tests specified.

6.4 Conclusions

The materials used in Pegasus Prime filter modules met the requirements of the USP Biological Reactivity Tests (*in vivo*) for Class VI-121 °C plastics. The tests included the Systemic Injection Test, the Intracutaneous Test and the Implantation Test.

Copies of the test reports can be obtained by contacting Pall Corporation.

7. Structural Robustness of Membrane Pack

7.1 Introduction

Virus filters are generally operated under structurally demanding conditions, as often high differential pressure such as 3.0 bard (45 psid) over extended periods (hours or days) is used. Pegasus Prime virus removal filters are available as filter cartridges for use in stainless steel housings, or as disposable filter capsules with polypropylene housing. To demonstrate structural robustness of Pegasus Prime filters part number NP6LUPRMP1S featuring a polypropylene housing was used.

7.2 Summary of Methods

Pegasus Prime virus removal filters part number NP6LUPRMP1S were wetted as described in section 3.3 and the Forward Flow integrity test conducted to confirm filter integrity prior to use. The filters were then subjected to a forward air pressure of 5.2 bard (75 psid) at 25 ºC or 4.1 bard (60 psid) at 40 ºC for not less than 25 hours. Filters were also subjected to 1 bard (15 psid) at 25 ºC under reverse flow conditions for 25 hours. The Forward Flow integrity test was conducted with each filter after being exposed to this sustained pressure.

7.3 Results

All filters passed the Forward Flow integrity test after exposure to the robustness test conditions.

Table 13

Structural robustness evaluation conditions of Pegasus Prime virus removal filters and Forward Flow integrity test results after exposure to elevated pressure and/or temperature

Test Condition	Test Unit	Post-Stress Forward Flow Test[1]	Pass/Fail
Forward Pressure 4.1 bard (60 psid) at 40 ºC for 25 hrs.	1	21.6	Pass
	2	20.1	Pass
	3	19.5	Pass
	4	22.3	Pass
Forward Pressure 5.2 bard (75 psid) at 25 ºC for 25 hrs.	1	18.1	Pass
	2	20.1	Pass
	3	26.5	Pass
	4	19.1	Pass
Reverse Pressure 1 bard (15 psid) at 25 ºC for 25 hrs.	1	21.6	Pass
	2	24.4	Pass
	3	29.2	Pass
	4	26.2	Pass

[1]Forward Flow values wet with water, at 20 °C ± 5 °C, maximum allowable limit value 35.0 mL/min at 4.150 bar (60 psi)

7.4 Conclusions

The test filters were exposed to conditions that can be considered worst case for a typical virus filter operation with respect to differential pressure and temperature. All test filters passed Forward Flow integrity testing after exposure to the pressure and temperature challenge test conditions, thus demonstrating the high structural robustness of Pegasus Prime virus removal filters.

8. Chemical Conpatibility

Chemical compatibility of a filter should be evaluated to avoid damage to the integrity of the filter as well as alteration of the product being processed. Compatibility testing should include the entire device under actual processing conditions, in terms of fluid type, processing time and temperature. Pegasus Prime filters have utilized chemically defined material of construction and a robust manufacturing process.

Pall has extensive information on compatibility of the filter device and the material of construction under various physicochemical conditions. A process-specific confirmation of the compatibility of Pall Pegasus Prime filters with the conditions of use and fluid composition is recommended. Process and/or filter validation study aspects such as extractable, leachables and nonvolatile residues (NVR) may also be used to address this aspect.

9. Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) Statement

Pegasus Prime filter cartridges do not contain materials of construction that are considered TSE or BSE-risk materials according to current legislation and guidance in both Europe and the United States:

1. The European CPMP Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products. (EMA/410/01).
2. The U.S. Code of Federal Regulations, Title 21 of part 189.5, which defines specified risk materials obtained from cattle.

Pall has an established program with our raw material suppliers to assess whether animal derived products (e.g. bovine / ovine / caprine) are present in the materials employed for our pharmaceutical grade products. We have identified that polypropylene resins, used to manufacture plastic components of the referenced products, contain trace levels of additives, which may be derived from bovine tallow.

Tallow derivatives are not considered specified BSE risk materials according to the current revision of Title 21, of the U.S. Code of Federal Regulations, part 189.5. Furthermore, the CPMP's Note for guidance (EMA 410/01) gives specific consideration to tallow derivatives and states they are unlikely to be infectious due to the rigorous processing steps used (an example of which is trans-esterification, or hydrolysis, at not less than 200 °C (392 °F) under pressure for not less than 20 minutes). The raw materials we purchase have been processed under these conditions. Additionally, during the conversion of polypropylene resin into plastic components further high temperature steps are performed.

10. References

1. USP 1050 Viral Safety Evaluation of Biotechnology Products Derived From Cell Line of Human or Animal Origin.
2. Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Line of Human or Animal Origin.
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PALL Biotech

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

Visit us on the Web at www.pall.com/biotech
Contact us at www.pall.com/contact

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