BIOTECH

Validation Guide

USTR 3871

Emflon® II Membrane in Mini Kleenpak™ 20 Filter Capsules

KM5V002P2G, KM5V002P2S

Version Number: 1.0
Date: February 2, 2023
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1 Overview

Sterilizing filtration of gases and liquids used in the manufacture of sterile pharmaceuticals is of paramount importance. All aspects of the aseptic manufacturing process should be validated to ensure the safety and efficacy of the final pharmaceutical and biological product. This validation guide is designed to assist the filter user in meeting the validation requirement of regulatory authorities within the pharmaceutical industry for the use of Emflon II membrane in Mini Kleenpak 20 filter capsule formats (part numbers [p/n]: KM5V002P2G, KM5V002P2S), henceforth referred to as the filter capsules.

These filter capsules incorporate a double-layer sterilizing grade membrane made of inherently hydrophobic polyvinylidene fluoride (PVDF), manufactured by Pall. The polypropylene hardware is specially formulated with protective antioxidants making the filter capsules suitable for incorporation into gamma irradiated single-use systems (SUS).

The filter capsules are designed, developed, and manufactured in accordance with an International Organization for Standardization (ISO) 9001 (*Quality management systems*) certified Quality Management System (QMS). They are manufactured in a controlled environment that meets the air quality standards in accordance with ISO 14644-1:2015 (*Cleanrooms and associated controlled environments Part 1: Classification of air cleanliness by particle concentration)* Class 8 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 capsules as follows:

- 100% fabrication integrity,
- Bacterial retention, tested with *Brevundimonas diminuta* (*B. diminuta*, American Type Culture Collection [ATCC♦] 19146),
- Effluent cleanliness,
- Endotoxins.

The materials of construction of these filter capsules have met the requirements for United States Pharmacopoeia (USP) <88> Biological Reactivity Test, *In Vivo*, for Class VI – 121 °C Plastics. The materials of construction are listed in U.S. Code of Federal Regulations (CFR) Title 21 Food and Drugs, Parts 170-199 (21 CFR Parts 170-199).

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

- Bacterial retention liquid challenge tests,
- Bacterial aerosol challenge tests,
- Endurance to autoclave sterilization conditions,
- Determination of air flow/pressure differential characteristics,
- Determination of extractables in water and ethanol,
- Biological reactivity tests on materials of construction,
- Determination of shelf-life.

Emflon II membrane in Mini Kleenpak 20 filter capsules may be used in conformance with current Good Manufacturing Practices (cGMP) per CFR Title 21 Food and Drugs, Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs (21 CFR Part 210) and CFR Title 21 Food and Drugs, Part 211: Current Food Practice for Finished Pharmaceuticals (21 CFR Part 211).

Capsules with a ‘G’ suffix designation in the p/n are supplied as non-sterile. These capsules can be autoclaved (by up to three (3) 60-minute cycles at 131 °C), or gamma irradiated (with doses up to 50 kGy) by the end user. These conditions ensure a minimum Sterility Assurance Level (SAL) of 10^{6}. The validation protocol of the gamma irradiation process has been described in Pall publication ‘Pall 0.2 µm-rated Filter Cartridges and Filter Capsules with Fluorodyne® II Grade DFL Membrane’ (Pall document reference number: USTR 2611). The sterilization process is validated and routinely controlled in compliance with the standards listed below:

- ISO 11137-1:2006 *Sterilization of health care products - Radiation – Part 1 – Requirements for development, validation and routine control of a sterilization process for medical devices*,
- ISO 11137-2:2006 *Sterilization of health care products- Radiation – Part 2 – Establishing the sterilization dose*,

- Advancing Safety in Health Technology Technical Information Report (AAMI TIR) 33:2005 *Sterilization of health care products – Radiation – Substantiation of a selected sterilization dose –Method* VD_{max}.

This guide may be complemented by other documentation for Emflon II membrane in Mini Kleenpak 20 filter capsules:

- Datasheet for Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G, KM5V002P2S) found on Pall.com (Pall document reference number USD 2307b),
- Certificate of Test (CoT) included in each filter packaging (see Appendix 1: Certificate of Test for a sample CoT). This document substantiates the product specification and quality control standards applied to Emflon II membrane in Mini Kleenpak 20 filter capsules.

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

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

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 Qualification Tests

2.1 Microbial Retention Testing

Emflon II membrane in Mini Kleenpak 20 filter capsules were tested for bacterial retention using *B. diminuta*, following procedures described in this validation guide and American Society for Testing and Materials (ASTM) Standard Test Method F838-15a (ASTM F838-15a), in accordance with the applicable requirements of the U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research: Guidance for Industry – Guidance on Sterile Drug Products Produced By Aseptic Processing – Current Good Manufacturing Practice (2004) (FDA cGMP guidelines). These tests demonstrated that filter capsules which passed bubble point (BP) integrity testing BP with a minimum bubble point of 1110 mbar (16.0 psi) when wetted with 60/40 (v/v) isopropanol (IPA)/water, will retain > 10^7 colony forming units (CFU) of *B. diminuta* per cm^2 of effective filtration area (CFU/cm^2) in liquid (water) and produce a sterile effluent.

Aerosol microbial challenge tests were also performed on the filter capsules produced under standard manufacturing conditions. These tests demonstrated that integral Emflon II membrane in Mini Kleenpak 20 filter capsules also retain 100% of aerosolized bacteria.

Table 1

Summary of microbial challenge testing with *B. diminuta*

Challenge Description	Minimum Challenge Level	Sterile Effluent
Liquid challenge	> 6.8 x 10^8	Yes
Aerosol challenge	> 1.13 x 10^9	Yes

2.2 Integrity Test Parameters

The user integrity (bubble point) limit value for the Emflon II membrane in Mini Kleenpak 20 filter capsules has been derived from historical membrane data and defined as follows:

Table 2

User integrity test parameters for the Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G, KM5V002P2S)

Wetting Liquid	Minimum Bubble Point	Temperature
60/40 (v/v) IPA/water	1110 mbar (16.0 psi)	20 ± 5 °C* (68 ± 9 °F)

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

2.3 Endurance to Autoclave Sterilization Conditions

Emflon II membrane in Mini Kleenpak 20 filter capsules demonstrated integrity retention after repeated autoclave cycles under the conditions listed in Table 3.

Table 3

Summary of autoclave conditions

Filter Part Number	Autoclave Temperature	Number and Duration of Cycles
KM5V002P2G non-irradiated – not wetted	131 °C (270 °F)	3 x 1 hour

Note: *When the filter capsule has been gamma irradiated, the filter capsule can be subjected to one autoclave cycle (1 hour at 131 °C) post use and before a post use integrity test only for decontamination purposes.*

Autoclaving filter capsules post gamma irradiation is not recommended before a process use.

2.4 Extractables Testing

The level of extractables obtained from the Emflon II membrane in Mini Kleenpak 20 filter capsules, under aggressive extraction conditions (after gamma irradiation, extraction with 50/50 (v/v) ethanol/water at 40 °C for 24 hours) was extremely low (< 1 mg non-volatile residue [NVR]).

While actual service will impose different conditions of use, the extractables conditions chosen in this study should typically represent worst-case conditions.

The data presented in this guide demonstrated the typical extractables level for Emflon II membrane in Mini Kleenpak 20 filter capsules, shown in Table 4.

Table 4

Summary of extractables testing

Filter Part Number	Effective Filtration Area (EFA)	Total NVR in Water at 80 °C ± 2 °C	50/50 v/v Ethanol/Water at Ambient Temperature
KM5V002P2G non-irradiated	20 cm²	0 mg	< 0.1 mg
KM5V002P2G gamma irradiated	20 cm²	0 mg	< 0.1 mg

Actual service in pharmaceutical applications will impose different conditions, such as sterilization parameters, exposure times, and temperatures. Evaluation under process conditions is therefore also recommended.

2.5 Biological Reactivity Test on Filter Components

The materials of construction of Emflon II membrane in Mini Kleenpak 20 filter capsules were tested and found to meet the requirements for USP <88> (Class VI – 121 °C plastics). *In vivo* tests included the systemic toxicity test, the intracutaneous test, and the implantation test.

2.6 Transmissible Spongiform Encephalopathy (TSE) / Bovine Spongiform Encephalopathy (BSE) Statement

Emflon II membrane in Mini Kleenpak 20 filter capsules, as other Pall pharmaceutical-grade products, do not contain animal derived materials (i.e., animal parts, tissues, or body fluids) and hence may be designated 'animal free' under many customer classification systems.

2.7 Shelf-Life

Pall 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 5 years of manufacture for non-sterile filter capsules. We recommend a shelf-life of 3 years from manufacture for gamma irradiated filter capsules.

3 Bacterial Retention Validation Using *B. Diminuta* Liquid Challenge Tests

The FDA cGMP guidelines 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 *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)".

For a filter to be defined as a sterilizing grade filter, it must meet the industry requirements of removing *B. diminuta* (ATCC 19146) at a minimum level of ≥ 1.0×10^7 CFU/cm^2 of EFA. This industry standard for performance characterization of a sterilizing grade filter was set out in FDA cGMP guidelines first published in 1987 and remained unchanged in the document's 2004 revision.

Emflon II membrane in Mini Kleenpak 20 filter capsules were tested for retention of *B. diminuta* using bacterial challenge tests following procedures described in this validation guide and correlated to the current revision of ASTM Standard Test Method F838 Standard Test (ASTM F838), and FDA cGMP guidelines, using a minimum of 1×10^7 CFU/cm^2 of EFA.

The FDA cGMP guidelines 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* liquid 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. The studies summarized in this document serve to demonstrate the Emflon II membrane in Mini Kleenpak 20 filter capsules that pass bubble point testing provide a sterile filtrate in liquid challenge testing. This test is employed due to the small filter area (19.6 cm^2) of the capsules, which hinders the use of the forward flow (FF) or water intrusion tests (WIT), as the gas and evaporative water flows during testing are extremely small and prevent a reliable user integrity test with this device type.

In the bubble point test, the pores of a filter are fully wetted with an appropriate test liquid, and an increasing gas pressure is applied to the upstream side of the filter assembly. At a certain pressure, the gas flow through the wetted membrane will increase significantly indicating the evacuation of the wetting liquid from the largest pore(s) in the membrane. This can be measured on the upstream side, using sensitive flow measurement equipment such as the Palltronic® Flowstar filter integrity test instrument.

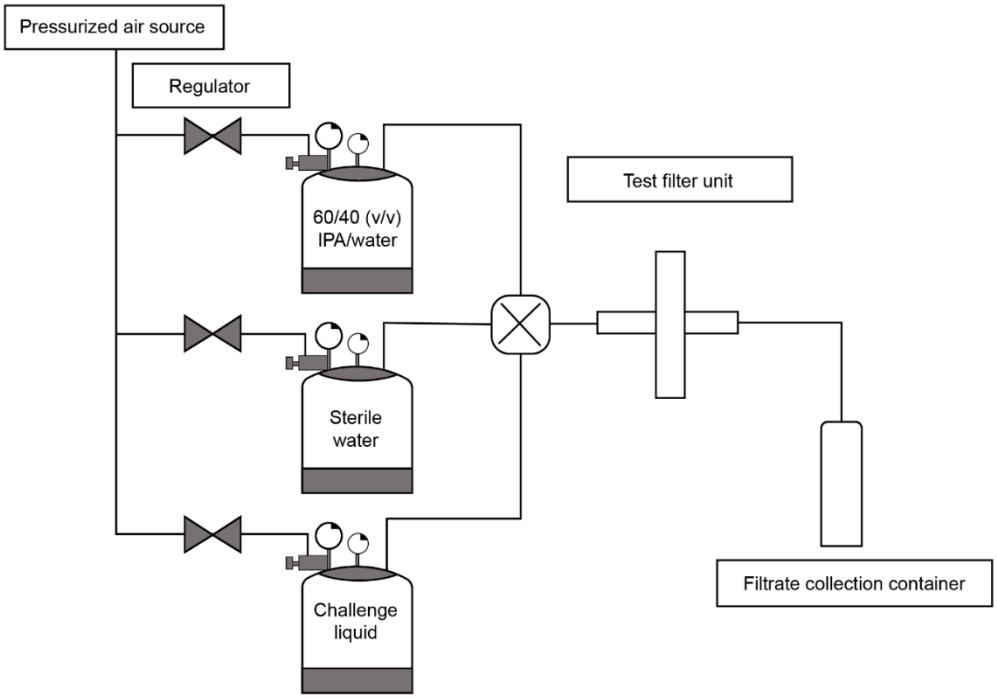
3.1 Method

Emflon II membrane in Mini Kleenpak 20 filter capsules (both gamma irradiated, and non-gamma irradiated) were subjected to bacterial challenge tests using an aqueous suspension of *B. diminuta* (ATCC 19146), which was prepared in accordance with standard test method ASTM F838.

Prior to the challenge tests, the filter capsules were tested for integrity using the BP test method. The non-gamma irradiated filter capsules were then autoclaved at 121 ºC (250 ºF) for 60 minutes. After autoclaving, all filter capsules were flushed with the wetting agent, integrity tested and flushed with water, then aseptically connected to both a downstream housing containing a pre-sterilized recovery membrane disc and the challenge reservoir, as shown in Figure 1.

Figure 1

Schematic of the bacterial challenge set-up



An inoculation of *B. diminuta* was passed through each test filter to achieve a challenge level of > 1.0 x 10^7 CFU/cm^2 (a total challenge level of 6.8 x 10^8 CFU per filter was achieved for all tests performed). The entire effluent from the test filter assembly was collected in a sterile container. Subsequently, the entire effluent was passed through a 0.2 µm rated recovery membrane, ensuring a full effluent stream analysis for bacteria penetration. Following the filtration of the effluent, the recovery membrane was places onto tryptic soy agar (TSA) plates. All agar plates were incubated at 30 ± 2 ºC (86 ± 4 ºF) for a minimum of 48 hours.

On completion of the challenge, a bubble point test was performed on the filter capsules.

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

$$TR = \frac{Total\ number\ of\ bacteria\ influent\ to\ the\ filter}{Number\ of\ colonies\ recorded\ on\ the\ downstream\ recovery\ disk}$$

For each filter capsule type (gamma irradiated and non-gamma irradiated) nine (9) capsules of three (3) different lots were tested.

3.2 Results

The BP and *B. diminuta* retention test results are shown in Table 5 for the gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2S) and in Table 6 for the non-gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G). The achieved challenge levels were higher than 6.8×10^8 CFU ($> 3.5 \times 10^7$ CFU/cm²).

Table 5

Result of BP and *B. diminuta* retention tests for the gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2S)

Filter Capsule Lot Number	Bubble Point* [psi]	Pass/Fail	Challenge Level [CFU]	Sterile Effluent
FE1039	21.76	Pass	1.0×10^9	Yes
FE1039	21.76	Pass	1.0×10^9	Yes
FE1039	21.76	Pass	1.0×10^9	Yes
FE3869	21.76	Pass	1.0×10^9	Yes
FE3869	22.48	Pass	1.0×10^9	Yes
FE3258	21.03	Pass	1.2×10^9	Yes
FE3258	21.03	Pass	1.2×10^9	Yes
FE3258	20.31	Pass	1.2×10^9	Yes
FE3698	21.76	Pass	1.2×10^9	Yes

** Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

Table 6

Result of BP and *B. diminuta* retention tests for the non-irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G)

Filter Capsule Lot Number	Bubble Point* [psi]	Pass/Fail	Challenge Level [CFU]	Sterile Effluent
FE3689	21.03	Pass	6.8×10^8	Yes
FE3689	21.03	Pass	6.8×10^8	Yes
FE3689	23.21	Pass	6.8×10^8	Yes
FE3258	20.31	Pass	6.8×10^8	Yes
FE0868	21.03	Pass	6.8×10^8	Yes
FE0868	21.03	Pass	6.8×10^8	Yes
FE4869	23.21	Pass	9.0×10^8	Yes
FE4869	23.21	Pass	9.0×10^8	Yes
FE4869	23.21	Pass	9.0×10^8	Yes

** Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

3.3 Conclusions

The results in this chapter demonstrated complete retention of *B. diminuta* at a challenge level of $> 3.5 \times 10^7$ CFU/cm² for gamma and autoclave sterilized Emflon II membrane in Mini Kleenpak 20 filter capsules.

4 Aerosol Challenge Test

The aim of these tests was to demonstrate the microbial aerosol retention capability of the Emflon II membrane in Mini Kleenpak 20 filter capsules, using *B. diminuta* (ATCC 19146).

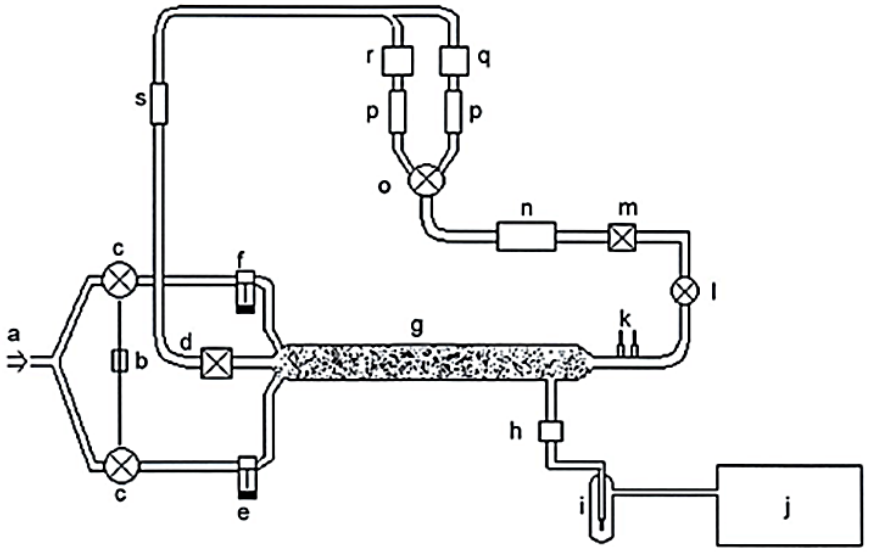
4.1 Summary of Methods

The suspension of microorganisms is nebulized by a collision spray to form a fine aerosol containing the challenge microorganisms. The generated aerosols are injected into a dry air stream flowing into a long stainless-steel tube. This causes liquid droplets surrounding the microorganisms to evaporate, leaving the challenge organisms free in the air stream at their minimum aerodynamic size. The efficiencies of the filter capsules are calculated by determining the airborne microbial concentration upstream and downstream of the test filter capsule.

The testing assembly was sterilized by autoclaving and aseptically connected to the sterile challenge apparatus, as shown schematically in Figure 2. The assembly consisted of a Collison nebulizer that was used to generate the microbial aerosols. This was housed in a chamber with a compressed air supply. The aerosol was generated in the chamber and introduced to the filter housing or capsule via stainless steel piping. Aerosol sampling devices and a vacuum pump were used to draw the air containing the microbial aerosols through the system at the required flow rate.

Figure 2

Henderson apparatus for challenging filters with microbial aerosols



Key:

a	Compressed air	k	Wet and Dry Thermometers
b	3-Way Switch	l	Valve
c	Solenoid Valves	m	Filter
d	Filter	n	Compressor-Vacuum Pump
e	Collison Spray Containing Challenge Micro-organisms	o	Valve
f	Collison Spray Containing Distilled Water	p	Flowmeters
g	Spray Tube	q	Humidifier
h	Filter to be Tested	r	Drier
i	Downstream Impinger	s	Flowmeter
j	External Vacuum Pump		

Sterile phosphate buffer containing Manucol♦ and antifoam (PBMA) was used as the collection fluid and was fed into the cyclone inlet at a rate of 1 mL/min using a peristaltic pump. Particles in the air stream were deposited by centrifugal force on the cyclone wall and were collected by the swirling liquid which was removed by a syringe at the end of the challenge period.

A cyclone sampler was used to collect the organisms generated in the system. Sterile collecting fluid was fed into the cyclone sampler and particles in the air stream were deposited by centrifugal force into the swirling liquid on the wall of the device. On completion of the challenge, the volume of collection fluid was measured and then assayed for the challenge organism using an appropriate technique.

Background levels were measured by operating the system with a filter capsule in place and with the Collison nebulizer sprays switched 'off'. Challenge levels were determined by operating the system with the filters removed and the Collison nebulizer sprays switched 'on'.

The titer reduction (TR) for each filter was determined as:

$$TR = \frac{Total\ number\ of\ bacteria\ influent\ to\ the\ filter}{Number\ of\ colonies\ recorded\ on\ the\ downstream\ recovery\ disc}$$

Note: *Calculation of the titer reduction accounts for the volume of collecting fluid.*

4.2 Results

Emflon II membrane in Mini Kleenpak 20 filter capsules were challenged with *B. diminuta* at > 10^7 CFU/cm^2 of EFA for 0.5 hour at the flow rate of 141.7 L/min, (5.0 SCFM, 8.5 Nm^3/h). The challenge results are shown in Table 7.

Table 7

Aerosol challenge results for gamma and non-gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (part numbers: KM5V002P2S, KM5V002P2G) using *B. diminuta*.

Filter Capsule Lot Number	Gamma Irradiated or Autoclaved	Challenge Level [CFU]	Sterile Effluent
FE5989	Gamma irradiated	> 2.65 x 10^9	Yes
FE5989	Gamma irradiated	> 2.65 x 10^9	Yes
FE4572	Gamma irradiated	> 1.75 x 10^9	Yes
FE4572	Gamma irradiated	> 1.75 x 10^9	Yes
FE5771	Gamma irradiated	> 1.13 x 10^9	Yes
FE5771	Gamma irradiated	> 1.13 x 10^9	Yes
FE4869	Autoclaved	> 5.95 x 10^9	Yes
FE4869	Autoclaved	> 5.95 x 10^9	Yes
FE0868	Autoclaved	> 5.30 x 10^9	Yes
FE0868	Autoclaved	> 5.30 x 10^9	Yes
FE3689	Autoclaved	> 5.60 x 10^9	Yes
FE3689	Autoclaved	> 5.60 x 10^9	Yes

4.3 Conclusion

The results of the microbial aerosol challenge tests demonstrate complete bacteria retention by the Emflon II membrane in Mini Kleenpak 20 filter capsules when challenged with > 10^7 CFU/cm² of EFA. This has been confirmed with capsules sterilized by autoclaving as well as by gamma irradiation.

5 Endurance to Autoclave Sterilization Conditions

Autoclave exposure of filter capsules during sterilization creates a substantial stress and can alter the physical structure of some filter capsules or cause them to lose integrity. These tests were performed to evaluate the ability of the Emflon II membrane in Mini Kleenpak 20 filter capsules to withstand multiple autoclave cycles.

5.1 Summary of Methods

The procedure for these tests was based on the recommendations for steam sterilization described in the Pall application note 'Steam Sterilization of Pall Filter Assemblies – Utilizing Replaceable Filter Cartridges' (Pall document reference: USTR 805).

Non-irradiated filter capsules were autoclaved for up to six (6) 1-hour cycles at 131 °C (267 °F). Filter capsules were tested with the bubble point method before and after the autoclave cycles. The filter capsules were dry when being autoclaved.

Although it is not recommended to autoclave filter capsules which have previously been subjected to gamma irradiation, this is a step that could be needed for safety reasons, for example to sterilize filter capsules that have been exposed to biologically hazardous products before performing the post-use integrity test. To confirm the safety of this operation, autoclave tests have been performed on gamma irradiated production filter capsules. Gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules were autoclaved for two (2) 30-minutes cycles at 125 °C. The filter capsules were tested with the bubble point method before and after the autoclave cycles.

5.2 Results

The results of bubble point testing post six (6) cycles of autoclaving are summarized in Table 8.

Table 8

Bubble point value after 6 x 1-hour cycles at 131 °C (267 °F) for non-irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G)

Filter Capsule Lot Number	Bubble Point Result* (psi)	Pass/Fail
FJ1099	20.31	Pass
FJ1099	20.31	Pass
FJ1099	20.31	Pass
FJ1099	21.31	Pass
FJ1099	21.31	Pass
FJ1099	21.03	Pass
FJ0987	20.31	Pass
FJ0987	20.31	Pass
FJ0987	20.31	Pass
FJ0987	21.31	Pass
FJ0987	21.03	Pass
FJ0987	21.03	Pass
FJ1520	21.03	Pass
FJ1520	22.48	Pass
FJ1520	22.48	Pass
FJ1520	21.76	Pass
FJ1520	21.76	Pass
FJ1520	21.03	Pass

**Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

The results of bubble point testing post two (2) cycles of autoclaving of gamma irradiated capsules are summarized in Table 9.

Table 9

Bubble point value after 2 x 30 minutes cycles at 125 °C (257 °F) for gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2S)

Filter Capsule Lot Number	Bubble Point Result* (psi)	Pass/Fail
FE0868	19.58	Pass
FE0868	20.31	Pass
FE3689	20.31	Pass
FE3689	20.31	Pass
FE4572	21.03	Pass
FE4572	21.76	Pass

**Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

5.3 Conclusions

The data presented in this section show that the Emflon II membrane in Mini Kleenpak 20 filter capsules withstand repeated autoclave cycles up to 131 °C, as demonstrated by maintaining integrity after exposure to six (6) autoclave cycles. These results support an autoclave claim of three (3) 60-minute cycles at up to 131 °C for these capsules.

The gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules passed bubble point tests, demonstrating their integrity after two autoclave cycles at 125 °C. These data demonstrate that the gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules can be subjected to a single 60-minute autoclave cycle at 125 °C for decontamination purpose post-use prior to integrity testing.

6 Air Flow and Differential Pressure Characteristics

The objective of these tests was to determine the air flow rates of the Emflon II membrane in Mini Kleenpak 20 filter capsules at different differential pressures (dp) when used as vent filters as well as assessing any potential impact of gamma irradiation on the gas flow of the filter capsules.

6.1 Summary of Methods

Filter samples from three lots were submitted to gamma irradiation and submitted to airflow testing together with samples from the same three lots that had not been gamma irradiated. The tests were performed such that they mimicked vent conditions, i.e., the downstream side of the filter capsule was open to atmospheric pressure and increasing air flow through the filter capsule was controlled from the upstream side.

6.2 Results

The flow rate at 10 mbar dp and 100 mbar dp for the non-irradiated filter capsules are shown in **Error! Reference source not found.** and the results for the gamma irradiated filter capsules are shown in Table 11.

Table 10

Flow rate (sL/min) vent mode – non-irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G)

Filter Capsule Lot Number	Vent Mode Average Flow Rate [sL/min] at 10 mbar dp	Vent Mode Average Flow Rate [sL/min] at 100 mbar dp
FE1039	0.288	2.619
FE3258	0.301	2.819
FE3689	0.293	2.670

Table 11

Flow rate (L/min) vent mode, gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2S)

Filter Capsule Lot Number	Vent Mode Average Flow Rate [sL/min] at 10 mbar dp	Vent Mode Average Flow Rate [sL/min] at 100 mbar dp
FE1039	0.298	2.689
FE3258	0.308	2.903
FE3689	0.299	2.716

6.3 Conclusions

The data presented in this section confirm that gamma irradiation, up to 50 kGy maximum, does not adversely impact the gas flow characteristics of the filter capsules. Both gamma irradiated and non-irradiated filter capsules displayed a gas flow of 0.3 sL/min at 10 mbar differential pressure and a flow of 2.7 sL/min at a differential pressure of 100 mbar.

To help users in assessing the flow rate for their specific applications, the mean flow dp for gamma irradiated and non-irradiated filter capsules up to 100 mbar is shown in Figure 3 and up to 1200 mbar is shown in Figure 4.

Figure 3

Air flow versus differential pressure under vent conditions up to 100 mbar

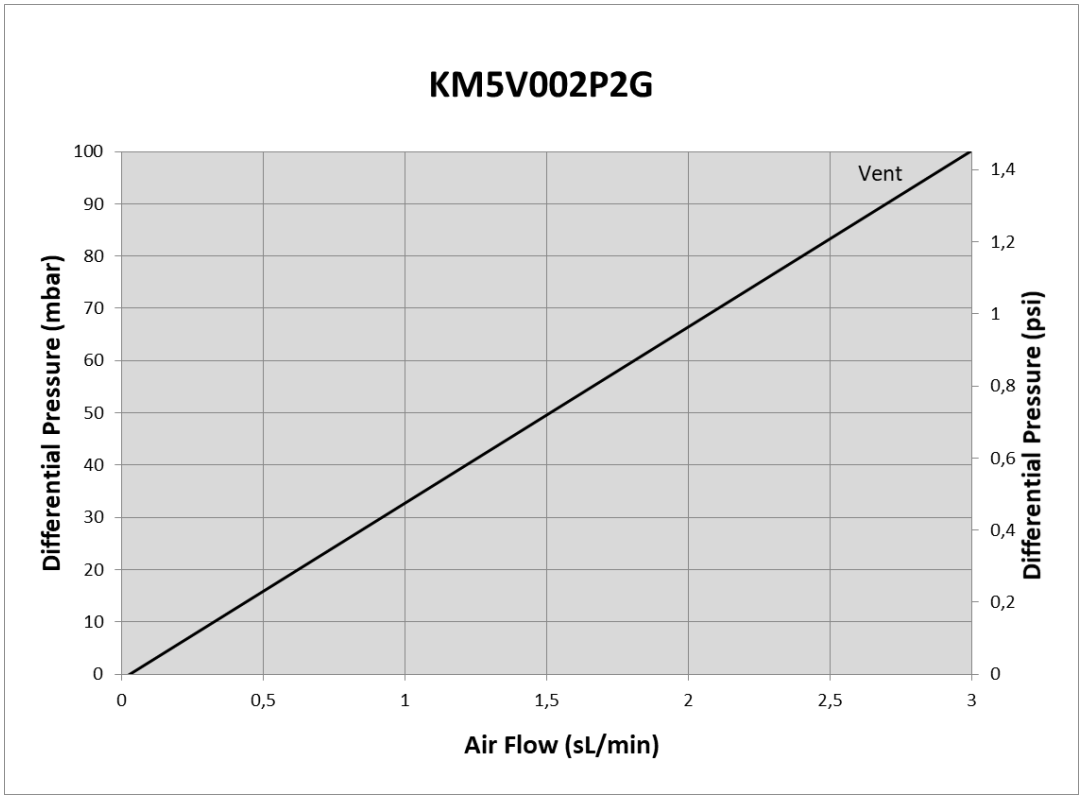
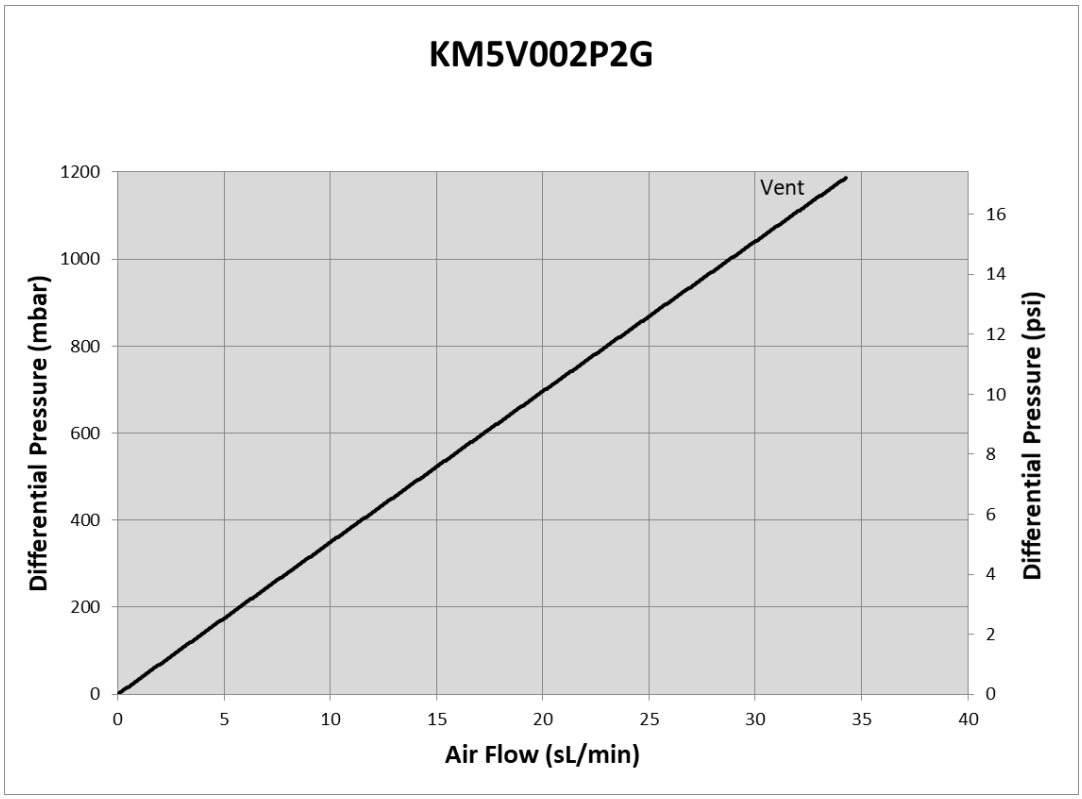


Figure 4

Air flow versus differential pressure under vent conditions up to 1200 mbar



7 Maximum Operating and Differential Pressure

The mechanical robustness of a filter capsule is important for its safe and reliable operation and use. It drives the operating and differential pressure specification. The maximum operating pressure for the Emflon II membrane in Mini Kleenpak 20 filter capsules is 2 bar (29 psi) at 20 °C.

Testing aimed to confirm that Emflon II membrane in Mini Kleenpak 20 filter capsules can maintain their integrity at this operating pressure, as demonstrated by passing the bubble point test.

7.1 Summary of Method

Samples of gamma irradiated (50 kGy dose) and non-gamma irradiated filter capsules were subjected to ten (10) cycles of air pressure at 2 bar (29 psi) operating pressure in the forward direction. The filter capsules were open to atmosphere; hence the operating pressure for the filter capsules also translated to differential pressure across the filter membrane. 60/40 (v/v) IPA/water wet bubble point measurements were performed prior to testing to ensure that only integral filter capsules were submitted to pressure cycling. Bubble point testing after the pressure cycles served to confirm that the filter capsules maintained integrity during the pressure cycling. Bubble point testing was performed using Palltronic Flowstar IV devices applying a 0.01 module factor as per Pall recommendation for this filter size. Table 12 shows the bubble point test results after pressure cycling.

Table 12

Bubble point measurements post-pressure cycling for Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G, KM5V002P2S)

Filter Capsule Lot Number	Gamma Irradiated	Bubble Point Post Exposure to 2 Bar dp (psi)*	Pass/Fail
FE3258	No	18.85	Pass
FE3258	No	18.85	Pass
FE3258	No	18.85	Pass
FE0868	No	19.58	Pass
FE0868	No	19.58	Pass
FE0868	No	20.31	Pass
FE1039	No	20.31	Pass
FE1039	No	21.03	Pass
FE1039	No	19.58	Pass
FE0868	Yes	18.85	Pass
FE3689	Yes	19.58	Pass
FE0868	Yes	18.85	Pass
FE0868	Yes	18.85	Pass
FE0868	Yes	20.31	Pass
FE4572	Yes	20.31	Pass
FC3951	Yes	19.58	Pass
FE4572	Yes	21.03	Pass
FE3690	Yes	19.58	Pass

**Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

Emflon II membrane in Mini Kleenpak 20 filter capsules passed bubble point testing after exposure to the pressure cycling.

7.2 Conclusions

The results in this section confirm that Emflon II membrane in Mini Kleenpak 20 filter capsules are robust and withstand multiple pressure cycles at 2 bar (29 psi) operating and differential pressure. This was confirmed with both non-irradiated and gamma irradiated filter capsules.

8 Burst Pressure

8.1 Burst Pressure Testing

The testing described in this section was conducted using a worst-case approach, i.e., the filter capsules were subjected to gamma irradiation (up to a dose of 50 kGy) and one autoclave cycle (131 °C, 30 mins) prior to commencing testing.

Samples of gamma-irradiated and autoclaved Emflon II membrane in Mini Kleenpak 20 filter capsules were subjected to hydraulic burst testing. Using hydraulic (water) pressure on the filter capsule the pressure was increased until a leak was detected. Table 13 shows the burst pressure test results for autoclaved and gamma irradiated filter capsules.

Table 13

Burst testing results for Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G, KM5V002P2S)

Filter Capsule Lot Number	Burst Pressure (psi)	Converted Burst Pressure (bar)
FJ1099	207	14.3
FJ1099	204	14.1
FJ1099	165	11.4
FJ1099	129	8.9
FJ1099	209	14.4
FJ1099	205	14.1
FJ0987	146	10.1
FJ0987	152	10.5
FJ0987	167	11.5
FJ0987	183	12.6
FJ0987	150	10.3
FJ0987	128	8.8
FJ1520	174	12.0
FJ1520	144	9.9
FJ1520	148	10.2
FJ1520	177	12.2
FJ1520	147	10.1
FJ1520	172	11.9

The lowest burst pressure that was measured was 128 psi (8.8 bar), thus confirming a high safety margin for Emflon II membrane in Mini Kleenpak 20 filter capsules above the maximum operating pressure of 2.0 bar.

8.2 Conclusions

The burst pressure test results confirm a high safety margin above the maximum operating pressure of 2.0 bar.

9 Extractables Testing

Extractables are an important aspect for components used in manufacturing of drug products. Emflon II membrane in Mini Kleenpak 20 filter capsules are designed for use as gas filters and are not generally expected to be in the fluid path of the liquid drug product. The objective of these tests was to quantify the material that can be extracted from Emflon II membrane in Mini Kleenpak 20 filter capsules under challenging extraction conditions that can be considered worst-case.

Table 14

Extraction conditions

Extraction Temperature	40 °C (104 °F)
Extraction Fluid	50/50 (v/v) ethanol/water
Extraction Duration	24 hours

To maximize the amount of extractables and mimic the actual conditions of preparation, both gamma-irradiated and non-irradiated filter capsules were autoclaved at 121 °C for 30 minutes 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 substances that could potentially be released by these filters into their drug product.

9.1 Summary of Methods

Both gamma irradiated and autoclaved filter capsules were tested. For each extraction, three (3) filter 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 was run 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 NVR was determined gravimetrically. Fourier transform infrared (FTIR) spectra of the NVR could not be prepared due to extremely low amount of residue.

9.2 Results

Table 15 shows the results of the non-irradiated capsules and Table 16 show the results of the gamma irradiated capsules.

Table 15

Non-volatile residue (19.6 cm^2 effective filtration area per capsules) with 50/50 (v/v) ethanol/water as extraction fluid, non-irradiated

Filter Capsule Lot Number	No. Test Units Tested Together	Total NVR per 3 Test Filter Devices (mg)
FE0868	3	< 0.1*
FE3689	3	< 0.1*
FE4572	3	< 0.1*

**Limit of detection is 0.1 mg.*

Table 16

Non-volatile residue (19.6 cm^2 effective filtration area per capsules) with 50/50 (v/v) ethanol/water as extraction fluid, gamma irradiated

Filter / Lot	Test Units Tested Together	Total NVR per 3 Test Filter Devices (mg)
FE0868	3	0.2
FE3689	3	< 0.1*
FE4572	3	< 0.1*

**Limit of detection is 0.1 mg.*

9.3 Conclusions

The level of extractables obtained from Emflon II membrane in Mini Kleenpak 20 filter capsules under aggressive extraction conditions (after gamma irradiation or autoclave cycle, extraction with 50/50 (v/v) ethanol/water at 40 °C for 24 hours) was extremely low (< 1 mg NVR for three [3] filter capsules extracted together).

10 Biological Reactivity Tests on Components

The aim of this study was to evaluate the biological safety of the materials of construction of Emflon II membrane in Mini Kleenpak 20 filter capsules.

Table 17

Materials of construction of Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2G)

Component	Material
Filter media	Hydrophobic polyvinylidenediflouride
Capsule	Polypropylene

10.1 Summary of Methods

The tests were performed at an independent testing laboratory in accordance with USP <88> (Class VI – 121 °C plastics). Filter capsule samples were gamma irradiated at 50 kGy prior to testing.

The testing procedures described in the USP <88> include:

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

The four extracting media listed in USP <88> simulate parenteral solutions and body fluids. These include:

- Sodium chloride injection,
- 1 in 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,
- 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.

10.1.1 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 a 1 in 20 solution of alcohol in sodium chloride were injected intravenously. Vegetable oil extract and polyethylene glycol 400 extract were injected intraperitoneally.

10.1.2 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.

10.1.3 Implantation Tests

Implantation tests were also performed to subject the materials of construction to the most stringent conditions included in USP <88>. Each of the materials of Emflon II membrane in Mini Kleenpak 20 filter capsules was implanted separately.

10.2 Results

All materials of construction used in the capsule passed all tests specified under USP <88> (Class VI – 121 °C plastics).

10.3 Conclusions

The material components used in Emflon II membrane in Mini Kleenpak 20 filter capsules have met the requirements for USP <88> (Class VI – 121 °C plastics). This includes the systemic toxicity test, the intracutaneous test, and the implantation test.

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

Emflon II membrane in Mini Kleenpak 20 filter capsules are assembled from components using polymeric resin and elastomeric materials. While some of the materials may contain chemicals produced from animal material substances, they are not considered a 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'.

11.1 Tallow-Derivatives

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 (CFR 21 Part 189.5). Furthermore, the European Committee for Proprietary Medicinal Products (CPMP) Notice From European Union Institutions, Bodies, Offices and Agencies European Commission EMA410/01 Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products (current version) [2011] OJ C73/1, and other international guidelines, gives specific consideration 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 200 °C or higher under pressure for 20 minutes or longer). Our suppliers have stated that these raw materials have been processed under conditions at least as rigorous as these.

The above information reflects Pall's current knowledge based on supplier's information and Pall process controls. The statements provided are subject to change as new information from our suppliers becomes available. Pall will notify customers if any new information is received that would impact TSE/BSE safety; however, we also recommend that users periodically confirm this information.

12 Shelf-Life

12.1 Non-Sterile Emflon II Membrane in Mini Kleenpak 20 Filter Capsules

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

- Store at a temperature of 0 - 30 °C in dry conditions,
- Do not expose filters to direct sunlight, uncontrolled radiation, or direct weather conditions,
- Store filters in original shipping bag and boxing,
- 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,
- Inspection and integrity testing are recommended prior to use.

12.2 Gamma Irradiated Emflon II Membrane in Mini Kleenpak 20 Filter Capsules

Gamma irradiation is known to accelerate the ageing process of polymeric materials. Therefore, Pall has defined a shelf-life up to three (3) years for the gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules after gamma irradiation.

12.3 Summary of Methods

The defined shelf-life is supported by accelerated aging tests performed in line with the American Society for Testing and Materials Standard Test Method F1980-07 (ASTM F1980-07) in which the Arrhenius equation is used to determine an accelerated aging time that allows the same level of physical property change to occur to the filter capsules as would occur if they were stored in real-time.

Gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules were subjected to accelerated aging equivalent to 3 years storage under ambient conditions after gamma irradiation. After this storage period they were subjected to liquid bacterial challenge tests at a challenge level of > 10^7 CFU/cm^2 of EFA using *B. diminuta* (challenge organism), bubble point tests, air flow determination and extractables tests applying the methods described in the respective section of this guide.

12.4 Results

The results of bacteria challenge, bubble point, air flow, and extractable testing on gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules after a three (3) year accelerated storage period are shown in Table 18 to Table 20.

Table 18

Result of bubble point test and *B. diminuta* retention for gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules (p/n: KM5V002P2S) after 3 year accelerated storage period

Filter Capsule Lot Number	Bubble Point [psi]*	Challenge Level [CFU]	Sterile Effluent
FE3689	21.76 (pass)	2.2×10^9	Yes
FE4572	21.76 (pass)	2.2×10^9	Yes
FE0868	21.76 (pass)	2.2×10^9	Yes

**Wetted with 60/40 (v/v) IPA/water. Minimum bubble point is 16.0 psi (1100 mbar) at 20 ± 5 °C.*

Table 19

Non-volatile residue (19.6 cm^2 effective filtration area per capsules) with 50/50 (v/v) ethanol/water as extraction fluid after 3 years of accelerated storage

Filter Capsule Lot Numbers	Test Units Tested Together	Total NVR per 3 Test Filter Devices (mg)
FE4572	3	< 0.1 mg*

**Limit of detection is 0.1 mg.*

Table 20

Flow rate (L/min) vent mode, after 3 years of accelerated storage

Filter Capsule Lot Numbers	Vent Mode Average Flow Rate [sL/min] at 10 mbar (0.145 psi) dp
FE4572	0.297
FE3689	0.305
FE0868	0.349

12.5 Conclusion

The following performance tests were conducted:

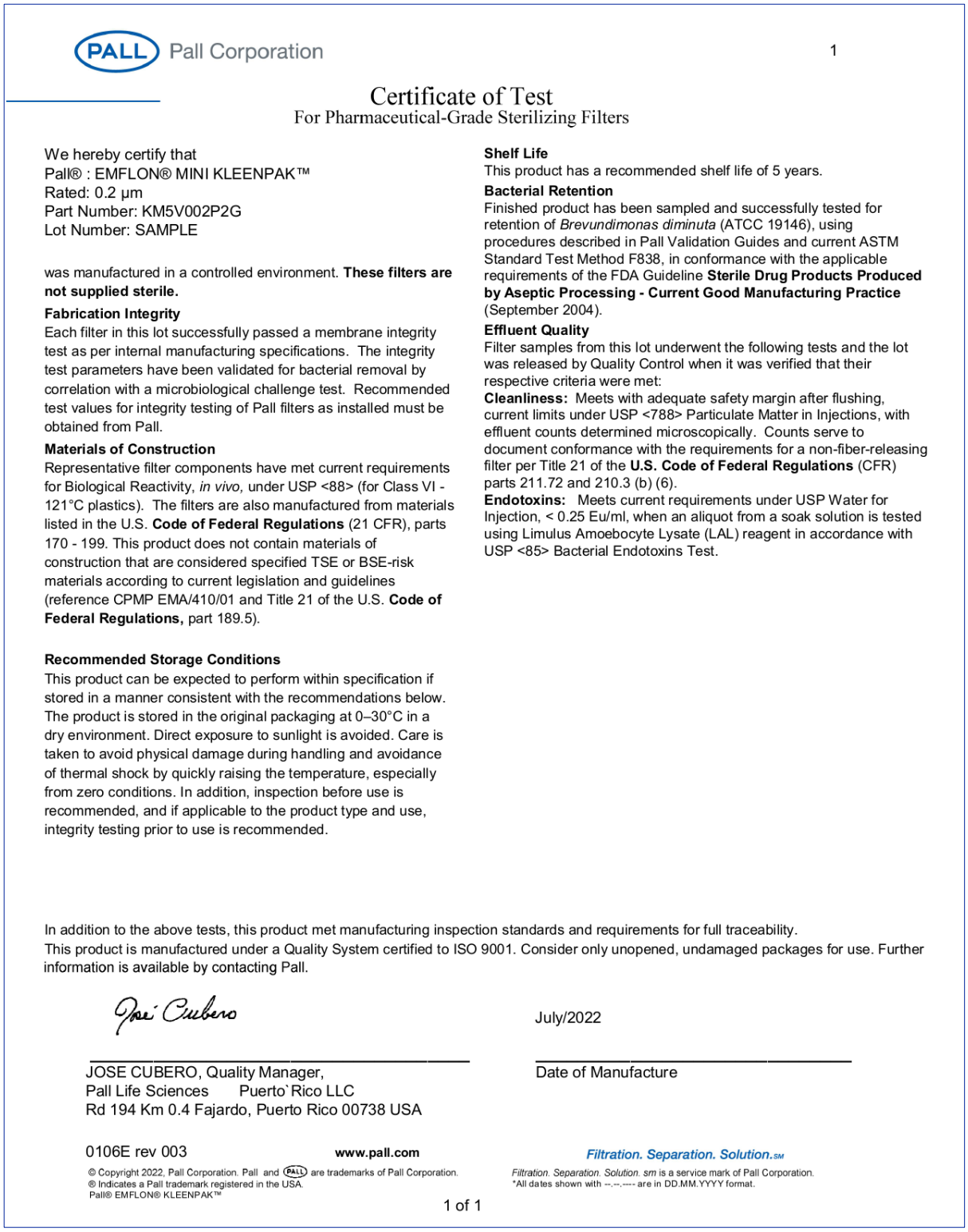
- Bacterial challenge tests,
- Integrity tests,
- Extractables tests,
- Air flow characteristics.

These tests confirmed that integrity and filter performance of the gamma irradiated Emflon II membrane in Mini Kleenpak 20 filter capsules is maintained during the three (3) years accelerated storage period under recommended storage conditions (see Section 12.1), and that the filter capsules continued to display extractables levels comparable to those prior to storage.

Appendix 1: Certificate of Test

Figure 5

Sample CoT for Emflon II membrane in Mini Kleenpak 20 filter capsules



Pall Corporation

1

Certificate of Test
For Pharmaceutical-Grade Sterilizing Filters

We hereby certify that
Pall® : EMFLON® MINI KLEENPAK™
Rated: 0.2 µm
Part Number: KM5V002P2G
Lot Number: SAMPLE

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

Fabrication Integrity
Each filter in this lot successfully passed a membrane integrity test as per internal manufacturing specifications. The integrity 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.

Materials of Construction
Representative filter components have met current requirements for Biological Reactivity, *in vivo,* under USP <88> (for Class VI - 121°C plastics). The filters are also manufactured from materials listed in the U.S. **Code of Federal Regulations** (21 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 CPMP EMA/410/01 and Title 21 of the U.S. **Code of Federal Regulations,** part 189.5).

Recommended Storage Conditions
This product can be expected to perform within specification if stored in a manner consistent with the recommendations below. The product is stored in the original packaging at 0–30°C in a dry environment. Direct exposure to sunlight is avoided. Care is taken to avoid physical damage during handling and avoidance of thermal shock by quickly raising the temperature, especially from zero conditions. In addition, inspection before use is recommended, and if applicable to the product type and use, integrity testing prior to use is recommended.

Shelf Life
This product has a recommended shelf life of 5 years.

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 current ASTM Standard Test Method F838, in conformance with the applicable requirements of the FDA Guideline **Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice** (September 2004).

Effluent Quality
Filter samples from this 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).
Endotoxins: Meets 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.

Jose Cubero

July/2022

JOSE CUBERO, Quality Manager,
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Date of Manufacture

0106E rev 003 **www.pall.com**

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USTR 3871 Version 1.0
February 2023