PALL Life Sciences

Validation Guide

USTR 2378

Validation Guide for Pall Fluorodyne® EX Filter Cartridges

*Filtration. Separation. Solution.*SM

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1. Overview

1.1 Introduction

This guide contains validation data applicable to 0.2 micrometer microbially rated **Fluorodyne** EX filter cartridges in AB style. These filters have been designed as liquid sterilizing filters for use within the pharmaceutical industry, as indicated by the letter 'P' in the part numbering code. The removal rating of 0.2 micrometer is assigned based on challenges with *Brevundimonas diminuta* (ATCC 19146). These filter cartridges feature a novel construction, being comprised of one layer of polyethersulfone (PES) membrane upstream and one layer of polyvinylidene fluoride (PVDF) membrane downstream. The asymmetric upstream membrane layer provides built-in prefiltration to the symmetric downstream sterilizing membrane layer.

The 254 mm (10 inch) AB-style filter is manufactured using the Ultipleat® construction. This laid-over pleat configuration maximizes membrane area in order to increase flow rates and maximize filter life.

This report summarizes the tests that were performed to qualify the performance of **Fluorodyne** EX filter cartridges under a range of test conditions.

The qualification program included:

- **Microbial retention validation tests**
- **Endurance to *in-situ* steam sterilization under wet and dry steaming conditions**
- **Determination of water flow characteristics**
- **Extractables testing using water**
- **Biological reactivity tests**

Materials of construction and performance parameters of **Fluorodyne** EX filters are described in the **Pall** datasheet 'Fluorodyne EX High Flow Filter Cartridge' (USD2384), which supplements this guide.

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 Pascals (Pa):

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

1.2 Summary of Conclusions

Microbial Retention Validation Tests

Fluorodyne EX filter cartridges were tested for bacterial retention of *Brevundimonas diminuta* (ATCC 19146) using bacterial tests correlated to ASTM Standard Test Method F838-83, and in accordance with the FDA's Guidance for Industry - Sterile Drug Products Produced By Aseptic Processing - Current Good Manufacturing Practice (September 2004).

The Forward Flow integrity test was shown to be a suitable non-destructive integrity test for **Fluorodyne** EX filter cartridges, and test parameters have been set as follows for 254 mm (10 inch) filters (part number AB1UEDF7PH4).

Forward Flow Integrity Test Parameters for 254 mm (10 inch) Fluorodyne EX Filter Elements, Part Number AB1UEDF7PH4

Test pressure	2760 mbar (40 psi)
Wetting liquid	Water
Temperature	20 °C ± 5 °C (68 °F ± 9 °F)
Test gas	Air
Maximum allowable Forward Flow limit*	30 mL/min

* During the test period the temperature of the filter assembly should not vary more than ± 1 °C (2 °F).

Endurance to *In-Situ* Steam sterilization

Fluorodyne EX filter cartridges have been demonstrated to be capable of withstanding multiple *in-situ* steam sterilization cycles under various standard steaming conditions while maintaining suitable water wettability for integrity testing. Tests performed demonstrate that the **Fluorodyne** EX filter cartridges are robust and capable of withstanding differential pressures up to 1 bar (14.5 psi) in the forward direction during steaming.

The data presented in this report support the following product claim for *in-situ* steaming of **Fluorodyne** EX filter cartridges:

Filter Part Number	Steaming Conditions	Maximum Recommended Steam Life Claim
AB1UEDF7PH4	*In-situ* steam cycles at 135 °C (275 °F)	5 one-hour cycles

The above claim is supported by data with a 100 % safety margin. Filters should be qualified in actual conditions of use.

Determination of Water Flow Characteristics

Differential pressure measurements at set water flow rates have been determined. The average pressure drop for a 254 mm (10 inch) filter (part number AB1UEDF7PH4) at 10 L/min clean water flow was 95 mbar (1.38 psi) at 20 °C (68 °F). These data can be used to assist users in sizing filter systems employing **Fluorodyne** EX filter cartridges.

Extractables Testing using Water

The typical amount of non-volatile residue (NVR) extracted from **Fluorodyne** EX filter cartridges in AB1 style has been determined using water as the extraction fluid. For the 254 mm (10 inch) filter cartridges tested (part number AB1UEDF7PH4) the aqueous extractables ranged from 29 to 47 mg.

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

Biological Reactivity Tests

All of the materials used in **Fluorodyne** EX filter cartridges meet the requirements of the USP Biological Reactivity Tests *(in vivo)* for Class VI-121 °C plastics. The tests included the Systemic Injection test, the Intracutaneous test and the Implantation test.

2. Microbial Validation Tests

2.1 Introduction

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

In accordance with the requirements of this guideline, liquid challenge tests using *Brevundimonas diminuta* (ATCC 19146) were performed with **Fluorodyne** EX filter cartridges using a minimum of 1×10^7 colony forming units (CFU)/cm^2 of effective filtration area.

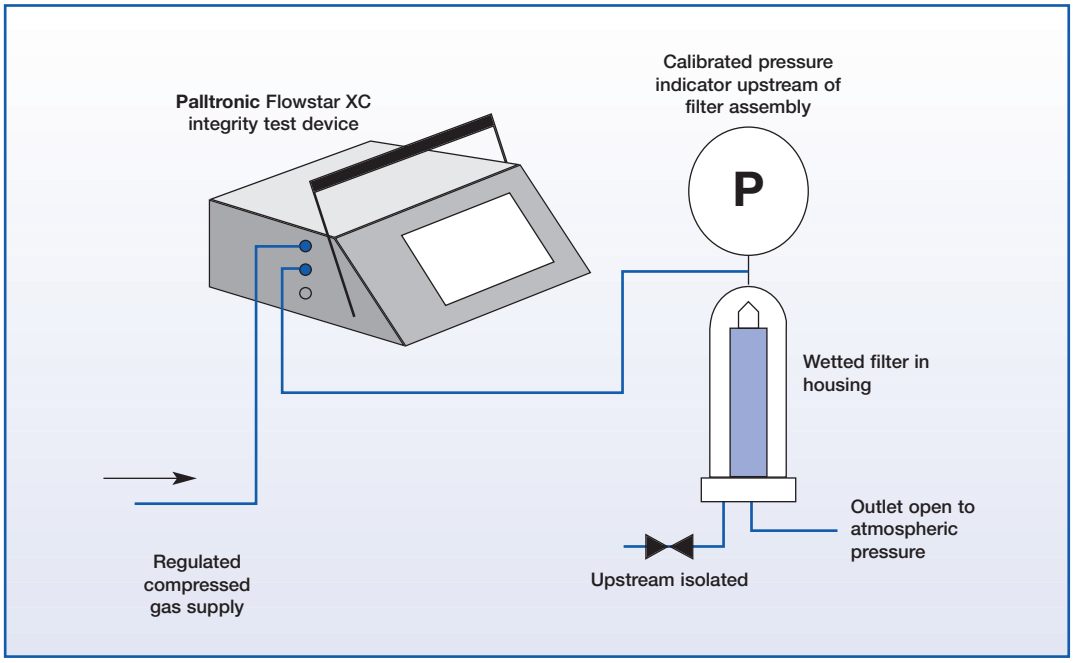
The FDA guideline further states: 'After a filtration process is properly validated for a given product, process and filter, it is important to ensure that identical filters (e.g. of identical polymer construction and pore size rating) are used in production runs....Integrity testing of the filter(s)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

The correlation between microbial retention and a non-destructive integrity test is an important aspect of the validation of sterilizing grade filters. The Forward Flow test was the integrity test used during this study.

The Forward Flow Test

In the Forward Flow test, a filter is wetted with an appropriate test liquid and a pre-determined gas pressure is applied to the upstream side of the filter assembly. After a stabilization period, the gas flow through the wetted membrane can be measured on the upstream side, using sensitive flow measurement equipment such as the Palltronic® Flowstar filter integrity test device, see Figure 2-1.

Figure 2.1 The Automated Integrity Test



The aim of this study was to demonstrate the microbial removal efficiency of typical **Fluorodyne** EX filter cartridges in liquid challenge tests using *Brevundimonas diminuta* (ATCC 19146) and to document the correlation of the integrity test parameters to the microbial removal efficiency.

2.2 Summary of Methods

Typical **Fluorodyne** EX filter cartridges, part number AB1UEDF7PH4 (membrane area 1.1 m^2 [12 ft^2]), from three separate manufacturing batches were subjected to standard microbial challenge tests using an aqueous suspension of *Brevundimonas diminuta* (ATCC 19146).

Prior to the challenge tests the filter cartridges were installed in an appropriate housing, flushed with deionized (DI) water at a flow rate of 7 L/min for 15 minutes, and then autoclaved at 121 °C (250 °F) for 60 minutes. A Forward Flow integrity test was then performed using a **Palltronic** integrity test device with an air test pressure of 2760 mbar (40 psi). The filter assembly was then aseptically connected to the pre-sterilized challenge apparatus, as shown in Figure 2-2.

An aqueous suspension of *B. diminuta* was passed through the filter to achieve a challenge level of > 1 x 10^7 colony forming units (CFU) per cm^2 of effective filtration area.

During the challenge test the entire filter effluent was passed through a 0.2 micrometer-rated analysis disc on the downstream side of the test filter assembly. The filter disc was incubated on agar and, following incubation, the disc was examined to determine if any colonies had grown, indicating whether or not bacteria had passed through the test filter during the challenge. The titer reduction (T_R) for each filter was determined as follows:

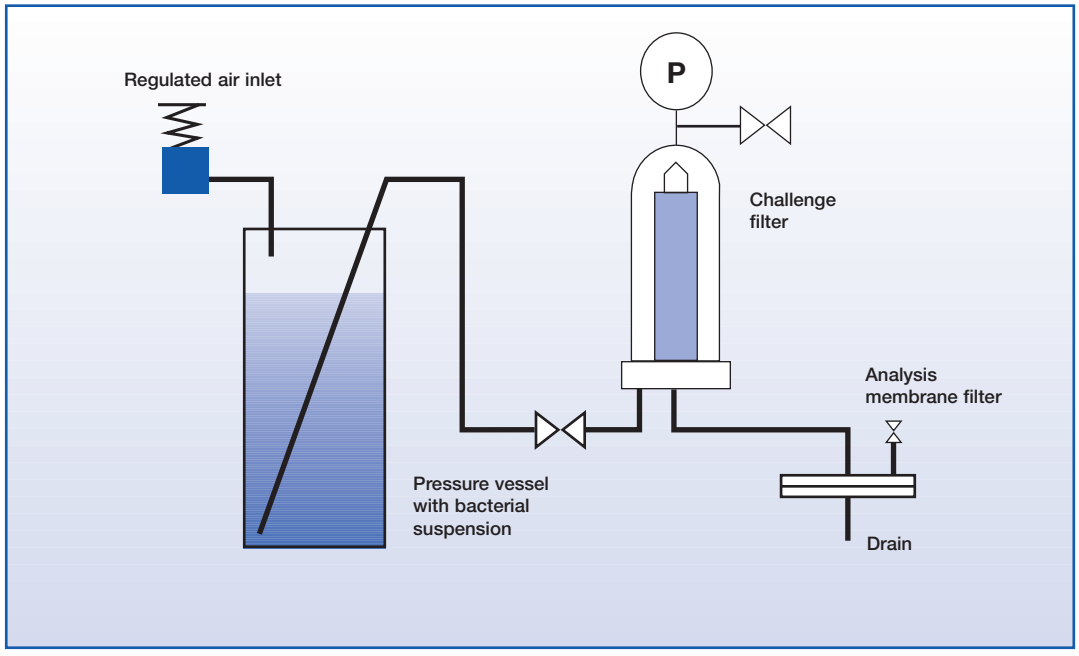
$$T_R = \frac{\text{Total number of bacteria influent to the filter}}{\text{Number of colonies recorded on the downstream analysis disc}}$$

When no colonies were detected downstream, the titer reduction was expressed as:

> Total number of bacteria influent to the filter (e.g. > 1 x 10^{10})

On completion of the challenge test the filter assemblies were autoclaved and then flushed and Forward Flow integrity tested as described previously.

Figure 2-2 Microbial Challenge Apparatus



2.3 Results

The Forward Flow and *B. diminuta* retention results are shown in Table 2-1. The higher of the two Forward Flow values (pre- and post-challenge) is presented and the data are arranged in order of increasing Forward Flow value.

All of the filter cartridges gave sterile effluent when challenged with ≥ 1 x 10^7 CFU per cm^2 of filtration area using *B. diminuta.*

Table 2-1 Results of Forward Flow and *B. diminuta* Retention for Typical Fluorodyne EX Filter Cartridges, Part Number AB1UEDF7PH4

Pall Cartridge Serial Number	Forward Flow* (mL/min)	Sterile Effluent	Titer Reduction
R01007013	20.2	Yes	> 2.85×10^{11}
R01007012	20.2	Yes	> 2.17×10^{11}
R01009038	20.4	Yes	> 6.41×10^{11}
R01007010	20.7	Yes	> 3.07×10^{11}
R01007003	20.8	Yes	> 2.24×10^{11}
R01009042	20.8	Yes	> 5.72×10^{11}
R01009034	20.8	Yes	> 4.15×10^{11}
R01009003	21.0	Yes	> 2.54×10^{11}
R01009036	21.6	Yes	> 5.42×10^{11}
R01007023	21.7	Yes	> 3.02×10^{11}
R01009032	22.7	Yes	> 3.14×10^{11}
R01007005	24.6	Yes	> 3.37×10^{11}
R01007004	25.4	Yes	> 2.63×10^{11}
R01009046	24.7	Yes	> 2.42×10^{11}
R01009026	26.4	Yes	> 3.57×10^{11}
IH9026167	26.3	Yes	> 2.64×10^{11}
IH9026172	26.8	Yes	> 2.80×10^{11}
R01009018	27.8	Yes	> 3.04×10^{11}
IH9026148	28.1	Yes	> 2.87×10^{11}
IH9026027	29.0	Yes	> 2.87×10^{11}
IH9026024	31.9	Yes	> 3.30×10^{11}
IH9026017	34.0	Yes	> 2.64×10^{11}

* Forward Flow values at 2760 mbar (40 psi) air test pressure, wet with water, at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.

2.4 Conclusions

Typical **Fluorodyne** EX filter cartridges from production (part number AB1UEDF7PH4), were found to pass the Forward Flow integrity test. All of the filters tested provided sterile effluent when subjected to aqueous microbial challenge tests using *B. diminuta* at a challenge level of > 1×10^7 CFU/cm^2.

Forward Flow integrity test parameters have been for **Fluorodyne** EX filter cartridges based on the above results of the microbial challenge tests and additional considerations and parameters.

Forward Flow Integrity Test Parameters for Fluorodyne EX Filter Cartridges, Part Number AB1UEDF7PH4*

Test pressure	2760 mbar (40 psi)
Wetting liquid	Water
Temperature	20 °C ± 5 °C (68 °F ± 9 °F)
Test gas	Air
Maximum allowable Forward Flow limit**	30 mL/min

* See Section 2.2 for test procedure.
** During the test period the temperature of the filter assembly should not vary more than ± 1°C (2°F).

3. Endurance to *In-Situ* Steam sterilization

3.1 Introduction

The purpose of these tests was to determine the effects of repeated exposure to *in-situ* steam cycles on filter integrity and water wettability using standard **Fluorodyne** EX filter cartridges from production. The tests were used to qualify the steam exposure claims for **Fluorodyne** EX filter cartridges.

3.2 Summary of Methods

In-situ steaming at 135 °C (275 °F) under water wet steaming conditions

Typical **Fluorodyne** EX filters from three different manufacturing batches (part number AB1UEDF7PH4) were used for the tests.

Six of the filter cartridges were flushed with DI water for 10 minutes with a back pressure of 1.5 barg (21.8 psi) and then Forward Flow integrity tested using an air test pressure of 2760 mbar (40 psi). The wet filter cartridges were then subjected to a one-hour *in-situ* steam cycle at 135 °C (275 °F).

A further four filter cartridges were tested, using a less rigorous wetting regime. These filter cartridges were flushed with DI water for 10 minutes with a lower back pressure of 1.0 barg (14.5 psi) prior to Forward Flow testing and steaming.

During the initial stages of the steam cycles, the wet filter membrane caused the differential pressure to increase across the filter cartridge as steam was introduced. The steam inlet valve was controlled so that the differential pressure across the wetted filter cartridge did not exceed 1.0 bar (14.5 psi).

Immediately after each one-hour steam cycle had finished, dry compressed air was flushed across the upstream side of the filter cartridge surface for 30 minutes in order to replace the steam and cool the assembly. The cartridges were then flushed with water prior to starting the next steam cycle.

This test sequence was repeated until each filter cartridge had been exposed to 10 one-hour steam cycles.

On completion of the 10 steam cycles, the filter cartridges were flushed with DI water and Forward Flow integrity tested again as described above.

In-Situ steaming at 135 °C (275 °F) under dry steaming conditions

Ten **Fluorodyne** EX filter cartridges from three different manufacturing batches (part number AB1UEDF7PH4) were used.

Six filter cartridges were flushed with DI water for 10 minutes with a back pressure of 1.5 barg (21.8 psi) and then Forward Flow integrity tested using an air test pressure of 2760 mbar (40 psi). Four filter cartridges were flushed with DI water for 10 minutes with a lower back pressure of 1.0 barg (14.5 psi) prior to Forward Flow testing and steaming. Upon completion of the integrity testing, the filter cartridges were dried thoroughly at 40 °C (104 °F) for at least 36 hours. The dry filter cartridges were then subjected to the steaming procedure with one-hour *in-situ* steam cycles at 135 °C (275 °F).

The steam inlet valve was controlled so that the differential pressure across the filter did not exceed 1.0 bar (14.5 psi).

Immediately after each one-hour steam cycle had finished, dry compressed air was flushed across the upstream side of the filter surface for 30 minutes in order to replace the steam and cool the assembly.

This sequence was repeated until each filter cartridge had been exposed to ten one-hour steam cycles.

3.3 Results

In-situ steaming at 135 °C (275 °F) under water wet steaming conditions

The Forward Flow integrity test results for **Fluorodyne** EX filter cartridges (part number AB1UEDF7PH4) before and after exposure to one-hour *in-situ* steam cycles are shown in Tables 3-1 and 3-2. All of the filter cartridges retained integrity and full water wettability under the wetting conditions applied (1.0 barg [14.5 psi] and 1.5 barg [21.8 psi] back pressure) following exposure to ten one-hour cycles at 135 °C (275 °F).

Table 3-1 Effects of Wet *In-Situ* Steam Exposure at 135 °C (275 °F) on Filter Integrity and Wettability for Fluorodyne EX AB1UEDF7PH4 Filter Cartridges when wetted with 1.5 barg (21.8 psi) Back Pressure for Integrity Testing

	Forward Flow* (mL/min) test results before and after exposure to 10 *in-situ* steam cycles at 135 °C (275 °F):	
Pall Cartridge Serial Number	**FF (mL/min) pre steaming**	**FF (mL/min) post steaming**
R01007015	22.4	21.5
R01007019	18.5	19.6
R01007024	20.1	19.6
R01009005	20.0	18.4
R01009010	18.7	18.0
R01009021	20.9	19.6

* Forward Flow values determined at 2760 mbar (40 psi) air test pressure, wet with water at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.

Table 3-2 Effects of Wet *In-Situ* Steam Exposure at 135 °C (275 °F) on Filter Integrity and Wettability for Fluorodyne EX Filter Cartridges in AB1UEDF7PH4 style when wetted with 1.0 barg (14.5 psi) Back Pressure for Integrity Testing

	Forward Flow* (mL/min) test results before and after exposure to 10 *in-situ* steam cycles at 135 °C (275 °F):	
Pall Cartridge Serial Number	**FF (mL/min) pre steaming**	**FF (mL/min) post steaming**
IH9026169	18.8	19.0
IH9026001	19.3	19.5
IH9026146	20.1	19.6
IH9026037	21.0	19.9

* Forward Flow values determined at 2760 mbar (40 psi) air test pressure, wet with water at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.

In-situ Steaming at 135 °C (275 °F) under dry steaming conditions

The Forward Flow integrity test results for **Fluorodyne** EX filter cartridges (part number AB1UEDF7PH4) before and after exposure to one-hour *in-situ* steam cycles are shown in Tables 3-3, 3-4 and 3-5.

All of the filter cartridges retained integrity and full water wettability following exposure to 10 one-hour cycles at 135 °C (275 °F), when suitable wetting conditions were applied. The results in Table 3-4 and 3-5 demonstrate that integrity testing after exposure to steaming under dry conditions requires the use of 1.5 barg (21.8 psi) back pressure to achieve complete water wetting for integrity testing.

Table 3-3 Effects of Dry In-Situ Steam Exposure at 135 °C (275 °F) on Filter Integrity and Water Wettability for Fluorodyne EX Filter Cartridges in AB1UEDF7PH4 style when wetted with 1.5 barg (21.8 psi) Back Pressure for Integrity Testing

	Forward Flow* (mL/min) test results before and after exposure to 10 *in-situ* steam cycles at 135 °C (275 °F):	
Pall Cartridge Serial Number	**FF (mL/min) pre steaming**	**FF (mL/min) post steaming**
R01007007	21.2	18.3
R01007001	21.3	18.2
R01007014	22.4	20.7
R01009019	19.3	19.5
R01009004	17.7	21.2
R01009037	18.8	20.2

* Forward Flow values determined at 2760 mbar (40 psi) air test pressure, wet with water at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.

Table 3-4 Effects of Dry In-Situ Steam Exposure at 135°C (275°F) on Filter Integrity and Water Wettability for Fluorodyne EX Filter Cartridges in AB1UEDF7PH4 style when wetted with 1.0 barg (14.5 psi) Back Pressure for Integrity Testing

	Forward Flow* (mL/min) test results before and after exposure to 10 *in-situ* steam cycles at 135 °C (275 °F):	
Pall Cartridge Serial Number	**FF (mL/min) pre steaming**	**FF (mL/min) post steaming**
IH9026174	20.1	34.3
IH9026020	21.2	32.6
IH9026103	18.3	28.2
IH9026178	22.3	> 200 Re-test**: 53.9 Re-test**: 26.2

* Forward Flow values determined at 2760 mbar (40 psi) air test pressure, wet with water at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.
** Each re-test followed re-wetting with 1.0 bar (14.5 psi) back pressure

Table 3-5. Re-Test of Fluorodyne EX Filter Cartridges Presented in Table 3-4 Re-wetted with 1.5 barg (21.8 psi) Back Pressure for Integrity Testing

	Forward Flow* (mL/min) test results before and after exposure to 10 *in-situ* steam cycles at 135 °C (275 °F):	
Pall Cartridge Serial Number	**FF (mL/min) pre steaming**	**FF (mL/min) post steaming**
IH9026174	20.1	20.7
IH9026020	21.2	20.5
IH9026103	18.3	22.0
IH9026178	22.3	26.9

* Forward Flow values determined at 2760 mbar (40 psi) air test pressure, wet with water at 20 °C ± 5 °C (68 °F ± 9 °F), maximum allowable limit value 30 mL/min.

3.4 Conclusions

Fluorodyne EX filter cartridges have been demonstrated to be capable of withstanding multiple *in-situ* steam sterilization cycles, while water wet and also while dry prior to steaming. Application of suitable wetting conditions (1.5 barg [21.8 psi] back pressure) will ensure that the filter cartridges will fully wet for integrity testing both before and after exposure to wet and dry *in-situ* steam cycles.

The data presented in this section support the following product claim for *in-situ* steaming **Fluorodyne** EX filter cartridges:

Filter Part Number	Steaming Conditions	Maximum Recommended Steam Life Claim
AB1UEDF7PH4	*In-situ* steam cycles at 135°C (275°F)	5 one-hour cycles

The above claim is supported by data with a 100 % safety margin.

4. Determination of Water Flow Characteristics

4.1 Introduction

The aim of these tests was to determine the typical differential pressure across **Fluorodyne** EX filter cartridges at set water flow rates.

4.2 Summary of Methods

The tests were performed on five standard production filter cartridges, part number AB1UEDF7PH4. The filter cartridges were sampled from three different manufacturing batches.

Pre-filtered DI water was pumped through the filters in the normal flow ('out to in') direction. Pressure readings from transducers on the upstream and downstream sides of the test assembly were monitored to calculate the differential pressure at set water flow rates.

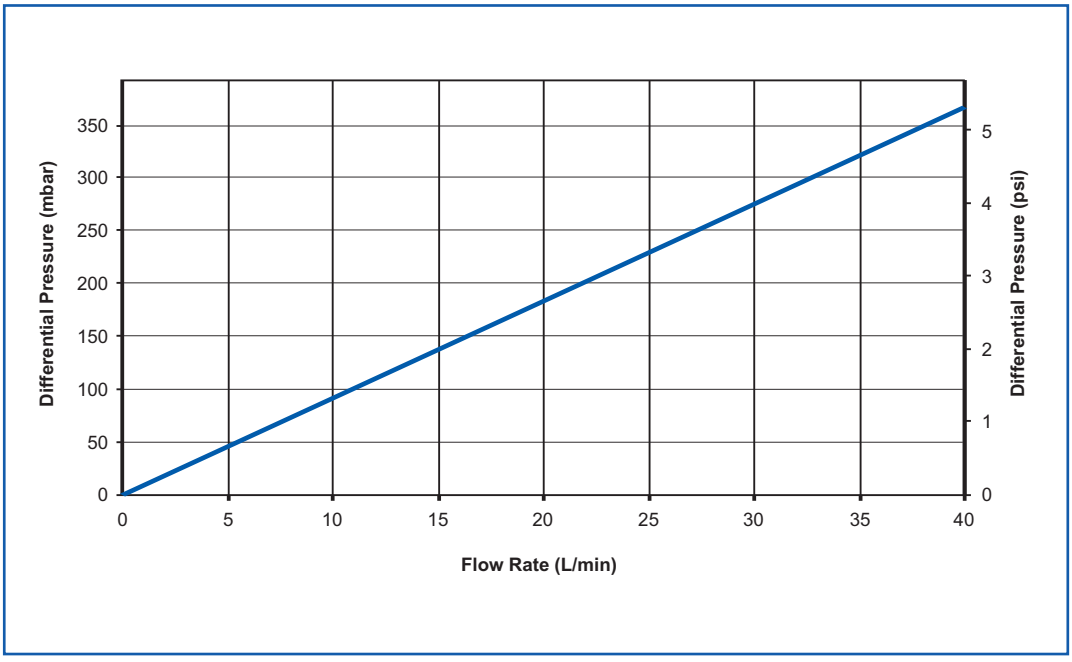
Further flow measurements were taken with the test rig with no filter cartridge installed so that the pipework/housing losses could be measured and then subtracted from the filter assembly results.

The results were corrected for a standard temperature of 20 °C (68 °F).

4.3 Results

Figure 4-1 shows the water flow characteristic for a typical **Fluorodyne** EX filter cartridge, part number AB1UEDF7PH4. The values in the graph represent average values taken from five different filter cartridges.

Figure 4-1 Water Flow/Differential Pressure Characteristics of a typical Fluorodyne EX Filter Cartridge, Part Number AB1UEDF7PH4



4.4 Conclusions

Water flow rates at set differential pressures have been determined. The average pressure drop for a 254 mm (10 inch) **Fluorodyne** EX filter cartridge (part number AB1UEDF7PH4) at 10 L/min clean water flow was 95 mbar (1.38 psi) at 20 °C (68 °F). These data can be used to assist users in sizing filter systems employing **Fluorodyne** EX filter cartridges.

5. Extractables Testing Using Water

5.1 Introduction

The aim of this series of tests was to quantify and characterize the material that can be extracted from **Fluorodyne** EX filter cartridges using water.

5.2 Summary of Methods

Typical production filters (part number AB1UEDF7PH4) were used for the tests.

Preparation of Filter Samples

Prior to the extraction test the filter samples were autoclaved in order to maximize the quantity of any extractable material present. The filter cartridges were wrapped in aluminum foil and autoclaved for one hour at 125 °C ± 5 °C (257 °F ± 9 °F), using a slow exhaust cycle. Visible droplets of water remaining on the filter cartridges were allowed to evaporate at room temperature before the extraction was performed.

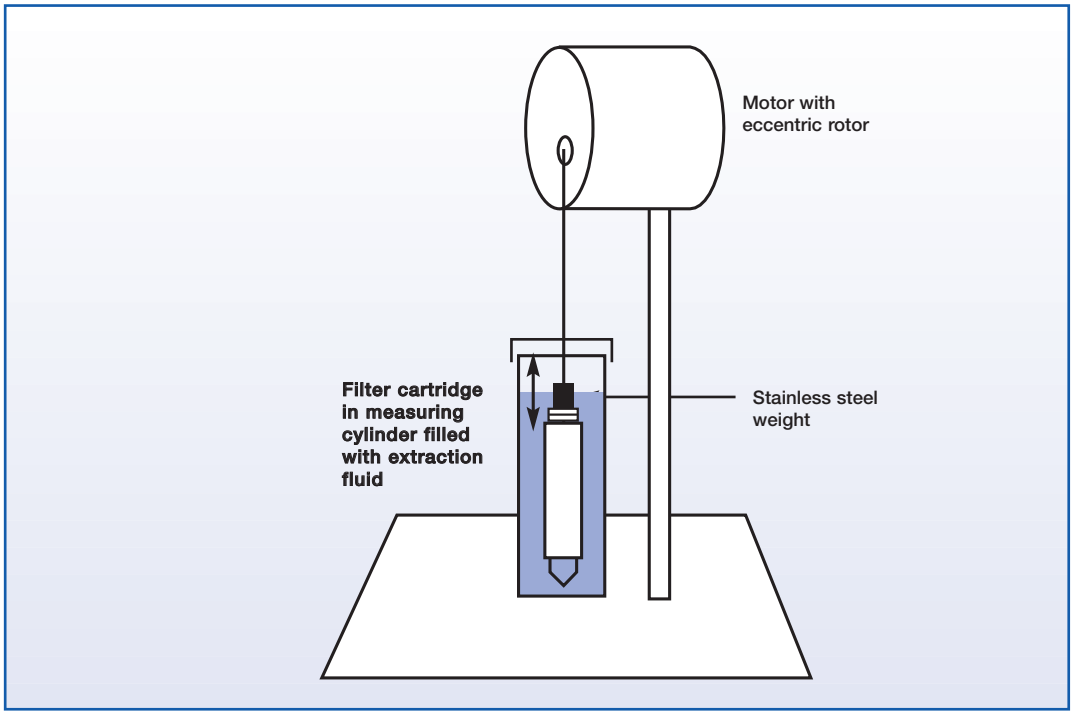
Extraction Procedure for Filter Cartridges

Dynamic extraction tests were performed in a known volume of water at ambient temperature. The test filters were immersed in the extraction fluid in a clean measuring cylinder, as shown in Figure 5-1. For four hours the filter was gently moved up and down. This movement created flow through the filter membrane as a result of the pressure head that was created each time the element was partially lifted out of the liquid.

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

The extractables were also analyzed by Fourier Transform Infra Red Spectroscopy (FTIR).

Figure 5-1 Filter Extraction Apparatus



5.3 Results

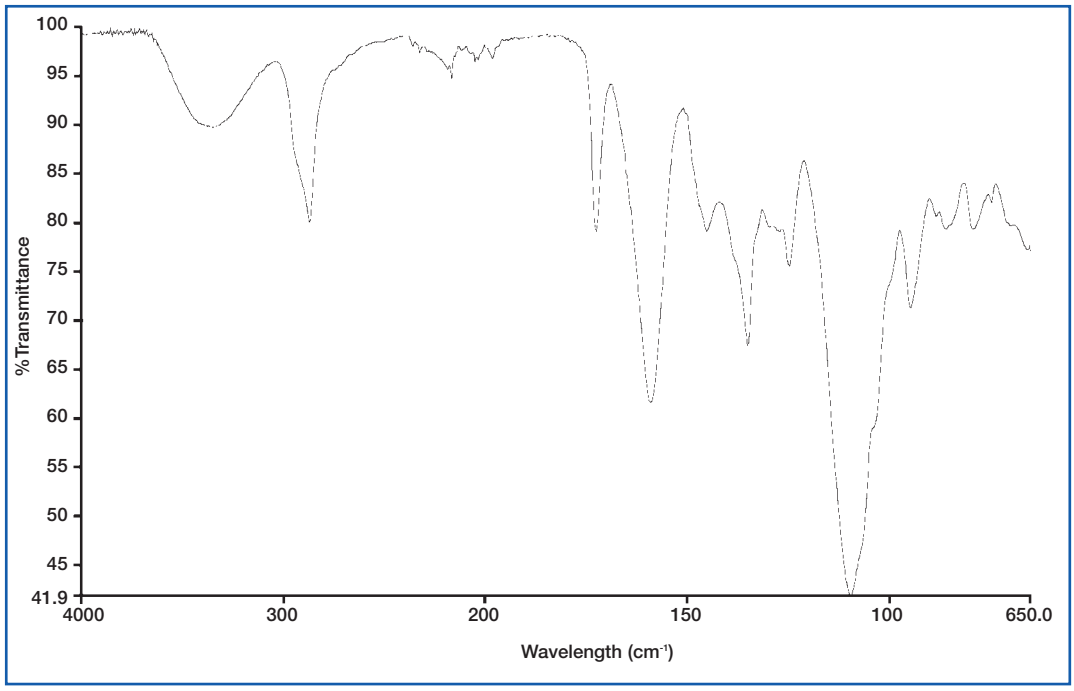
Table 5-1 shows the levels of aqueous extractables obtained from the **Fluorodyne** EX filter cartridges that were tested.

Table 5-1. Non-volatile Aqueous Extractables Obtained Using Fluorodyne EX Filter Cartridges After Autoclaving at 125 °C ± 5 °C (257 °F ± 9 °F) (4 Hours Extraction Time at Ambient Temperature)

Filter Cartridge Part Number	Extraction Fluid	Filter Cartridge Serial Number	Non-Volatile Residue (mg)
AB1UEDF7PH4	DI water	R01007021	47
		R01009040	29
		R01009047	41
		IH9026107	34
		IH9026153	34

A typical infrared spectrum of an aqueous extract from a **Fluorodyne** EX filter cartridge (part number AB1UEDF7PH4) is shown in Figure 5-2.

Figure 5-2 Typical Infra Red Spectrum of the Aqueous Extractables from Fluorodyne EX Filter Cartridges



5.4 Conclusions

The typical amount of non-volatile residue (NVR) extracted from **Fluorodyne** EX filter cartridges in AB1 style has been determined using water as the extraction fluid. For the 254 mm (10 inch) filter cartridges tested (part number AB1UEDF7PH4) the aqueous extractables ranged from 29 to 37 mg.

The levels of aqueous extractables were determined for **Fluorodyne** EX filter cartridges with the part number AB1UEDF7PH4. The FTIR spectrum of the extract indicates the presence of extractables typical of polyethersulfone resins and the copolymer used to render the polyethersulfone membrane hydrophilic. It also indicates the presence of the acrylate polymer used to render the polyvinylidenedifluoride membrane hydrophilic. Water extractables of polypropylene components are extremely low and were therefore not detected in this test.

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

6. Biological Reactivity Tests on the Materials of Construction

6.1 Introduction

The aim of this study was to evaluate the biological suitability of the materials of construction of **Fluorodyne** EX filter cartridges. The materials of construction of the filters are as follows:

Membranes:	**Upstream layer:** **Pall** hydrophilic polyethersulfone (PES) membrane **Downstream layer:** **Pall** hydrophilic polyvinylidenedifluoride (PVDF) membrane
Membrane support and drainage layers:	Polypropylene
Core and endcaps:	Polypropylene
Filter cage:	Polypropylene with titanium dioxide
O-rings:	Silicone elastomer for 'H4' option

6.2 Summary of Methods

The tests were performed in accordance with the Biological Reactivity Tests (*in vivo)* for Class VI Plastics (121 °C) as described in the current United States *Pharmacopeia.*

The testing procedures described in the USP include:

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

The four extracting media listed in the USP 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)**

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

Acute Systemic Injection Tests

An Acute Systemic Injection Test was performed to evaluate the potential of a single injection of an extract to produce systemic toxicity. Sodium Chloride Injection and 1 in 20 Solution of Alcohol in Sodium Chloride Injection were injected intravenously. Vegetable oil extract and Polyethylene Glycol 400 extract were injected intraperitoneally.

Intracutaneous Tests

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

Implantation Tests

Implantation tests were also performed, in order to subject the materials of construction to the most stringent conditions included in the USP. Each of the materials of the **Fluorodyne** EX filter cartridge was implanted separately.

6.3 Results

No biological response was observed in any of the tests performed and therefore the materials used in **Fluorodyne** EX filter cartridges passed all of the tests specified.

6.4 Conclusions

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

Copies of the test reports are available by contacting Pall Corporation.

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SM/07/2006