



Acrodisc® 0.2 µm 25 mm Filter Capsules Part Number KM292HPL

Revision Number: 2.0
Date: January 7, 2022
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1 Overview

This document is designed to assist users in meeting the validation requirements of regulatory authorities within the pharmaceutical industry for the use of Acrodisc 0.2 µm 25 mm filter capsule with part number (p/n) KM292HPL, henceforth referred to as the capsule.

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

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

The materials of construction of these devices have met the requirements for biological activity, *In Vivo*, specified in United States Pharmacopoeia (USP) <88> Biological Reactivity Test, *In Vivo*, for Class VI - 121 °C ⁽¹⁾ and a Minimal Essential Medium (MEM) Elution Test (USP <87> Biological Reactivity Test, *In Vitro* ⁽²⁾ or International Organization for Standardization (ISO) 10993-5: 2009 *Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity* ⁽³⁾). The materials of construction are listed for food contact usage per the U.S **Code of Federal Regulations** (CFR) Title 21 Food and Drugs, Parts 170 to 199 (21 CFR Parts 170-199⁽⁴⁾).

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

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

The capsules may be used in conformance with current Good Manufacturing Practices (cGMP) per the CFR Title 21 Food and Drugs, Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; (21 CFR Part 210)⁽⁵⁾ and CFR Title 21 Food and Drugs, Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211) ⁽⁶⁾. The capsules are manufactured in accordance with an ISO 9001 *Quality management system* ⁽⁷⁾. The capsules are manufactured in a controlled environment that meets the air quality standards for an ISO Class 7 room ⁽⁸⁾ with respect to viable and nonviable particulate and positive pressure. They are subject to stringent quality control measures including in-process controls and testing of the capsules as follows:

- 100% fabrication integrity
- Bacterial retention using *Brevundimonas diminuta* (*B. diminuta*) (American Type Culture Collection (ATCC•) 19146)
- Effluent cleanliness
- Oxidizable substances
- pH
- Endotoxins

This guide may be complemented by other documentation for Acrodisc 0.2 µm 25 mm vent filter capsules, p/n KM292HPL, namely:

- Datasheet (USD 3574: Acrodisc 0.2 µm 25 mm Filter Capsules), found on pall.com.
- Certificate of Test (included in each filter packaging; see Section 7 showing a sample certificate)

This package substantiates the product specification and quality control standards for these capsules.

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):

$$1 \text{ bar} = 1 \times 10^5 \text{ Pa}$$

$$1 \text{ psi} = 6.89476 \times 10^3 \text{ Pa}$$

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

$$1 \text{ sL/min} = 0.0353 \text{ SCFM}$$

$$1 \text{ sL/min} = 1000 \text{ SCCM}$$

2 Summary of Validation/Qualification Tests

2.1 Microbial Retention Testing

Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, were tested for bacterial retention using *B. diminuta* (ATCC 19146) following procedures described in this validation guide and American Society for Testing and Materials Standard Test Method F838-15a⁽⁹⁾ (ASTM F838-15a) in accordance with applicable requirements in the US Federal Drug Administration (FDA) Guidance for Industry: Sterile Drug Products Produced By Aseptic Processing – Current Good Manufacturing Practice (2004)⁽¹⁰⁾ (FDA cGMP guidelines). These tests demonstrated that the capsules, with a minimum bubble point of 1000 mbar (14.5 psi) when wetted with 60/40 (v/v) isopropanol/water, retain > 10⁷ colony forming units (cfu) of *Brevundimonas diminuta* per cm² of effective filtration area (cfu/cm²) 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 these capsules.

Table 1

Summary of microbial retention testing

Filter Part Number	Challenge Organism	Challenge Description	Microbial Recovery	Titer Reduction*
KM292HPL	<i>Brevundimonas diminuta</i> (ATCC 19146)	Liquid challenge level > 10 ⁷ cfu/cm ² effective filtration area (EFA)	No	3.16 x 10 ⁷

*Calculated based on the actual total challenge level for KM292HPL filter capsules (2.8 cm² effective filtration area, >10⁷ cfu/cm²)

2.2 Resistance to Autoclaving

The capsules have been demonstrated to retain integrity and the bacterial retention capabilities of a sterilizing grade filter after repeated autoclaving cycles under the conditions listed in Table 2.

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 test (bubble point) limit for the capsules has been defined as shown in Table 3, based on correlation to bacterial retention testing.

Table 3

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

Bubble Point Limit	Wetting Liquid	Temperature
1000 mbar (14.5 psi)	60/40 (v/v) isopropanol/water	20 °C ± 5 °C*

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

The user integrity test (bubble point) limit for the alternative wetting fluid 100% isopropanol has been defined as shown in Table 4, based on surface tension ratio and actual bubble point measurement with both fluids.

Table 4

Bubble point limit for 100% isopropanol

Bubble Point Limit	Wetting Liquid	Temperature
900 mbar (13.0 psi)	100% isopropanol/water	20 °C ± 5 °C*

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

The user integrity test (bubble point) limit for the alternative wetting fluid 70/30 (v/v) isopropanol/water has been defined as shown in Table 5, based on surface tension ratio and actual bubble point measurement with both fluids.

Table 5

Bubble point limit for 70/30 (v/v) isopropanol/water

Bubble Point Limit	Wetting Liquid	Temperature
1000 mbar (14.5 psi)	70/30 (v/v) isopropanol/water	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

Capsules were evaluated for air flow at a set upstream and differential pressure of 0.2 bar (3 psi). Ninety (90) test units from three (3) production lots (30 test units per lot) were tested. Air flow results are expressed as standard liters per minute (sL/min). The lowest flow measured was 2 sL/min. The highest air flow measured was 4 sL/min, while the average for each of the three lots amounted to 3.2 sL/min, 3.1 sL/min and 2.7 sL/min. The results support a typical air flow of 3 sL/min at 0.2 bar (3 psi) differential pressure for use in sizing calculations.

2.5 Isopropanol Liquid Pressure Test to Confirm Maximum Operating Pressure Conditions

Capsules were subjected to liquid (isopropanol) pressure testing at a set upstream pressure of 2.1 barg (30 psig) and observed for leakage. Six hundred (600) test units from three (3) production lots with two hundred (200) test units from each lot (200 test units per lot) were tested. No leakage or sudden increase in flow was observed. A sample of fifteen (15) test units were also evaluated for filter integrity using bubble point testing and demonstrated values that exceed the minimum bubble point, thus passing this test. The test results demonstrate that the capsules are robust and withstand an operating and differential pressure of 2.1 bar (30 psi).

2.6 Water Breakthrough Test

Capsules were subjected to water breakthrough testing at an upstream pressure of 2.1 barg (30 psig). Three hundred and seventy-five (375) capsules with one hundred and twenty-five (125) capsules each from three production lots were tested. When no leakage was observed the pressure was slowly ramped up to 3.4 barg (50 psig). No leakage or water breakthrough was observed up to a test pressure of 3.4 barg (50 psig). The test results demonstrate that the capsules retain their hydrophobic property and do not allow water to break through up to a pressure of 2.1 bar (30 psi).

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

Five (5) capsules for each of three (3) production lots were connected in series, representing a total of 14 cm² of effective filtration area (EFA) per test set up. These were autoclaved (125 °C, 1 hour) and extracted twice in 50/50 (v/v) ethanol/water at 40 °C for 24 hours. The non-volatile gravimetric residue (NVR) was determined. Total NVR for the five capsules in this extraction fluid was found to be less < 1 mg with an average value of 0.6 mg/5 filter capsules.

2.8 Biological Reactivity Tests on the Materials of Construction

The materials of construction 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)⁽¹⁾, and *In Vitro* cytotoxicity testing. *In Vivo* tests include 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> or ISO 10993-5 Tests for *In Vitro* Cytotoxicity.

3 Validation Testing

3.1 Bacterial Retention Testing and Bubble Point Testing

3.1.1 Background

FDA cGMP guidelines state: “A sterilizing filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent”. The guidance also states: “The microorganism *B. 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)”.

The minimum bacterial challenge level of $\geq 1.0 \times 10^7$ colony forming units (cfu) per cm² of effective filtration area (EFA) is the industry standard for performance characterization of a sterilizing-grade filter (2004)⁽¹⁰⁾. While Acrodisc 0.2 µm 25 mm filter capsules were developed for microbial retention from gases, the test units in this study were tested to the more stringent requirements for a sterilizing-grade filter and microbial retention from liquids. Thus, the filters were tested for retention of *B. diminuta* (ATCC 19146) using bacterial challenge tests in accordance with ASTM F838-15a⁽⁹⁾ and in line with the applicable recommendations of the FDA cGMP guidelines⁽¹⁰⁾ using a minimum of 1×10^7 cfu/cm² of effective filtration area.

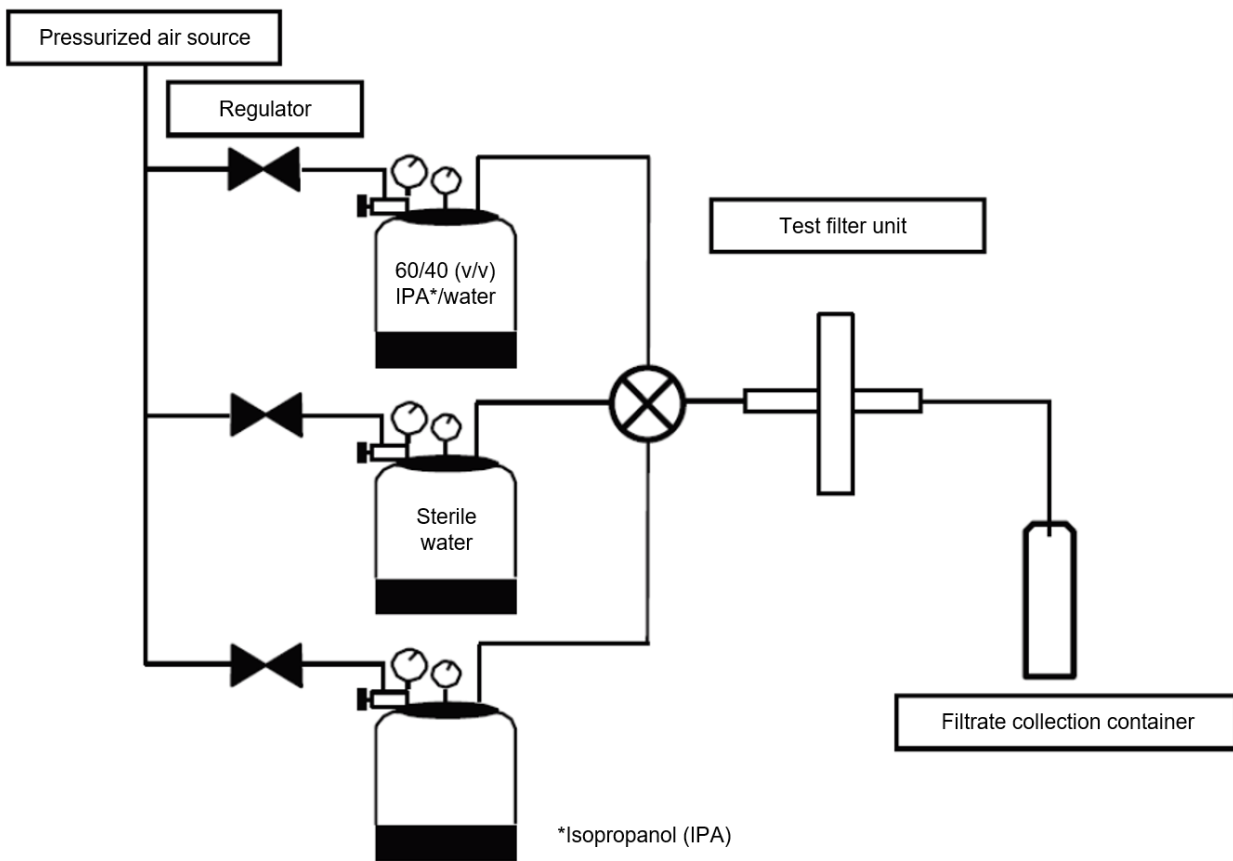
The correlation between *B. diminuta* bacterial retention and a non-destructive integrity test is an essential aspect of the validation of sterilizing grade filters. The integrity test employed in this study was the bubble point test. This test was employed due to the small filter area (2.8 cm²) of the 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 integrity test with this device type. This study is further supported by the extensive additional study performed with Acro[®] 50 0.2 µm vent filter p/n 6074270L⁽¹¹⁾ which uses an identical membrane that demonstrated the direct correlation between bubble point values and bacterial retention.

3.1.2 Summary of Methods

3.1.2.1 Bacterial Challenge Testing

Capsules from three (3) different production lots were subjected to bacterial challenge testing using an aqueous suspension of *B. diminuta* (ATCC 19146). Fifteen (15) filter devices were tested, five (5) from each batch. A schematic representation of 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 F838-15a⁽⁹⁾ 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 capsule to achieve a challenge level of $>1.0 \times 10^7$ cfu/cm². The challenge was carried out at 0.34 barg (5 psig) upstream pressure. The filtrate was collected in sterile containers. After the bacterial challenge test, the entire effluent was passed through a 0.2 μ m 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 ± 5 °C for 48 hours.

After incubation, the recovery membranes were examined for growth, to determine whether bacteria have passed through the test filter during the challenge. The titer reduction (TR) ratio for each filter was determined as follows:

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

When no colonies were detected downstream, the titer reduction was expressed as being greater than the total number of bacteria influents to the filter (e.g., $> 1 \times 10^7$).

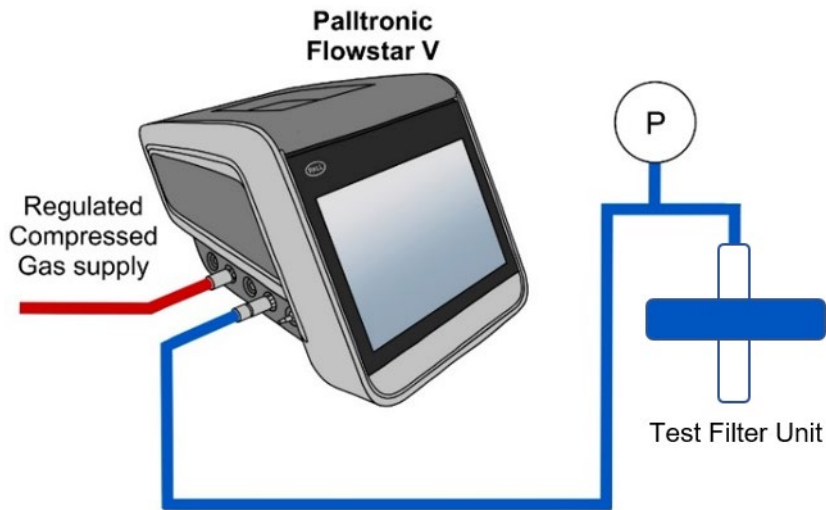
On completion of the challenge, the test filter units were flushed with 60/40 (v/v) isopropanol/water and bubble point tests were performed as per the method described in Section 3.1.3.

3.1.3 Bubble Point Integrity Testing

The bubble point test is based on measuring the gas flow across a completely wetted membrane at increasing gas pressure on the upstream side. Air pressure was applied to the pressure vessel to transfer the wetting fluid from the pressure vessel to the test manifold and to fill the system with wetting fluid. A test capsule was installed on the test manifold and wetting fluid was flushed through the capsule to achieve complete wetting for approximately 5 minutes at 0.7 barg (10.0 psig). The bubble point was measured using Palltronic® Flowstar filter integrity test instrument.

Figure 2

Test configuration for bubble point testing



3.1.4 Results

The data from the bacterial retention test versus the bubble point integrity test values is listed in Table 6.

Table 6

B. diminuta retention and bubble point measurement results for Acrodisc 0.2 µm 25 mm vent filter capsules

Test Unit	Lot Number	Total Challenge per Test Filter (cfu)	Challenge per cm ² of Effective Filtration Area (cfu/cm ²)	Number of cfu in Effluent	Titer Reduction*	Bubble Point (psi)**
1	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
2	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	20.31
3	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
4	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
5	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
6	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
7	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
8	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
9	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
10	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
11	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
12	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.03
13	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
14	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
15	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76

*Titer reduction 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 Acrodisc 0.2 µm 25 mm filter capsules are retentive for *B. diminuta* at a challenge level of > 10⁷ cfu/cm². The lowest bubble point value of a test filter measured in this study was 19.58 psi when wetted with 60/40 (v/v) isopropanol/water. The bacteria retention performance fulfils the requirements of a sterilizing-grade filter.

3.2 Autoclave Resistance and Bacterial Retention Testing

3.2.1 Introduction

Heat and steam exposure of filters during autoclave sterilization cycles create 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 Acrodisc 0.2 µm 25 mm filter capsule, p/n KM292HPL, to withstand one or multiple autoclave cycles. The bacterial retention capabilities of the test filter units were assessed after exposure to the autoclave cycles.

3.2.2 Summary of Methods

Test filters were subjected to an autoclave cycle of 125 °C for 30 mins. The autoclave cycle was liquid autoclave cycle. This test sequence was repeated until five (5) autoclave cycles had been completed. Test filter units were submitted to bacterial challenge testing following the procedure described under Section 3. Some test filter units were bacteria challenge tested in the forward flow direction; some were tested in the reverse flow direction.

3.2.3 Results

Table 7 shows the bubble point and bacterial challenge test results of the twelve (12) capsules subjected to the autoclave resistance testing.

Table 7

Bubble point and titer reduction values of Acrodisc 0.2 µm 25 mm filter capsules after five autoclave cycles of 125 °C, 30 minutes

Test Unit	Lot Number	Flow Direction for Challenge*	Total Challenge per Test Unit (cfu)	Challenge per cm ² of Effective Filtration Area (cfu)	Number of cfu in Effluent	Titer Reduction**	Bubble Point After Challenge (psi)***
1	FJ0031	Forward	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 3.55 x 10 ⁷	18.01
2	FJ0031	Forward	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 3.55 x 10 ⁷	19.15
3	FJ0031	Forward	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 3.55 x 10 ⁷	18.99
1	FJ0032	Forward	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 3.40 x 10 ⁷	18.85
2	FJ0032	Forward	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 3.40 x 10 ⁷	18.70
3	FJ0032	Forward	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 3.40 x 10 ⁷	18.70
4	FJ0032	Forward	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 3.40 x 10 ⁷	18.72
1	FJ0032	Reverse	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 3.35 x 10 ⁷	18.85
2	FJ0032	Reverse	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 3.35 x 10 ⁷	18.85
1	FJ0033	Reverse	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 3.35 x 10 ⁷	18.26
2	FJ0033	Reverse	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 3.35 x 10 ⁷	18.26
3	FJ0033	Reverse	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 3.35 x 10 ⁷	18.45

*Flow Direction:

- Forward testing: Test fluid enters device through inlet side
- Reverse testing: Test fluid enters device through outlet side

** 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 section demonstrate that Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, display resistance to five (5) autoclave cycles at a temperature of 125 °C and a duration of 30 minutes per cycle. All test units delivered sterile filtrate in bacterial challenge testing using *B. diminuta* as the test organism after exposure to the autoclave cycles, irrespective of the applied flow direction for the challenge (forward or reverse). The capsules were thus confirmed as having maintained their sterilizing-grade filter bacterial retention performance. The lowest bubble point value of a test filter measured in this study was 1.24 bar (18.01 psi) when wetted with 60/40 (V/V) isopropanol/water.

3.3 Integrity Test (Bubble Point) Limit Values for User

3.3.1 User Integrity Test (Bubble Point) Limit Values for 60/40 (v/v) Isopropanol/Water

Studies performed on Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, included bubble point testing as a non-destructive test and bacterial challenge testing employing an aqueous suspension of *B. diminuta* (ATCC 19146). The methods and results of these studies are reported in Sections 3.1 and 3.2.

The integrity of the test filters was assessed with the non-destructive integrity test method, the bubble point test after wetting with 60/40 (V/V) isopropanol/water. Table 8 lists the bacterial retention and bubble point test results from the above studies on a total of forty (40) filter capsules arranged by decreasing bubble point order. The lowest bubble point value of a test filter that fully retained *B. diminuta* during bacterial retention testing in these studies was 18.01 psi when wetted with 60/40 (v/v) isopropanol/water.

Table 8Bubble point results and *B. diminuta* retention for Acrodisc 0.2 µm 25 mm vent filter capsules

Test Unit*	Lot Number	Total Challenge per Test Filter (cfu)	Challenge per cm ² of Effective Filtration Area (cfu/cm ²)	Number of cfu in Effluent	Titer Reduction**	Bubble Point (psi)***
11	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
13	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
14	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
15	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.76
6	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
7	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
8	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
9	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
10	FJ0032	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	21.03
12	FJ0033	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	21.03
2	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	20.31
17	FJ0031	3.20 x 10 ⁷	1.14 x 10 ⁷	0	> 1.14 x 10 ⁷	20.31
20	FJ0031	3.25 x 10 ⁷	1.16 x 10 ⁷	0	> 1.16 x 10 ⁷	19.95
23	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	19.58
1	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
3	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
4	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
5	FJ0031	4.00 x 10 ⁷	1.43 x 10 ⁷	0	> 1.43 x 10 ⁷	19.58
16	FJ0031	3.20 x 10 ⁷	1.14 x 10 ⁷	0	> 1.14 x 10 ⁷	19.58
18	FJ0031	3.20 x 10 ⁷	1.14 x 10 ⁷	0	> 1.14 x 10 ⁷	19.58
26	FJ0031	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	19.48
21	FJ0031	3.25 x 10 ⁷	1.16 x 10 ⁷	0	> 1.16 x 10 ⁷	19.27
24	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	19.21
29	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	19.15
27	FJ0031	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	19.04
19	FJ0031	3.25 x 10 ⁷	1.16 x 10 ⁷	0	> 1.16 x 10 ⁷	19.02
30	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	18.99
22	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	18.88
31	FJ0032	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 1.21 x 10 ⁷	18.85
35	FJ0032	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 1.21 x 10 ⁷	18.85
36	FJ0032	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 1.20 x 10 ⁷	18.85
37	FJ0032	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 1.20 x 10 ⁷	18.85

Test Unit*	Lot Number	Total Challenge per Test Filter (cfu)	Challenge per cm ² of Effective Filtration Area (cfu/cm ²)	Number of cfu in Effluent	Titer Reduction**	Bubble Point (psi)***
34	FJ0032	3.40 x 10 ⁷	1.21 x 10 ⁷	0	>1.21 x 10 ⁷	18.72
32	FJ0032	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 1.21 x 10 ⁷	18.70
33	FJ0032	3.40 x 10 ⁷	1.21 x 10 ⁷	0	> 1.21 x 10 ⁷	18.70
40	FJ0033	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 1.20 x 10 ⁷	18.45
25	FJ0031	3.15 x 10 ⁷	1.13 x 10 ⁷	0	> 1.13 x 10 ⁷	18.29
38	FJ0033	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 1.20 x 10 ⁷	18.26
39	FJ0033	3.35 x 10 ⁷	1.20 x 10 ⁷	0	> 1.20 x 10 ⁷	18.26
28	FJ0031	3.55 x 10 ⁷	1.27 x 10 ⁷	0	> 1.27 x 10 ⁷	18.01

*Test filters are arranged in descending order of bubble point value. Filter with number > 13 have undergone > 1 autoclave cycle.

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

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

As indicated in Table 8 all filters with a bubble point value of 18.01 psi or greater produced a sterile filtrate in bacteria challenge testing. Earlier studies using identical membrane (Acro 50 vent filter p/n 6074270L) have demonstrated that filters with bubble point as low as 14.50 psi yielded sterile effluent (USTR 3374 Validation Guide Acro 50 0.2 µm Vent Filter)⁽¹²⁾. Based on the data reported in here and the supporting evidence from the qualification of Acro 50 capsule p/n 6074270L, the minimum bubble point for user integrity testing using 60/40 (v/v) isopropanol/water can be set to 1000 mbar (14.5 psi).

Table 9

Bubble point limit

Bubble Point Limit (Minimum Bubble Point Pressure)	Wetting Liquid	Temperature
1000 mbar (14.5 psi)	60/40 (v/v) isopropanol/water	20 °C ± 5 C*

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

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

3.2.2.1 Ratio of Measured Bubble Point Values

An alternative wetting fluid to perform a bubble point on Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, is 100% isopropanol. Actual bubble point measurement studies with twenty-four (24) filter capsules from three (3) production lots, wetted with 60/40 (V/V) isopropanol/water and 100% isopropanol were performed for the determination of the corresponding bubble point ratios of these liquids. Each test filter was wetted with the two wetting fluids using the procedures described in Section 3.1.3. At the end of each wetting the bubble point was determined as described in previous sections.

The results of the bubble point measurements are shown in Table 10. The mean bubble point ratio for 100% isopropanol and 60/40 (v/v) isopropanol/water was 0.8885.

Table 10

Bubble point measurement results on Acrodisc 0.2 µm 25 mm filter capsules when wetted with 100% isopropanol and 60/40 (v/v) isopropanol/water.

Test Unit	Lot Number	Bubble Point When Wetted with 100% IPA (psi)	Bubble Point When Wetted with 60/40 IPA/Water (psi)	Bubble Point Ratio
1	FJ0031	17.40	19.58	0.8887
2	FJ0031	17.40	20.31	0.8567
3	FJ0031	17.40	19.58	0.8887
4	FJ0031	17.40	19.58	0.8887
5	FJ0031	17.40	19.58	0.8887
6	FJ0031	17.40	19.58	0.8887
7	FJ0031	18.13	20.31	0.8927
8	FJ0031	18.13	20.31	0.8927
1	FJ0032	19.58	21.03	0.9311
2	FJ0032	19.58	21.03	0.9311
3	FJ0032	20.31	21.03	0.9658
4	FJ0032	20.31	21.03	0.9658
5	FJ0032	18.85	21.03	0.8963
6	FJ0032	19.58	21.76	0.8998
7	FJ0032	19.58	20.31	0.9641
8	FJ0032	20.31	21.03	0.9658
1	FJ0033	18.13	21.03	0.8621
2	FJ0033	18.13	21.76	0.8332
3	FJ0033	18.13	21.76	0.8332
4	FJ0033	17.40	21.03	0.8274
5	FJ0033	18.13	21.76	0.8332
6	FJ0033	18.13	21.76	0.8332
7	FJ0033	18.13	21.03	0.8621
8	FJ0033	18.13	21.76	0.8332
		Minimum: 17.40	Minimum: 19.58	Minimum: 0.8274
		Maximum: 20.31	Maximum: 21.76	Maximum: 0.9658
		Mean: 18.46	Mean: 20.79	Mean: 0.8885
		Standard deviation: 1.03	Standard deviation: 0.79	Standard deviation: 0.0461

3.3.3 User Integrity (Bubble Point) Limit for 70/30 (v/v) Isopropanol/Water

70/30 (v/v) isopropanol/water is an alternative wetting fluid for Acrodisc 0.2 µm 25 mm filter capsules. The results of the bubble point measurements in this wetting fluid are shown in Table 11. The mean bubble point ratio for 70/30 isopropanol/water and 60/40 (v/v) isopropanol/water was 0.9442.

Table 11

Bubble point measurement results on Acrodisc 0.2 µm 25 mm filter capsules when wetted with 70/30 (v/v) isopropanol/water and 60/40 (v/v) isopropanol/water.

Test Unit	Lot Number	Bubble Point When Wetted with 70/30 IPA/Water (psi)	Bubble Point When Wetted with 60/40 IPA/Water (psi)	Bubble Point Ratio
1	FJ0031	18.85	19.58	0.9627
2	FJ0031	19.58	20.31	0.9641
3	FJ0031	19.58	19.58	1.0000
4	FJ0031	18.85	19.58	0.9627
5	FJ0031	19.58	19.58	1.0000
6	FJ0031	19.58	19.58	1.0000
7	FJ0031	19.58	20.31	0.9641
8	FJ0031	19.58	20.31	0.9641
1	FJ0032	19.58	21.03	0.9311
2	FJ0032	19.58	21.03	0.9311
3	FJ0032	18.85	21.03	0.8963
4	FJ0032	20.31	21.03	0.9658
5	FJ0032	19.58	21.03	0.9311
6	FJ0032	20.31	21.76	0.9334
7	FJ0032	19.58	20.31	0.9641
8	FJ0032	19.58	21.03	0.9311
1	FJ0033	19.58	21.03	0.9311
2	FJ0033	20.31	21.76	0.9334
3	FJ0033	19.58	21.76	0.8994
4	FJ0033	19.58	21.03	0.9311
5	FJ0033	19.58	21.76	0.8998
6	FJ0033	20.31	21.76	0.9334
7	FJ0033	19.58	21.03	0.9311
8	FJ0033	19.58	21.76	0.8998
		Minimum: 18.85	Minimum: 19.58	Minimum: 0.8963
		Maximum: 20.31	Maximum: 21.76	Maximum: 1.0000
		Mean: 19.61	Mean: 20.79	Mean: 0.9442
		Standard Deviation: 0.40	Standard Deviation: 0.79	Standard Deviation: 0.0308

3.3.3.2 Surface Tension Ratio

If a filter is wetted with two different wetting fluids (wetting fluid A and wetting fluid B), the ratio of the bubble points measured with wetting fluid A and wetting fluid B is expected to correspond to the surface tension ratio the two wetting fluids^(12, 13). Surface tension information for aqueous mixtures of isopropanol (2-propanol) in increasing concentrations by mass percent can be found in the reference cited⁽¹⁴⁾. The surface tension for 60/40 isopropanol/water solution, 70/30 (v/v) isopropanol/water solution or 100% isopropanol calculated based on this literature are as follows:

Table 12

Surface tension of 60/40 (v/v) isopropanol/water, 70/30 (v/v) isopropanol/water and 100% isopropanol

Fluid	Surface Tension	Surface Tension Ratio for Fluids (Basis, Surface Tension of Isopropanol/Water 60/40 (v/v))
60/40 (v/v) isopropanol/water	24.47 mN/m	1.0000
70/30 (v/v) isopropanol/water	23.63 mN/m	0.9657
100% isopropanol	21.74 mN/m	0.8884

The mean bubble point ratios are shown in Table 10 for 100% isopropanol and 60/40 (v/v) isopropanol/water as 0.8885 and in Table 11 for 70/30 (v/v) isopropanol/water and 60/40 (v/v) isopropanol/water as 0.9442. Both ratios are comparable to the theoretical calculated ratios shown in Table 12.

Bubble point limits for the alternative wetting liquids were set based on a worst-case approach, i.e., using the higher ratio for calculation of the bubble point limits of each alternative wetting liquid thus leading to a higher bubble point limit.

Based on the surface tension ratio (0.9657) at 20 °C, a bubble point value of 14.5 psi for 60/40 (v/v) isopropanol/water will correspond to a bubble point value of (14 psi) for 70/30 (v/v) 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.

Based on the surface tension ratio (0.8884) at 20 °C, a bubble point value of 14.5 psi for 60/40 (v/v) isopropanol/water will correspond to a bubble point value of 12.9 psi for 100% isopropanol with the same filter type. This results in a user bubble point limit value of 900 mbar (13 psi) based on Pall's rounding rules for user limit integrity test data.

3.3.4 Conclusions

A comparison of the ratios obtained in these validation studies with the surface tension data/ratios available in the literature for these alternative wetting liquids confirm that the ratios are comparable. The higher of the experimentally determined and the literature described ratios was used as a worst-case approach to determine the bubble point limit value for the alternative fluids. In addition, Pall's rounding rules applied for setting the bubble point limits adds an additional safety margin.

Table 13

Bubble point limit values for 100% isopropanol

Bubble Point Limit Value (Minimum Bubble Point Pressure)	Wetting Liquid	Temperature
900 mbar (13.0 psi)	100% isopropanol	20 °C ± 5 °C*

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

Table 14

Bubble point limit value for 70/30 (v/v) isopropanol/water

Bubble Point Limit Value (Minimum Bubble Point Pressure)	Wetting Liquid	Temperature
1000 mbar (14.5. psi)	70/30 (v/v) isopropanol/water	20 °C ± 5 °C*

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

3.4 Air Flow

3.4.1 Introduction

The objective of these tests was to determine the air flow of Acrodisc 0.2 µm 25 mm filter capsule, p/n KM292HPL, at a set pressure differential.

3.4.2 Summary of Methods

Thirty (30) capsules from three (3) production lots were tested, resulting in a total of ninety (90) test units. The capsules were installed in a suitable air flow test rig with the pressure regulator and flow measurement installation upstream of the test capsule and its outlet open to atmosphere. Air flow was measured at a set upstream system pressure of 0.2 barg (3 psig), which also represented a differential pressure of 0.2 bar (3 psi) in this test installation. The measured air 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 15. The lowest air flow measured was 2 sL/min. The highest air flow measured was 4 sL/min. The average of each of the three test lots amounted to 3.2 sL/min, 3.1 sL/min and 2.7 sL/min.

Table 15

Air flow test results

<u>Filter Lot Number</u>	<u>Number of Test Units</u>	<u>Minimum Flow (sL/min)</u>	<u>Maximum Flow (sL/min)</u>	<u>Average Flow (sL/min)</u>	<u>Standard Deviation</u>
FJ0031	30	3	4	3.2	0.38
FJ0032	30	3	4	3.1	0.31
FJ0033	30	2	3	2.7	0.48

3.4.4 Conclusions

The test results in this section demonstrate a typical air flow of 3 standard liters/min at 0.2 bar (3 psi) differential pressure for Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL.

3.5 Isopropanol Liquid Pressure Test to Confirm Maximum Operating Pressure Conditions

3.5.1 Introduction

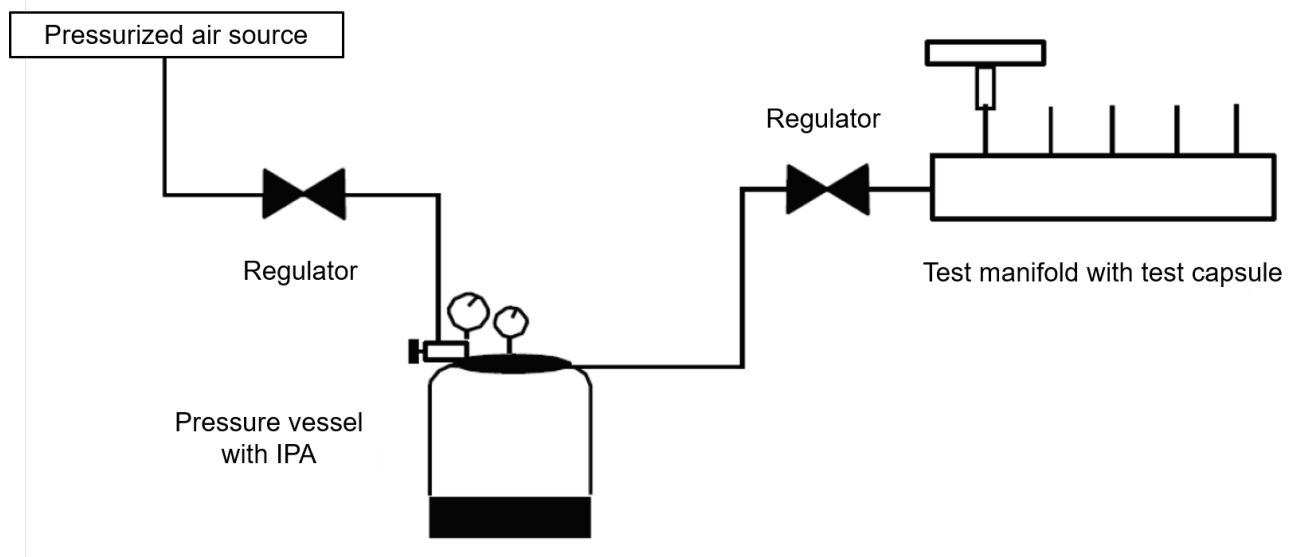
The mechanical robustness of a filter device is important for its safe and reliable operation and use and drives the operating and differential pressure specification. Capsules were subjected to a liquid isopropanol pressure test at ambient temperature to assess their mechanical robustness and confirm the operating pressure specification of 2.1 barg (30 psig).

3.5.2 Summary of Methods

Capsules from three (3) production lots were subjected to a liquid (isopropanol) pressure test at 2.1 barg (30 psig) upstream pressure. Six hundred (600) capsules were tested, two hundred (200) from each batch. The test set up 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 2.1 barg (30 psig) and the valve to the test manifold slowly opened until 2.1 barg (30 psig) was maintained. After testing, the flow valve was closed, and the system depressurized. Five (5) filter capsules from each lot were also integrity tested by bubble point at the end of the tests.

Figure 3

Test setup for isopropanol liquid pressure test



3.5.3 Results

The results of the liquid pressure test carried out at an upstream pressure of 2.1 barg (30 psig) are shown in Table 16. The corresponding bubble point test shows filters maintained a bubble point value that is greater than the set minimum bubble point value of 1000 mbar (14.5 psi) (Table 17), in addition to having demonstrated no leaks.

Table 16

Liquid pressure test results

<u>Filter Lot Number</u>	<u>Number of Test Units</u>	<u>Leak Observed</u>	<u>Test Result</u>
FJ0031	200	No	Pass
FJ0032	200	No	Pass
FJ0033	200	No	Pass

Table 17

Liquid pressure challenge at 2.1 barg (30 psig) and subsequent and bubble point test results

Test	Filter Lot Number	Bubble Point Wetted with 60/40 (v/v) IPA/Water (psid)*	Test Result
1	FJ0031	21.03	Pass
2	FJ0031	21.03	Pass
3	FJ0031	21.76	Pass
4	FJ0031	21.03	Pass
5	FJ0031	20.31	Pass
6	FJ0032	20.31	Pass
7	FJ0032	21.03	Pass
8	FJ0032	21.03	Pass
9	FJ0032	21.76	Pass
10	FJ0032	21.76	Pass
11	FJ0033	21.76	Pass
12	FJ0033	21.76	Pass
13	FJ0033	21.03	Pass
14	FJ0033	21.03	Pass
15	FJ0033	21.76	Pass

*Minimum bubble point limit when wetted with 60/40 (v/v) isopropanol/water is 1000 mbar (14.5 psi)

3.5.4 Conclusions

The results of the liquid pressure test demonstrate that Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, are mechanically robust and withstand an operating and differential pressure of 2.1 barg (30 psig) without leak or membrane rupture and maintain functional integrity.

3.6 Water Breakthrough Test

3.6.1 Introduction

The water breakthrough test is performed to determine the hydrophobic character of the membrane contained within the capsule and to verify that an integral membrane seal has been achieved.

3.6.2 Summary of Methods

One hundred twenty-five (125) capsules from three (3) production lots were tested. The test capsules were first installed onto a multifilter test rig. The capsules were then primed with a test fluid (water containing dye) and pressurized to 2.1 barg (30.0 psig). Contact of the dye water with the filter membrane was visually verified and the pressure held for a minimum of 15 seconds. Throughout the duration and at the conclusion of the test, the test capsules were examined for any water penetration through the membrane and for leaks around the ring mold. If dye water penetration was not observed at 2.1 barg (30.0 psig), the pressure was slowly increased to a maximum of 3.45 barg (50.0 psig) to determine the breakthrough pressure.

3.6.3 Results

The result of the water breakthrough test is shown in Table 18.

Table 18

Water breakthrough test results

Filter Lot Number	Number of Test Units	Water Breakthrough /Leak Observed at 2.1 barg (30 psig)*	Test Result
FJ0031	125	No	Pass
FJ0032	125	No	Pass
FJ0033	125	No	Pass

**In all cases pressure was increased up to 3.45 barg (50 psig) without observing water breakthrough*

3.6.4 Conclusion

The hydrophobic property the filter capsules is maintained and does not allow water to breakthrough up to a pressure of 2.1 barg (30 psig).

3.7 Extractables

3.7.1 Introduction

The objective of this series of tests was to quantify and characterize the material that can be extracted from the capsules under challenging extraction conditions. The conditions chosen were above ambient temperature (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

Test capsules were autoclaved at 125 °C for 1 hour. For each extraction, five (5) 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. Two (2) extractions were performed. At the end of the extraction time, the extraction liquid in the capsules was pushed out with fresh 50/50 (v/v) ethanol/water, collected, and then evaporated to dryness. The non-volatile residues (NVR) were determined gravimetrically.

3.7.3 Results

Table 19 shows the levels of the extractables obtained from two batches of capsules that were tested using 50/50 (v/v) ethanol/water as extraction fluid. The total NVR values obtained from two (2) extractions for five (5) filters extracted together were < 1 mg/5 test units with a mean value of 0.6 mg/5 test units.

Table 19

Non-volatile residue using 50/50 (v/v) ethanol/water as the extraction fluid

Filter Lot Number	Number of Test Units Extracted	Total NVR (mg/5 Test Filter Units)
FJ0031	5	0.8
FJ0032	5	0.4
FJ0033	5	0.7
		Mean: 0.6

3.7.4 Conclusions

The level of extractables obtained from Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, 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 x 2), was extremely low (<1 mg NVR/5 capsules).

While actual service will impose different conditions, the extractables conditions chosen will typically represent worst-case conditions for the 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 Acro 0.2 µm 25 mm vent filter capsules, p/n KM292HPL. The materials of construction of the filters are as follows:

Table 20

Materials of construction

<u>Membrane</u>	<u>Hardware Parts</u>
Hydrophobic polytetrafluorethylene (PTFE) backed with a polypropylene non-woven support	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 - 121 °C Plastics (USP <88>) as described in the current United States Pharmacopeia (USP) ⁽¹⁾.

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)

USP <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 conditions not resulting in physical changes in the plastic is recommended, therefore the filter materials were extracted at 121 °C for 1 hour.

4.2.1 Acute Systemic Injections Tests

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

4.2.2 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.

4.2.3 Implantation Tests

Implantation tests were also performed to subject the materials of construction to the most stringent conditions included in the United States Pharmacopoeia. Each of the materials of the Acrodisc 0.2 µm 25 mm filter capsule 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 test method followed USP <87> ⁽²⁾.

4.3 Results

All materials of construction passed all the tests specified under USP <88> and a MEM Elution Test assessing cytotoxicity ⁽¹⁾.

4.4 Conclusions

The materials of construction used in Acrodisc 0.2 µm 25 mm filter capsules meet the requirements of USP <88>⁽¹⁾ and a MEM Elution test ^(2, 3) assessing cytotoxicity. The tests under USP <88> included the Systemic Injection Test, the Intracutaneous Test and the Implantation Test. The results demonstrate that the materials of construction of Acrodisc 0.2 µm 25 mm filter capsules are biologically safe and fit for use in manufacturing of drug products under cGMP.

5 Transmissible Spongiform Encephalopathy (TSE) / Bovine Spongiform Encephalopathy (BSE)

Acrodisc 0.2 µm 25 mm filter capsules, p/n KM292HPL, are assembled from components using polymeric resin materials. While some of the materials may contain chemicals produced from animal material substances, they are not considered a Transmissible Spongiform Encephalopathies/Bovine Spongiform Encephalopathies (TSE/BSE) risk based on their source (sourcing takes into consideration animal species, tissue, and country of origin) and/or exposure to processing conditions known to inactivate infectious agents associated with TSE/BSE diseases. See below for further information on polymeric chemical additives produced from 'tallow'.

Tallow derivative: Some polymeric resin manufacturers employ trace levels of additives in the resin formulation. These additives may be manufactured using animal tallow as a starting substance ('tallow-derivatives'). The tallow may have been sourced from bovine species or, less commonly, from non-TSE relevant species. Please be advised that bovine tallow-derivatives are not considered risk material for TSE/BSE according to the current revision of the CFR Title 21 Food and Drugs, Part 189.5: Prohibited cattle material. Furthermore, the European Committee for Proprietary Medicinal Products' (CPMP) note for guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products (EMS410/01 current version), as well as other international guidelines, gives specific considerations to tallow-derivatives and states that they are unlikely to be infectious due to the rigorous processing steps used during their manufacture (for example, transesterification or hydrolysis at not less than 200 °C under pressure for not less than 20 minutes). Our suppliers have stated that these raw materials have been processed under conditions at least as rigorous as these.

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, to assist our biopharmaceutical customers, who require a defined shelf life, we conservatively recommend usage within five (5) 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 for Acrodisc 0.2 µm 25 mm Filter Capsules Part Number KM292HPL

Figure 4

Sample Certificate of Test for Acrodisc 0.2 µm 25 mm filter capsules p/n KM292HPL

 Pall Corporation	
<h3>Certificate of Test</h3> <p>For Pharmaceutical-Grade Sterilizing Filters</p>	
We hereby certify that	
Pall®: ACRODISC® VENT FILTER	
Rated: 0.2 µm	
Part Number: KM292HPL	
Lot Number: FJ0033	
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.	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:
Bacterial Retention Finished product has been sampled and successfully tested for retention of <i>Brevundimonas diminuta</i> (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).	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).
Materials of Construction Representative filter components have met the requirements for biological reactivity, <i>in vivo</i> , 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/41001 and Title 21 of the U.S. Code of Federal Regulations (CFR), part 189.5).	Oxidizable Substances Meets the current USP requirements after flushing under Sterile Purified Water, as determined by a Potassium Permanganate 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.	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.
 _____ Jose Cubero, Quality Manager, Pall Life Sciences Puerto Rico Pall Boulevard #98, Road 194 KM 0.4, Fajardo, Puerto Rico 00738 CoTD 104E rev 01	17/August/2021 _____ Date of Manufacture
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