



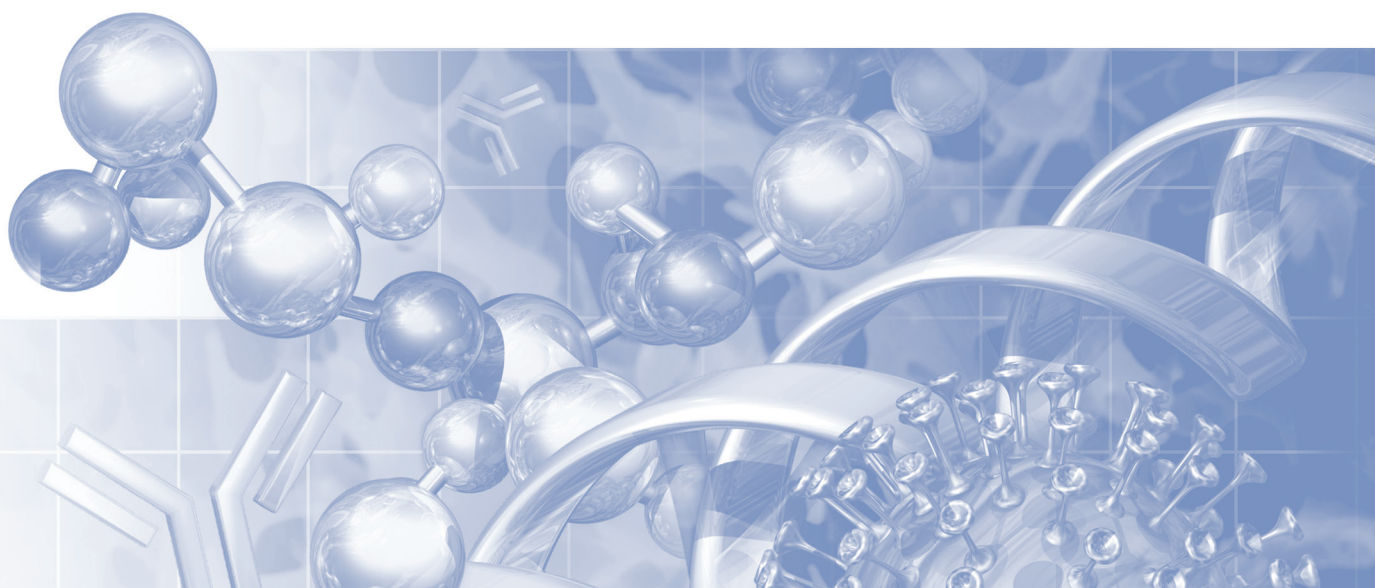
Life Sciences

## Validation Guide

USTR3178

# 0.2 $\mu\text{m}$ Acro<sup>®</sup> 50 Vent Filter Capsules

*Part Number 6074270*



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## 1. Overview

This document is designed to assist the filter user in meeting the validation requirements of regulatory authorities within the pharmaceutical industry for the use of 0.2 µm Acro 50 vent filter capsules, part number 6074270, henceforth referred to as filter capsules.

These filter capsules have been specifically designed for the sterilizing filtration of compatible gases in vent and gas supply applications.

They incorporate a proprietary single-layer (0.2 µm sterilizing grade) membrane made of inherently hydrophobic polytetrafluoroethylene (PTFE), which is supported by a polypropylene non-woven material, manufactured by Pall. All hardware components are manufactured from polypropylene.

The materials of construction of these capsules have met the requirements for biological reactivity, in vivo, specified in United States Pharmacopoeia (USP) <88> (for Class VI–121 °C plastics)<sup>(1)</sup> and a MEM Elution test (USP <87><sup>(2)</sup> or ISO 10993-5, 2009<sup>(3)</sup>). The materials of construction are listed for food contact usage per 21 CFR Parts 170-199<sup>(4)</sup>.

The tests that were performed to qualify the performance under a range of test conditions include the following:

- Bacteria retention and bubble point tests
- Air flow characterization
- Autoclaving
- Isopropanol liquid pressure
- Extractables in 50/50 (v/v) ethanol/water
- Biological reactivity tests on filter components

0.2 µm Acro 50 vent filter capsules, part number 6074270 may be used in conformance with current Good Manufacturing Practices (cGMP) per Title 21 of the U.S. Code of Federal Regulations (21 CFR Part 210)<sup>(5)</sup> and cGMP for Finished Pharmaceuticals (21 CFR Part 211)<sup>(6)</sup>.

These capsules are made from materials listed for food contact usage per 21 CFR Parts 170-199. They are manufactured in accordance with an ISO 9001<sup>(7)</sup> certified Quality Management System in a controlled environment that meets the air quality standards of an ISO Class 8 room<sup>(8)</sup> with respect to viable and non-viable particulate and positive pressure and are subject to stringent quality control including in-process controls and testing of the filter elements as follows

(1) 100% fabrication integrity

(2) Bacterial retention (*Brevundimonas diminuta*, ATCC 19146)

(3) Effluent cleanliness

(4) Oxidizable substances

(5) pH

(6) Endotoxins

This guide may be complemented by other documentation for 0.2 µm Acro 50 vent filter capsules, part number 6074270 namely

- Datasheet (Pall Document Number USD3202 Acro 50 Vent Filter Capsules)
- Certificate of Test for 0.2 µm Acro 50 vent filter capsules, part number 6074270 (included in each filter packaging; see section 7 for a sample certificate)

This package substantiates the product specification and quality control standards applied to 0.2 µm Acro 50 vent filter capsules, part number 6074270.

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 × 10<sup>5</sup> Pa

- 1 psi = 6.89476 x 10<sup>3</sup> Pa

Note: Air flow rates are quoted in standard liters per minute (sL/min). Conversions to standard cubic feet per minute (SCFM and standard cubic centimeter per minute (SCCM) are shown below

- 1 sL/min = 0.0353 SCFM
- 1 sL/min = 1000 SCCM

## 2. Summary of Validation/Qualification Tests

### 2.1 Microbial Retention Testing

0.2 µm Acro 50 vent filter capsules, part number 6074270 were tested for bacterial retention using *Brevundimonas diminuta* (American Type Culture Collection (ATCC) 19146), in accordance with the American Society for Testing and Materials (ASTM) Standard Test Method F838 (current revision)<sup>(9)</sup>, the US Federal Drug Administration (FDA) Guidelines on Sterile Products Produced by Aseptic Processing (1987)(10) and FDA Guidance for Industry: Sterile Drug Products Produced By Aseptic Processing - Current Good Manufacturing Practice (2004)<sup>(11)</sup>. These tests demonstrated that filter capsules, with a minimum Bubble Point of 990 mbar (16.0 psi) when wetted with 60/40 (v/v) isopropanol/water retain >10<sup>7</sup> colony forming units (cfu) of *Brevundimonas diminuta* per cm<sup>2</sup> of effective filtration area (EFA) in liquid (water) and produce a sterile effluent. This bubble point value is thus validated to be a suitable non-destructive integrity test limit for 0.2 µm Acro 50 vent filter capsules, part number 6074270.

**Table 1**

*Summary of microbial retention testing*

<b>Filter Part Number</b>	<b>Challenge Organism</b>	<b>Challenge Description</b>	<b>Microbial Recovery</b>	<b>Titer Reduction *</b>
6074270	<i>Brevundimonas diminuta</i> (ATCC19146)	Liquid challenge level >10 <sup>7</sup> cfu/cm <sup>2</sup> of effective filtration area (EFA)	No	>1.96 x 10 <sup>8</sup>

\* Calculated based on the minimum total challenge level for 6074270 filter capsules (19.6 cm<sup>2</sup> effective filtration area, >10<sup>7</sup> cfu/cm<sup>2</sup>)

### 2.2 Resistance to Autoclaving and Bacteria Retention Testing

0.2 µm Acro 50 vent filter capsules, part number 6074270, have been demonstrated to retain integrity and the bacterial retention capabilities of a sterilizing grade filter after repeated autoclaving cycles under the conditions listed below.

**Table 2**

*Summary of autoclave testing conditions*

Autoclaving	Liquid cycle
Temperature	125 °C
Cycle Time	30 minutes
Number of Cycles	5

### 2.3 Integrity (Bubble Point) Limit Values for Users

The user integrity (bubble point) limit value for 0.2 µm Acro 50 vent filter capsules, part number 6074270, has been defined as follows, based on correlation to bacteria retention testing:

**Table 3**

*Bubble point limit value for 60/40 (v/v) isopropanol/water*

Bubble Point Limit Value (Minimum Bubble Point Pressure)	1100 mbar (16.0 psi)
Wetting Liquid	60/40 (v/v) isopropanol/water
Temperature*	20 °C ± 5 °C *

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

The user integrity (bubble point) limit value for 0.2 µm Acro 50 vent filter capsules, part number 6074270, for the alternative wetting fluid 100% isopropanol has been defined as follows, based on surface tension ration and actual bubble point measurement with both fluids:

**Table 4**

*Bubble point limit value 100% isopropanol*

Bubble Point Limit Value (Minimum Bubble Point Pressure)	1000 mbar (14.5 psi)
Wetting Liquid	100% isopropanol
Temperature*	20 °C ± 5 °C *

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

#### 2.4 Air Flow

0.2 µm Acro 50 vent filter capsules, part number 6074270, were evaluated for air flow at a set upstream and differential pressure of 3 psi (0.2 bar). One hundred and fifty (150) test units from three (3) production batches (50 test units per batch) were tested. Airflow results are expressed as standard liters per minutes (sL/min). The lowest air flow measured was 21.2 sL/min. The highest air flow measured was 27.4 sL/min, while the average of three batches amounted to 24.6 sL/min, 24.5 sL/min and 25.7 sL/min. The results show that filter capsules consistently exceed the minimum air flow specification of 8.0 sL/min at 0.2 bar (3 psi) differential pressure. This data can be used for system sizing calculations.

#### 2.5 Isopropanol Liquid Pressure Test to Confirm Maximum Operating Pressure Conditions

0.2 µm Acro 50 vent filter capsules, part number 6074270, were subjected to liquid (isopropanol) pressure testing at a set upstream pressure of 60 psig (4.1 barg) and observed for leakage. Three hundred and seventy five (375) test units from three (3) production batches (125 test units per batch) were tested. No leakage or sudden increase in flow was observed. The test results demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270 are robust and withstand an operating and differential pressure of 4.1 bar (60 psi).

#### 2.6 Water Breakthrough Test to Confirm Hydrophobic Nature of the Filter Media and Resistance to Fluid Penetration

0.2 µm Acro 50 vent filter capsules, part number 6074270 from three (3) batches were subjected to a water breakthrough test at 30 psig (2.1 barg) upstream pressure. Three hundred and seventy five (375) capsules were tested, one hundred and twenty five (125) from each batch. No water breakthrough or leak was observed. The test results demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270, feature a hydrophobic filter media and withstand a water column pressure of 2.1 barg (30 psid) without water breakthrough or leak.

#### 2.7 Extractables (50/50 (v/v) Ethanol/Water at 40 °C)

Two (2) 0.2 µm Acro 50 vent filter capsules, part number 6074270 were connected in series, representing a total of 39.2 cm<sup>2</sup> of effective filtration area (EFA). These were autoclaved (125 °C, 1 hour) and extracted in 50/50 (v/v) ethanol/water at 40 °C for 24 hours. The non-volatile gravimetric residue (NVR) was determined. Two (2) filter device batches were evaluated following this method. Total non-volatile residue for the two filters in this extraction fluid was found to be less than 1 mg of NVR. Fourier Transform Infrared (FTIR) spectra could not be obtained due to the extremely low residue levels.

## 2.8 Biological Reactivity Tests on the Materials of Construction

The materials of construction of 0.2 µm Acro 50 vent filter capsules, part number 6074270, were tested and found to meet the requirements for biological reactivity, *in vivo*, under United States Pharmacopeia (USP) <88> (for Class VI – 121 °C plastics), and *in vitro* cytotoxicity testing. *In vivo* tests included the Systemic Toxicity Test, the Intracutaneous Test, and the Implantation Test. *In vitro* cytotoxicity was assessed determining the biological reactivity of mammalian cell cultures following contact with extracts of the polymeric materials of construction (Minimum Essential Medium (MEM) Elution testing). The method followed either USP <87><sup>(2)</sup> or ISO 10993-5, 2009: Biological Evaluation of Medical Devices – Part 5: Tests for *In Vitro* Cytotoxicity<sup>(3)</sup>.

## 3. Validation Testing

### 3.1 Bacterial Retention Testing and Bubble Point Testing

#### 3.1.1 Background

FDA's Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (2004)<sup>(11)</sup> states 'A sterilizing filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent'. The guideline also states 'the microorganism *Brevundimonas diminuta* (ATCC 19146), when properly grown, harvested and used, is a common challenge organism for 0.2 µm rated filters because of its small size (0.3 µm mean diameter)'.

In order for a filter to be defined as a sterilizing grade filter, the filter must meet the industry requirements of removing *B. diminuta* (ATCC 19146) at a minimum level of  $\geq 1.0 \times 10^7$  colony forming units (cfu) per cm<sup>2</sup> of effective filtration area (EFA). Although FDA's 'Guidance for Industry' document was updated in 2004, the minimum bacterial challenge level for a sterilizing grade filter, as defined in the previous version (1987)<sup>(10)</sup> remains the industry standard for performance characterization of a sterilizing grade filter.

0.2 µm Acro 50 vent filter capsules, part number 6074270 were tested for retention of *B. diminuta* (ATCC 19146) using bacterial challenge tests in accordance with ASTM Standard Test Method F838 (current method)<sup>(9)</sup>, the US Federal Drug Administration (FDA) Guidelines on Sterile Products Produced by Aseptic Processing (1987)<sup>(10)</sup> and the FDA's Guidance for Industry - Sterile Drug Products Produced By Aseptic Processing - Current Good Manufacturing Practice (September 2004)<sup>(11)</sup> using a minimum of  $1 \times 10^7$  cfu/cm<sup>2</sup> of effective filtration area.

The FDA guideline further states: 'After a filtration process is properly validated for a given product, process and filter, it is important to ensure that identical filters (e.g. of identical polymer construction and pore size rating) are used in production runs.... Integrity testing of the filter(s) can be performed prior to processing, and should be routinely performed post-use.... Forward Flow and bubble point tests, when appropriately employed, are two integrity tests that can be used. A production filters' integrity test specification should be consistent with the data generated during bacterial retention validation studies.'

The correlation between *B. diminuta* bacterial retention and a non-destructive integrity test is an essential aspect of the validation of sterilizing grade filters. The integrity test employed in this study was the bubble point test. This test was employed due to the small filter area (19.6 cm<sup>2</sup>) of the capsules, which hinders the use of the Forward Flow or Water Intrusion tests, as the gas and evaporative water flows during testing are extremely small and prevent a reliable user integrity test with this device type.

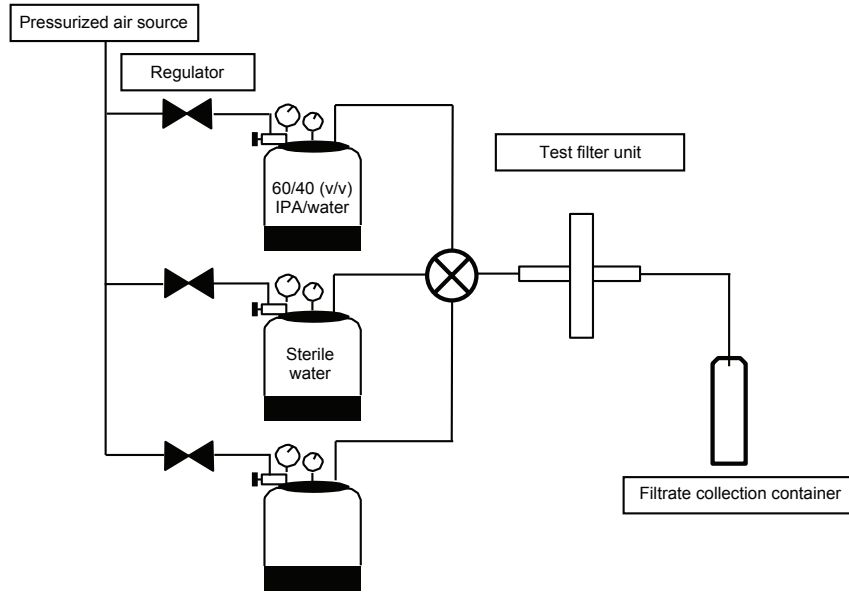
### 3.1.2 Summary of Methods

#### Bacterial challenge testing

0.2 µm Acro 50 vent filter capsules, part number 6074270 from three (3) different batches were subjected to bacterial challenge tests using an aqueous suspension of *B. diminuta* (ATCC 19146). Fifteen (15) filter capsules were tested, five (5) from each batch. The challenge test rig used is shown in Figure 1.

**Figure 1**

*Bacterial challenge testing set-up*



The *B. diminuta* suspension was prepared in accordance with standard test method ASTM F838-05<sup>(9)</sup> and diluted to achieve a cell count of  $>1 \times 10^7$  cfu/mL. Prior to challenge, the test filter units were flushed with a 60/40 (v/v) isopropanol/water mixture to wet out the hydrophobic membrane and allow passage of the aqueous challenge suspension. After flushing with isopropanol/water, the filters were flushed with water before the challenge suspension was passed through the test filter units.

A total volume of 10 mL containing  $>1 \times 10^7$  cfu/mL of *B. diminuta* was passed through each test filter to achieve a challenge level of  $>1.0 \times 10^7$  cfu/cm<sup>2</sup>. The challenge was carried out at 30 psig (2.1 bar) upstream pressure. The filtrate was collected in sterile containers. After the bacterial challenge test, the entire filter effluent was passed through a 0.2 µm rated recovery membrane. Following the challenge test, the recovery membrane was aseptically removed from the filter housing in a laminar flow cabinet and placed onto Tryptic Soy Agar (TSA) plates. All agar plates were incubated at  $30 \pm 5$  °C, for 48 hours.

After incubation, the recovery membranes were examined for growth, to determine whether or not bacteria had passed through the test filter during the challenge. The titer reduction (TR) ratio for each filter was determined as follows:

$$TR = \frac{\text{Total number of bacteria influent to the filter (cfu)}}{\text{Total number of colonies recorded on the downstream analysis disc (cfu)}}$$

When no colonies were detected downstream, the titer reduction was expressed as: greater than the total number of bacteria influent to the filter (e.g.  $>1 \times 10^8$ ).



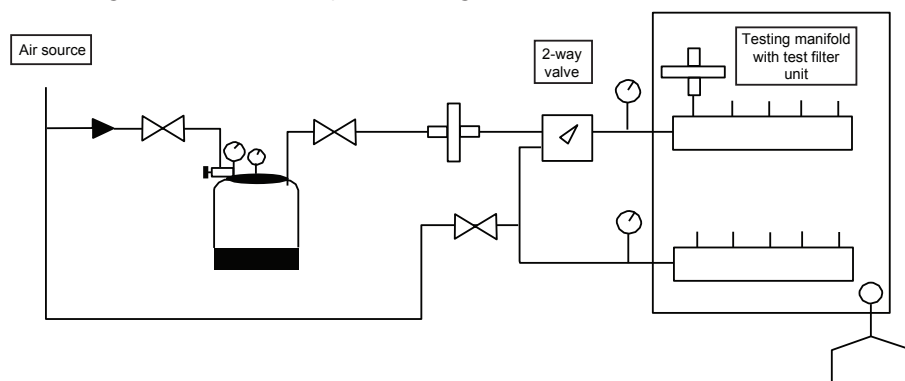
On completion of the challenge, the test filter units were flushed with 60/40 (v/v) isopropanol/water and bubble point tests were performed as per method described below.

### 3.1.3 Bubble Point Testing

The bubble point test setup that was used to determine the bubble point value of 0.2 µm Acro 50 vent filter capsules, part number 6074270 is shown in Figure 2. Air pressure was applied to the pressure vessel, to transfer the wetting fluid from the pressure vessel to the test manifold to fill the system with wetting fluid. A test filter unit was installed on the test manifold and wetting fluid was flushed through the test filter unit to achieve complete wetting (about 5 seconds). The air source was opened to test the unit via the 2-way valve. Excess wetting fluid was drained from the system via the drain valve on the manifold. Air pressure was slowly increased to fill the test filter unit until the wetting liquid was visually observed at the outlet. Pressure was gradually increased until a steady stream of air bubbles was observed at the test unit outlet. The pressure value observed on the pressure gauge at this point was recorded.

**Figure 2**

*Test configuration for bubble point testing*



### 3.1.4 Results

The bubble point test and *B. diminuta* retention results for 0.2 µm Acro 50 vent filter capsules, part number 6074270 are shown in Table 5. All test units tested gave a sterile effluent when challenged with  $>1.0 \times 10^7$  cfu/cm<sup>2</sup> of effective filtration area.

**Table 5**

*Brevundimonas diminuta* retention for 0.2 µm Acro 50 vent filter capsules, part number 6074270

Test Unit	Lot Number	Total Challenge per Test Filter (cfu)	Challenge per cm <sup>2</sup> of Effective Filtration (cfu)	Number of cfu in Effluent Area (cfu)	Titer Reduction*	Challenge Bubble Point Wet with 60/40 IPA/Water (psi) **
1	Lot 1 (21913434)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	28
2	Lot 1 (21913434)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	28
3	Lot 1 (21913434)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	30
4	Lot 1 (21913434)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	30
5	Lot 1 (21913434)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	30
6	Lot 2 (21913435)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	27
7	Lot 2 (21913435)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	29
8	Lot 2 (21913435)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	28
9	Lot 2 (21913435)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	29
10	Lot 2 (21913435)	2.29 x 10 <sup>10</sup>	1.17 x 10 <sup>8</sup>	0	>2.29 x 10 <sup>10</sup>	38
11	Lot 3 (21913436)	6.47 x 10 <sup>8</sup>	3.30 x 10 <sup>7</sup>	0	>6.47 x 10 <sup>8</sup>	22
12	Lot 3 (21913436)	6.47 x 10 <sup>8</sup>	3.30 x 10 <sup>7</sup>	0	>6.47 x 10 <sup>8</sup>	30
13	Lot 3 (21913436)	6.47 x 10 <sup>8</sup>	3.30 x 10 <sup>7</sup>	0	>6.47 x 10 <sup>8</sup>	28
14	Lot 3 (21913436)	6.47 x 10 <sup>8</sup>	3.30 x 10 <sup>7</sup>	0	>6.47 x 10 <sup>8</sup>	24
15	Lot 3 (21913436)	6.47 x 10 <sup>8</sup>	3.30 x 10 <sup>7</sup>	0	>6.47 x 10 <sup>8</sup>	30

\* Calculated based on total challenge per test filter unit

\*\* Wetted with 60/40 (v/v) isopropanol (IPA)/water at 20 °C + 5 °C

### 3.1.5 Conclusions

The results in this chapter demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270 are retentive for *B. diminuta* at a challenge level of >10<sup>7</sup> cfu/cm<sup>2</sup>. The lowest bubble point value of a test filter measured in this study was 22 psi (wetted with 60/40 (v/v) isopropanol/water). The bacteria retention performance fulfills the requirements of a sterilizing grade filter.

## 3.2 Autoclave Resistance and Bacteria Retention Testing

### 3.2.1 Introduction

Heat and steam exposure of filters during autoclave sterilization cycles creates a substantial stress and can alter the physical structure of some filters or cause them to lose integrity. These tests were performed to evaluate the ability of 0.2 µm Acro 50 vent filter capsules, part number 6074270, to withstand multiple autoclave sterilization cycles. The bacterial retention capabilities of the test filter units were assessed after exposure to the autoclave cycles.

### 3.2.2 Summary of Methods

Ten (10) capsules from three (3) filter device batches were wetted with 100% isopropanol and their integrity confirmed using the bubble point test method described in chapter 2. The filters were dried with pressurized air to remove the isopropanol and placed into an autoclave. An autoclave cycle of 125 °C, 30 min was run. The capsules were allowed to cool to ambient temperature, wetted again with 100% isopropanol and submitted to bubble point testing. This test sequence was repeated until five (5) autoclave cycles had been completed. After the last bubble point test, the capsules were air dried and submitted to bacteria challenge testing following the procedure described under section 2. Some capsules were bacteria challenge tested in the forward flow direction; some were tested in the reverse flow direction.

### 3.2.3 Results

Table 6 shows the bubble point test results of the ten (10) test filter units 0.2 µm Acro 50 vent filter capsules, part number 6074270 in the course of the autoclave resistance testing.

**Table 6**

*Bubble point values for 0.2 µm Acro 50 vent filter capsules, part number 6074270P after multiple autoclave cycles of 125 °C, 30 minutes*

Test Unit	Lot Number	Initial Bubble Point* (psi)	Post-Autoclave Bubble Point* Value (psi) After Cycle Number				
			1	2	3	4	5
1	Lot 1 (21913434)	25	22	22	21	20	21
2	Lot 1 (21913434)	25	23	23	22	22	22
3	Lot 1 (21913434)	24	22	22	21	21	21
4	Lot 2 (21913435)	25	22	21	21	21	21
5	Lot 2 (21913435)	24	22	21	21	21	21
6	Lot 2 (21913435)	25	23	22	21	21	21
7	Lot 3 (21913436)	24	23	21	22	22	21
8	Lot 3 (21913436)	24	23	22	21	21	21
9	Lot 3 (21913436)	22	22	22	22	21	21
10	Lot 3 (21913436)	23	22	22	21	22	22

\* Wetted with 100% isopropanol

Table 7 shows the bacteria retention test results of the ten (10) capsules after exposure to the five (5) autoclave cycles. All capsules delivered a sterile filtrate independent of the flow direction for challenge (forward or reverse).

**Table 7**

*Brevundimonas diminuta* retention after multiple autoclave cycles of 125 °C, 30 minutes

Test Unit #	Lot Number	Flow Direction for Challenge*	Total Challenge per Test Filter Unit (cfu)	Challenge per cm <sup>2</sup> of Effective Filtration Area (cfu)	Number of cfu in Effluent (cfu)	Titer Reduction**	Bubble Point After Challenge (psi) ***
1	Lot 1 (21913434)	Forward	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	25
2	Lot 1 (21913434)	Reverse	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	24
3	Lot 1 (21913434)	Forward	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	23
4	Lot 2 (21913435)	Reverse	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	26
5	Lot 2 (21913435)	Forward	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	26
6	Lot 2 (21913435)	Reverse	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	16
7	Lot 3 (21913436)	Forward	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	18
8	Lot 3 (21913436)	Reverse	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	18
9	Lot 3 (21913436)	Forward	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	16
10	Lot 3 (21913436)	Reverse	1.90 x 10 <sup>9</sup>	9.7 x 10 <sup>7</sup>	0	>1.90 x 10 <sup>9</sup>	20

\* Flow direction:

Forward testing: Test fluid enters device through port labelled INLET SIDE

Reverse testing: Test fluid enters device through Outlet Port

\*\* Titer reduction calculated based on total challenge per test filter unit

\*\*\* Wetted with 60/40 (v/v) isopropanol/water

### 3.2.4 Conclusions

The results in this chapter demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270 display resistance to multiple (5) autoclave cycles at a temperature of 125 °C. Capsules displayed bubble point values no less than 20 psi when wetted with 100% isopropanol after exposure to the autoclave cycles. All delivered sterile filtrate in bacteria (*B. diminuta*) challenge testing subsequent to the exposure to the autoclave cycles independent of the flow direction (forward or reverse). The lowest bubble point value of a test filter measured in this study was 16 psi (wetted with 60/40 (v/v) isopropanol/water). The filters were thus confirmed having maintained their sterilizing grade filter bacterial retention performance during multiple (5) autoclave cycles.

### 3.3 Integrity Test (Bubble Point) Limit Values for Users

#### 3.3.1 User Integrity Test (Bubble Point) Limit Value for 60/40 (v/v) Isopropanol/water

In the course of validation testing for 0.2 µm Acro 50 vent filter capsules, part number 6074270, two studies were performed that included bubble point testing as non-destructive test and bacteria challenge testing employing an aqueous suspension of *B. diminuta* (ATCC 19146). The methods and results of these studies are reported in chapter 3.1 (Bacterial Retention Testing and Bubble Point Testing) and 3.2 (Autoclave Resistance and Bacteria Retention Testing). The results demonstrate that integral capsules fully retain *B. diminuta* from aqueous suspension.

The integrity of the test filters was assessed with the bubble point non-destructive integrity test method and the filters wetted with 60/40 (v/v) isopropanol/water. The lowest bubble point value of a test filter that fully retained *B. diminuta* during bacteria retention testing in these studies was 16.0 psi wetted with 60/40 (v/v) isopropanol/water.

Based on these studies Pall defined the following bubble point limit value for filter users:

**Table 8**

*Bubble point limit value for 60/40 (v/v) isopropanol/water*

Bubble Point Limit Value (Minimum Bubble Point Pressure)	1100 mbar (16.0 psi)
Wetting Liquid	60/40 (v/v) isopropanol/water
Temperature*	20 °C ± 5 °C *

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

#### 3.3.2 User Integrity (Bubble Point) Limit Value for 100% Isopropanol

##### 3.3.2.1 Surface Tension Ratio – Literature Data

An alternative wetting fluid for 0.2 µm Acro 50 vent filter capsules, part number 6074270, is 100% isopropanol. When a filter is wetted with two different wetting fluids (wetting fluid A and wetting fluid B), the expected ratio of the bubble points measured with wetting fluid A and wetting fluid B is the surface tension ratio of the two wetting fluids<sup>(12,13)</sup>. Surface tension information for aqueous mixtures of isopropanol (2-propanol) in increasing concentrations by mass percent can be found in the CRC Handbook of Chemistry and Physics<sup>(14)</sup>. 60/40 (v/v) isopropanol/water translates to 54% by mass. The surface tension for this mixture and that of 100% isopropanol based on this literature reference is as follows:

**Table 9**

*Surface tension\* of 60/40 (v/v) isopropanol/water and 100% isopropanol*

60/40 (v/v) Isopropanol/Water	23.95 N/m
100% Isopropanol	21.22 N/m

\* At a temperature of 25 °C

Based on the surface tension ratio (0.8860), a bubble point value of 16.0 psi for 60/40 (v/v) isopropanol/water will correspond to a bubble point value of 14.2 psi for 100% isopropanol with the same filter type. This results in a user bubble point limit value of 1000 mbar (14.5 psi) based on Pall's rounding rules for user limit integrity test data.

### 3.3.2.2 *Ratio of Actually Measured Bubble Point Values*

Actual bubble point measurement studies with twenty four (24) 0.2 µm Acro 50 vent filter capsules, part number 6074270, wetted with both wetting liquids were performed to confirm that the calculated limit value reflects a worst-case approach when compared with actual measurements. The bubble point measurements were performed following the method described under chapter 3.1.2.

The results of the bubble point measurements are shown in detail in Table 11. The average bubble point ratio was 0.9023 and thus confirmed the usability of the following user bubble point limit value for 0.2 µm Acro 50 vent filter capsules, part number 6074270 wetted with 100% isopropanol.

**Table 10**

*Bubble point limit value for 100% isopropanol*

Bubble Point Limit Value (Minimum Bubble Point Pressure)	1000 mbar (14.5 psi)
Wetting Liquid	100% isopropanol
Temperature*	20 °C ± 5 °C *

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

**Table 11**

*Bubble point measurements with 100% isopropanol and 60/40 (v/v) isopropanol/water as wetting fluid*

Test Unit Number	Filter Serial Number	Bubble Point when Wetted with 100% IPA (psi)	Bubble Point when Wetted with 60/40 IPA/Water (psi)	Bubble Point Ratio
1	25362	23.0	25.0	0.9200
2	25373	25.0	27.0	0.9259
3	25378	22.0	24.0	0.9167
4	25380	23.0	26.0	0.8846
5	25383	23.0	27.0	0.8519
6	25385	25.0	27.0	0.9259
7	25392	25.0	27.0	0.9259
8	25399	23.0	27.0	0.8519
9	25400	23.0	25.5	0.9020
10	25401	23.0	25.0	0.9200
11	25403	24.0	26.5	0.9057
12	25404	22.0	24.0	0.9167
13	25413	23.0	25.0	0.9200
14	25429	23.0	27.0	0.8519

Table 11 (continued)

Test Unit Number	Filter Serial Number	Bubble Point when Wetted with 100% IPA (psi)	Bubble Point when Wetted with 60/40 IPA/Water (psi)	Bubble Point Ratio
15	25439	22.0	26.0	0.8462
16	25441	23.0	25.0	0.9200
17	25450	24.0	27.0	0.8889
18	25456	25.0	27.0	0.9259
19	25484	16.0	18.0	0.8889
20	25486	23.0	26.0	0.8846
21	25491	23.0	25.0	0.9200
22	25493	24.0	27.0	0.8889
23	25494	23.0	25.0	0.9200
24	25519	24.0	26.0	0.9231
	Min =	16.00	18.00	0.8846
	Max =	25.00	27.00	0.9259
	Avg =	23.10	25.60	0.9023
	StDD =	1.77	1.91	0.0271

\* Lot number 2193435

### 3.4 Air Flow

#### 3.4.1 Introduction

The objective of these tests was to determine the air flow of 0.2 µm Acro 50 vent filter capsules, part number 6074270 at a set pressure differential.

#### 3.4.2 Summary of Methods

Thirty (30) capsules from three (3) batches were measured, resulting in a total of ninety (90) test units. The test filter units were installed in a suitable air flow test rig with the pressure regulator and flow measurement installation upstream of the test filter unit and its outlet open to atmosphere. Air flow was measured at a set upstream system pressure of 3 psig (0.2 barg), which also represented a differential pressure of 0.2 bar (3 psi) in this test installation. The measured gas flow is reported as standard liters per minute (sL/min).

#### 3.4.3 Results

The results of the air flow tests are shown in Table 12. The lowest air flow measured was 21.2 sL/min. The highest air flow measured was 27.4 sL/min, while the average of three batches amounted to 24.6 sL/min, 24.5 sL/min and 25.7 sL/min.

Table 12

Air flow test results

Filter Lot	Number of Test Units	Minimum Flow (Standard L/Min)	Maximum Flow (Standard L/Min)	Average Flow (Standard L/Min)	Standard Deviation
Lot 1 (21913434)	50	23.2	25.7	24.6	0.54
Lot 2 (21913435)	50	23.3	25.5	24.5	0.34
Lot 3 (21913436)	50	21.2	27.4	25.7	1.21

### 3.4.4 Conclusions

The test results in this section confirm that 0.2 µm Acro 50 vent filter capsules, part number 6074270 consistently meet the minimum air flow of 8.0 sL/min at 0.2 barg (3 psid) differential pressure for this part number.

## 3.5 Isopropanol Liquid Pressure Test to Confirm Maximum Operating Pressure Conditions

### 3.5.1 Introduction

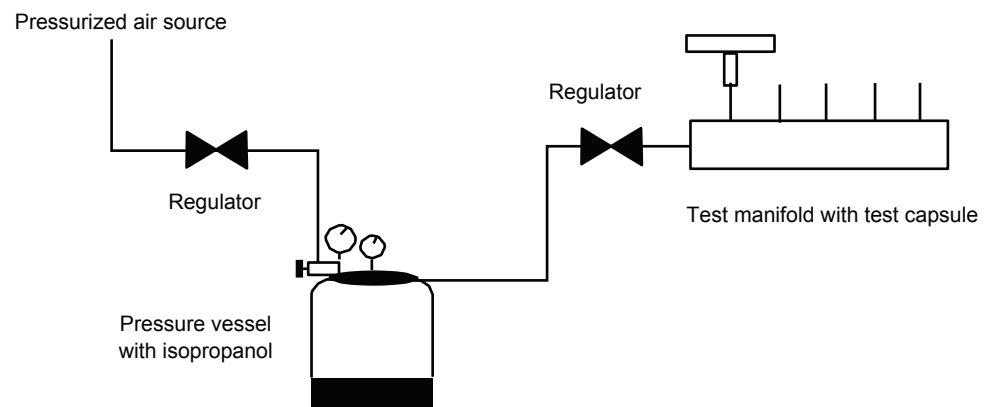
The mechanical robustness of a filter device is important for its safe and reliable operation and use, and drives the operating and differential pressure specification. 0.2 µm Acro 50 vent filter capsules, part number 6074270 were subjected to a liquid (isopropanol) pressure test at ambient temperature to assess their mechanical robustness and confirm the operating pressure specification of 4.1 barg (60 psig).

### 3.5.2 Summary of Methods

Capsules from three (3) batches were subjected to a liquid (isopropanol) pressure test at 60 psig (4.1 barg) upstream pressure. Three hundred and seventy five (375) capsules were tested, one hundred and twenty five (125) from each batch. The test setup is shown in Figure 3. The pressure vessel was filled with isopropanol and the test filter unit installed on the test manifold. The pressure in the pressure vessel was set to 60 psig (4.1 barg) and the valve to the test manifold slowly opened until 60 psid (4.1 barg) were reached at the test unit. Isopropanol was flushed through the test unit and the unit observed for any leaks and sudden flow increase while the pressure of 60 psid (4.1 barg) was maintained. After testing the flow valve was closed and the system depressurized.

**Figure 3**

*Test setup for isopropanol liquid pressure test*



### 3.5.3 Results

The results of the liquid pressure test carried out at 60 psig (4.1 barg) are shown in Table 13.

**Table 13**

*Liquid pressure test results*

<u>Filter Lot</u>	<u>Number of Test Units</u>	<u>Leak Observed</u>	<u>Test Result</u>
Lot 1 (21913434)	125	No	Pass
Lot 2 (21913435)	125	No	Pass
Lot 3 (21913436)	125	No	Pass



### 3.5.4 Conclusions

The results of the liquid pressure test demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270 are mechanically robust and withstand an operating and differential pressure of 4.1 barg (60 psig) without leak and membrane rupture.

## 3.6 Water Breakthrough

### 3.6.1 Introduction

In some applications the resistance to fluid penetration is a relevant feature of a vent filter. 0.2 µm Acro 50 vent filter capsules, part number 6074270 contain an inherently hydrophobic PTFE membrane that is able to repel water and other fluids with higher surface tension and withstand the intrusion and breakthrough of a liquid phase for such fluids. A water breakthrough test confirms the hydrophobic nature of the filter media. It can also serve as a structural integrity test, confirming the correct seal of the filter media and absence of gross leaks.

### 3.6.2 Summary of Methods

Capsules from three (3) batches were subjected to a water breakthrough test at 30 psig (2.1 barg) upstream pressure. Three hundred and seventy five (375) capsules were tested, one hundred and twenty five (125) from each batch.

Test procedure for water breakthrough testing:

1. A pressure vessel was filled with a solution consisting of 0.6% colored dye in filtered water. The dye serves to increase the optical contrast during visual assessment.
2. Using a regulated pressurized air source, pressure was introduced to force the dyed water to the inlet of the test unit. Visual checks ensured that the water phase reached the filter media surface.
3. The pressure was slowly increased to reach 30 psig (2.1 barg) and held for at least 15 seconds.
4. The test units were visually inspected for water penetration through the filter media and for leaks.
5. Absence of water penetration and leaks were considered a “pass”.

### 3.6.3 Results

The results of the water breakthrough tests carried out at 30 psig (2.1 barg) are shown in Table 14.

**Table 14**

*Water breakthrough test results*

<u>Filter Lot</u>	<u>Number of Test Units</u>	<u>Water Breakthrough or Leak Observed at 30 psid (2.1 barg)</u>	<u>Test Result</u>
Lot 1 (21913434)	125	No	Pass
Lot 2 (21913435)	125	No	Pass
Lot 3 (21913436)	125	No	Pass

### 3.6.4 Conclusions

The results of the water breakthrough test demonstrate that 0.2 µm Acro 50 vent filter capsules, part number 6074270 are able to withstand a water column pressure of 2.1 barg (30 psid) without breakthrough of the liquid phase and without leaking.

## 3.7 Extractables

### 3.7.1 Introduction

The objective of these series of tests was to quantify the material that can be extracted from 0.2 µm Acro 50 vent filter capsules, part number 6074270 under challenging extraction conditions. The conditions chosen were above ambient (extraction temperature of 40 °C) with a non-aqueous extraction fluid (50/50 (v/v) ethanol/water) and for a prolonged extraction duration (24 hours). To maximize the amount of extractables and mimic the actual conditions of use, the test filter units were autoclaved at 125 °C for 1 hour prior to extraction. These aggressive extraction conditions aim to present worst-case conditions for extractables release and thus allow users to assess the maximum amount of extractables released by these filters into their drug product.

### 3.7.2 Summary of Methods

Capsules were autoclaved at 125 °C for 1 hour. For each extraction, two capsules were connected in series using PTFE-lined tubing and filled with 50/50 (v/v) ethanol/water by means of a syringe. The extraction took place for 24 hours at 40 °C. At the end of the extraction time, the extraction liquid in the filters was pushed out with fresh 50/50 (v/v) ethanol/water, the liquid collected and evaporated to dryness. The non-volatile residue (NVR) was determined gravimetrically. Fourier Transform Infrared (FTIR) spectra of the NVRs could not be prepared due to extremely low amount of residue.

### 3.7.3 Results

Table 9 shows the levels of the extractables obtained from two batches of capsules that were tested. The NVR values were below 1 mg (limit of detection) for the two filters extracted together.

**Table 15**

*Non-volatile residue (19.6 cm<sup>2</sup> effective filtration area per capsules) with 50/50 (v/v) ethanol/water as extraction fluid.*

<u>Filter Lot</u>	<u>Number of Test Units Extracted Together</u>	<u>Total NVR (mg/2 Test Filter Units)</u>
Lot 1 (21913435)	2	<1
Lot 2 (21913436)	2	<1

*\*Limit of Detection*

### 3.7.4 Conclusions

The level of extractables obtained from 0.2 µm Acro 50 vent filter capsules, part number 6074270, even under aggressive extraction conditions (after autoclaving at 125 °C for 1 hour, extraction with 50/50 (v/v) ethanol/water at 40 °C for 24 hours) was extremely low (<1 mg NVR).

While actual service will impose different conditions, the extractables conditions chosen will typically represent worst-case conditions for use of these capsules.

## 4. Biological Reactivity Tests on the Materials of Construction

### 4.1 Introduction

The aim of these studies was to evaluate the biological suitability of the materials of construction of 0.2 µm Acro 50 vent filter capsules, part number 6074270. The materials of construction of the filters are as follows:

**Table 16**

*Material of construction*

Membrane	Hydrophobic polytetrafluorethylene (PTFE) backed with a polypropylene non-woven support
Hardware Parts	Polypropylene

### 4.2 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).

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 for 72 hours, 70 °C for 24 hours or 121 °C 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 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 0.2 µm Acro 50 vent filter capsules, part number 6074270 was implanted separately.

*In vitro* cytotoxicity was assessed determining the biological reactivity of mammalian cell cultures following contact with extracts of the polymeric materials of construction (MEM Elution testing). The method followed either USP <87><sup>(2)</sup> or ISO 10993-5, 2009: Biological Evaluation of Medical Devices – Part 5: Tests for In Vitro Cytotoxicity<sup>(3)</sup>.

### 4.3 Results

All materials of construction used in the capsule passed all of the tests specified under USP <88> Biological Reactivity Tests (*in vivo*) for Class VI Plastics (121 °C)<sup>(1)</sup> and a MEM Elution test assessing cytotoxicity<sup>(2,3)</sup>.

### 4.4 Conclusions

The materials of construction used in 0.2 µm Acro 50 vent filter capsules, part number 6074270 meet the requirements of the USP Biological Reactivity Tests (*in vivo*) for Class VI-121 °C plastics<sup>(1)</sup> and a MEM Elution test<sup>(2,3)</sup> assessing cytotoxicity. The tests under USP Biological Reactivity Tests (*in vivo*) for Class VI-121 °C included the Systemic Injection Test, the Intracutaneous Test and the Implantation Test. The results demonstrate that the materials of construction of 0.2 µm Acro 50 vent filter capsules, part number 6074270 are biologically safe and fit for use in manufacturing of drug products under cGMP.

## 5. Transmissible Spongiform Encephalopathy

(TSE) / Bovine Spongiform Encephalopathy (BSE) Statement Conclusions

0.2 µm Acro 50 vent filter capsules, part number 6074270 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).
3. 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 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.

## 6. Shelf Life Statement

Pall Corporation does not assign specific expiration dates to non-sterile pharmaceutical grade filters. Given the stable nature of our filter materials of construction, we have not seen any deterioration of filter performance over time. However, in order to assist our biopharmaceutical customers who require a defined shelf life, we conservatively recommend usage within five years.

To achieve satisfactory performance, it is advised that the following storage conditions are maintained:

1. Store at a temperature of 0-30 °C in dry conditions.
2. Do not expose filters to direct sunlight, radiation or direct weather conditions.
3. Store filters in original shipping bag and boxing.
4. Exercise care during filter handling to avoid physical damage. Ensure shipping bag and any seals are intact prior to use. Plastics can be damaged if roughly handled, particularly at sub-zero temperatures. Thermal shock by quickly raising the temperature from sub-zero conditions should also be avoided.
5. Inspection and integrity testing is recommended prior to use.

## 7. Certificate of Test 0.2 µm Acro 50 Vent Filter Capsules, Part Number 6074270



### Certificate of Test

For Pharmaceutical-Grade Sterilizing Filters

We hereby certify that

Pall® : ACRO® 50 VENT FILTER

Rated: 0.2 µm

Part Number: 6074270

Lot Number: SAMPLE CERTIFICATE

was manufactured in a controlled environment. **These filters are not supplied sterile.**

#### Fabrication Integrity

Each filter in this lot successfully passed a bubble point integrity test as per internal manufacturing specifications. The bubble point test parameters have been validated for bacterial removal by correlation with a microbiological challenge test. Recommended test values for integrity testing of Pall filters as installed must be obtained from Pall.

#### Bacterial Retention

Finished product has been sampled and successfully tested for retention of *Brevundimonas diminuta* (ATCC 19146), using procedures described in Pall Validation Guides and ASTM Standard Test Method F838-15, in conformance with the applicable requirements of the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (September 2004).

#### Materials of Construction

Representative filter components have met the requirements for biological reactivity, *in vivo*, under USP <88> (for Class VI - 121°C plastics).

These filters also are made from materials listed in Title 21 of the U.S. Code of Federal Regulations (CFR) parts 170-199.

This product does not contain materials of construction that are considered specified TSE or BSE risk materials according to current legislation and guidelines (reference European CPMP EMA/410/01 and Title 21 of the U.S. Code of Federal Regulations (CFR), part 189.5).

#### Effluent Quality

Filter samples from this manufacturing lot underwent the following tests and the lot was released by Quality Control when it was verified that their respective criteria were met:

#### Cleanliness

Meets with adequate safety margin after flushing, current limits under USP <788> Particulate Matter in Injections, with effluent counts determined microscopically. Counts serve to document conformance with the requirements for a non-fiber-releasing filter per Title 21 of the U.S. Code of Federal Regulations (CFR) parts 211.72 and 210.3 (b)(6).

#### Oxidizable Substances

Meets the current USP requirements after flushing under Sterile Purified Water, as determined by a Potassium Permanganate test.

#### pH

Meets internal specifications after flushing, upstream versus downstream differential not to exceed +/- 0.5 pH units, when tested in accordance with USP <791> pH.

#### Endotoxins

Meets the current requirements under USP Water for Injection, 0.25 EU/ml, when an aliquot from a soak solution is tested using Limulus Amoebocyte Lysate (LAL) reagent in accordance with USP <85> Bacterial Endotoxins Test.

In addition to the above tests, this product met manufacturing inspection standards and requirements for full traceability. This product is manufactured under a Quality System certified to ISO 9001. Consider only unopened, undamaged packages for use. Further information is available by contacting Pall.

1/November/2016

Jose Cubero, Quality Manager, Pall Life Sciences Puerto Rico  
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CoT0104E rev 01

Date of Manufacture

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