PALL Life Sciences

Validation Guide

USTR 2569

Fluorodyne® EX Grade EDT Filter Cartridges

Filtration. Separation. Solution.SM

CONTENTS

1. Overview

1.1 Introduction

This guide contains validation data applicable to 0.1 µm microbially rated Fluorodyne EX Grade EDT filter cartridges in AB style. These filters have been designed as sterilizing-grade liquid filters, additionally providing a high titer reduction capability for mycoplasma-type bacteria, which are known to penetrate bacterially rated 0.2 µm sterilizing-grade filters. The removal rating of 0.1 µm is based on challenges with *Acholeplasma laidlawii* (ATCC 23206*). Fluorodyne EX Grade EDT filters are also qualified for retention of *Brevundimonas diminuta* (ATCC 19146*) at $>10^7$ colony forming units (cfu)/cm^2 according to ASTM Standard F838-05 and US FDA guidance. The filter cartridges feature a novel construction, being comprised of one layer of 0.2 µm rated asymmetric polyethersulfone (PES) membrane upstream and two layers of 0.1 µm rated polyvinylidene fluoride (PVDF) membrane downstream. The asymmetric upstream membrane layer provides built-in prefiltration for the symmetric downstream membrane layers.

The 254 mm (10 in.) AB-style filter is manufactured using patented Ultipleat® construction combined with an optimization of the core. This laid-over pleat configuration and the narrow core design maximize membrane area to enable increased flow rates and extend filter life.

This report summarizes the tests that were conducted to qualify the performance of Fluorodyne EX Grade EDT filter cartridges under a range of standard test conditions. The following Pall Fluorodyne EX filter part number has been tested during this study: AB1UEDT7PH4.

The qualification program included:

- Microbial retention validation tests with *Brevundimonas diminuta* (ATCC 19146) and *Acholeplasma laidlawii* (ATCC 23206)
- Resistance to in situ steam under steam-autoclave conditions
- Determination of water flow characteristics
- Extractables testing using water
- Rinse-up studies based on Total Organic Carbon (TOC) measurements
- Biological reactivity tests

Materials of construction and performance parameters of Fluorodyne EX Grade EDT filter cartridges are described in the Pall Fluorodyne EX Grade EDT datasheet (USD2561), which supplements this guide.

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

1 bar = 1×10^5 Pa

1 psi = 6.89476×10^3 Pa

1.2 Summary of Conclusions

1.2.1 Microbial Retention Validation Tests

Fluorodyne EX Grade EDT filter cartridges were tested for bacterial retention of *Brevundimonas diminuta* (ATCC 19146) using bacterial tests per modified ASTM Standard F838-05 Test Method, and in accordance with the U.S. FDA's Guidance for Industry — Sterile Drug Products Produced By Aseptic Processing (September 2004). They were also tested for bacterial retention of mycoplasma-type bacteria, *Acholeplasma laidlawii* (ATCC 23206).

The result of the tests support the following microbial retention claims for Fluorodyne EX Grade EDT filter cartridges as indicated in Table 1: Microbial Retention Claims for Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4.

Table 1 Microbial Retention Claims for Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4

Test Organism	Titer Reduction Claim
Brevundimonas diminuta	Sterilizing grade (providing a sterile filtrate when challenged with $>10^7$ colony forming units (cfu)/cm^2 of filter area)
Acholeplasma laidlawii	$> 10^{10}$

The Forward Flow integrity test was shown to be a suitable non-destructive integrity test for Fluorodyne EX Grade EDT filter cartridges. Test parameters have been set for 254 mm (10 in.) filters (part number AB1UEDT7PH4) as indicated in Table 2.

Table 2 Forward Flow Integrity Test Parameters for 254 mm (10 in.) Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4

Test pressure	4475 mbar (65 psi)
Wetting liquid	Water
Temperature	20 °C ± 5 °C
Test gas	Air
Maximum allowable forward flow limit[1]	32.0 mL/min

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

1.2.2 Resistance to In Situ Steam and Autoclave Conditions

Fluorodyne EX Grade EDT filter cartridges have demonstrated the ability to withstand multiple in situ steam cycles under various standard steaming conditions (125 °C and 135 °C). Tests performed demonstrate that Fluorodyne EX Grade EDT filter cartridges in AB style are robust and capable of withstanding differential pressures up to 0.3 bar (4.35 psi) in the forward direction during steaming, while maintaining full water wettability under the wetting conditions applied (4 L/min water flush for 10 minutes, no back pressure). The filters have also shown to maintain their specified microbial retention capabilities during steaming. The physical test conditions for in situ steaming can be considered as worst case for any sterilization process by steam and therefore include autoclaving process conditions with the same temperature exposure and cycles times. To confirm autoclavability of the Fluorodyne EX Grade EDT filters, additional autoclaving tests at 135 °C have been performed.

The data presented in this report support the product claims shown in Table 3.

Table 3 Product Claims for Steam Resistance (In Situ Steaming and Autoclaving) Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4

Pall Filter Part Number	Steam Exposure Conditions	Maximum Recommended Steam Life Claim
AB1UEDT7PH4	Steaming cycles at 125 °C	10 x 1-hour cycle
AB1UEDT7PH4	Steaming cycles at 135 °C	5 x 1-hour cycle

The claims in Table 3 are supported by data with a 100 % safety margin. Filters should be qualified in actual conditions of use.

1.2.3 Determination of Water Flow Characteristics

Differential pressure measurements at set water flow rates have been determined. The typical clean water flow at 20 °C for a 254 mm (10 in.) Fluorodyne EX Grade EDT filter cartridge (part number AB1UEDT7PH4) at 100 mbar pressure drop (1.45 psi) is 2.7 L/min.

These data can be used to assist users in sizing filter systems employing Fluorodyne EX Grade EDT filter cartridges.

1.2.4 Extractables Testing using Water

The average amount of non-volatile residue (NVR) extracted from Fluorodyne EX Grade EDT filter cartridges in AB1 style after "worst case" autoclaving without pre-rinsing has been determined using water as the extraction fluid. For the 254 mm (10 in.) filter cartridges tested (part number AB1UEDT7PH4) the values for a extraction ranged from 23.9 mg to 59.7 mg, resulting in an average NVR of 34.6 mg with a standard deviation of 9.6 mg. The values of a second (consecutive) extraction were always significantly lower than those obtained in the first extraction and ranged from 5.9 mg to 20.3 mg, demonstrating that quantitative extractables determination is not solubility limited.

The contents of the various inorganic ions analyzed by Inductively Coupled Plasma (ICP) were extremely low. The measurement results of almost all extract samples analyzed were under the limit of detection. The only exception was a slightly increased value for Ni (0.23 µg/L) in the first extract of one of the two cartridges tested. In the second (consecutive) extract, the content of Ni was below detection limit (< 0.1 µg/L).

The Total Organic Carbon (TOC) content of the first extract of one filter cartridge was determined as 25.2 ppm, while the second extract of another filter cartridge was determined as 10.5 ppm.

The lower NVR, inorganic ion and TOC content in the second (consecutive) extracts demonstrates the depletion of total soluble material available to the solvent in the finite test time and indicates that exposures greater than 48 hours will not result in a significant increase in the quantity of extractables.

In a rinse-up study, the TOC content in the filtrate samples of all Fluorodyne EX Grade EDT filter cartridges in AB1 style, part number AB1UEDT7PH4, exponentially decreased during flushing with ultra pure water and was below 500 ppb (0.5 ppm) after 20 minutes (equivalent of 20 liters) of flushing.

Actual service in pharmaceutical applications will impose different conditions, such as different steaming conditions, exposure times, temperature, liquid types, and filter system configuration. Evaluation under process conditions is therefore also recommended.

Contact Pall for assistance in determining process-specific extractables.

1.2.5 Biological Reactivity Tests

All of the materials used in Fluorodyne EX Grade EDT filter cartridges meet the requirements of the Biological Reactivity Tests (in vivo) for Class VI-121 °C plastics, listed in the current revision of the United States Pharmacopeia (USP). The tests included the Systemic Injection test, the Intracutaneous test and the Implantation test. Test reports are available on request.

2. Microbial Retention Validation Tests for 254 mm (10 in.) Fluorodyne EX Grade EDT Filter Cartridges

2.1 Introduction

The FDA's Guidance for Industry — Sterile Drug Products Produced By Aseptic Processing — Current Good Manufacturing Practice (2004) states:

> 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 *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 recommendations of this guidance, liquid challenge tests using *Brevundimonas diminuta* were performed with Fluorodyne EX Grade EDT filter cartridges using a minimum of 1 x 10^7 cfu/cm^2 of effective filtration area to demonstrate its ability to perform as a sterilizing filter per FDA definition.

The control of mycoplasma-type bacteria is important to many pharmaceutical processes. Mycoplasma species are parasites or commensals of higher organisms, such as plants, animals, and humans. Being deformable due to their lack of a rigid cell wall, they can pass through bacterially rated 0.2 µm sterilizing grade filters. Well-known sources of mycoplasma contamination in pharmaceutical processes are animal and plant derived raw materials, such as animal serum and plant peptide digests, and operator contact.

Contamination by mycoplasma species in fluids can be reliably controlled by the use of an adequately designed filter, ie. employing 0.1 µm rated membranes. The validation of such a filter for its mycoplasma retention capabilities requires a suitable challenge organism, which can serve as a model for mycoplasma-type deformable bacteria, is relatively easy to culture, and can be grown to high titers.

The ubiquitous bacterium *Acholeplasma laidlawii* has been used as a challenge organism model for 0.1 µm rated filters for almost 30 years. It was selected based on recognition as a penetrant of 0.2 µm sterilizing grade filters in both water and plasma, and its ability to grow to high titers in cell-free culture media. The strain *Acholeplasma laidlawii* (ATCC 23206) was chosen as challenge organism for the validation of the mycoplasma retention capabilities of Fluorodyne EX Grade EDT filter cartridges, using a minimum of 1 x 10^7 cfu/cm^2 of effective filtration area.

The FDA guidance 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 filter's integrity test specification should be consistent with the data generated during bacterial retention validation studies.

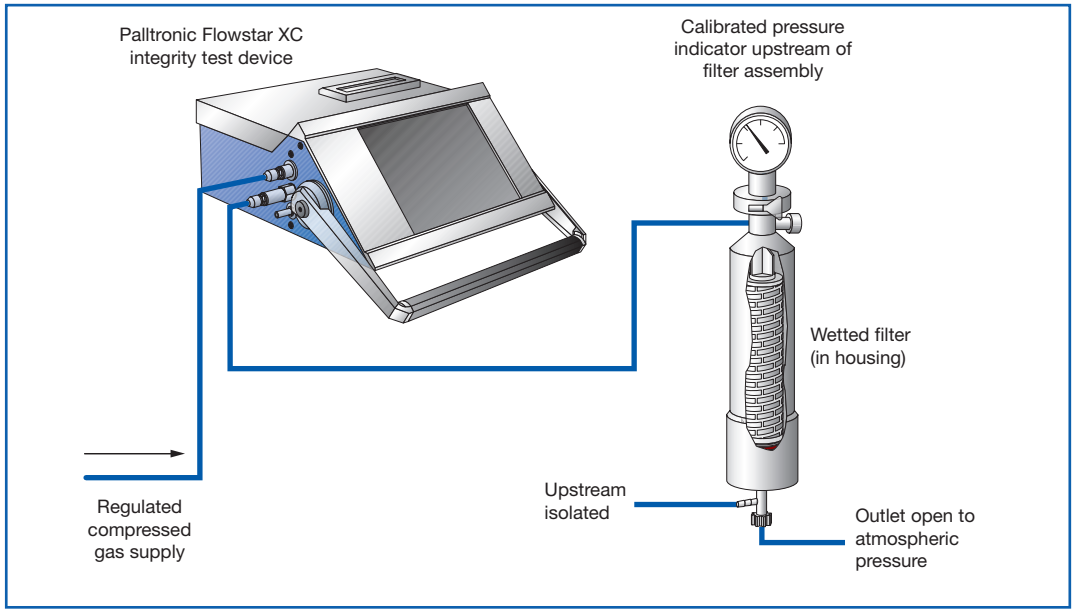
The correlation between microbial retention and a non-destructive integrity test is an important aspect of the validation of sterilizing-grade filters. The Forward Flow test[1] was the integrity test used during this study.

1. Pall, David B., "Quality Control of Absolute Bacteria Removal Filters," *Bulletin of the Parenteral Drug Assoc.*, 1975.

2.1.1 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 suitable stabilization period, the gas flow through the wetted membrane can be measured on the upstream side, using sensitive flow measurement equipment such as the Palltronic® Flowstar filter integrity test instrument (Figure 1). This gas flow is comprised of diffusion plus bulk flow through any unwetted pores.

Figure 1 The Automated Integrity Test



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

2.2 Summary of Methods

2.2.1 Microbial challenge testing with *Brevundimonas diminuta* and *Acholeplasma laidlawii*

Typical Fluorodyne EX Grade EDT filter cartridges, part number AB1UEDT7PH4, membrane area 0.945 m^2 (10.17 ft^2), from three separate manufacturing batches were subjected to standard microbial challenge tests using aqueous suspensions of *Brevundimonas diminuta* and *Acholeplasma laidlawii* respectively.

Prior to the challenge tests the filters were installed in an appropriate housing and flushed with deionized (DI) water at a flow rate of 4 L/min for 10 minutes. With the filters submitted to challenge testing with *Acholeplasma laidlawii*, a Forward Flow integrity test was performed using a Palltronic Flowstar integrity test instrument with an air test pressure of 4475 mbar (65 psi) at this point. All filters were then autoclaved at 121 °C for 60 minutes. After autoclaving, a Forward Flow integrity test was performed with all filters using a Palltronic Flowstar integrity test instrument with an air test pressure of 4475 mbar (65 psi). The filter assembly was then aseptically connected to the pre-sterilized challenge apparatus, as shown in Figure 2: Microbial Challenge Apparatus.

An aqueous suspension of *Brevundimonas diminuta* or *Acholeplasma laidlawii* was passed through the filter cartridge to achieve a challenge level of > 1 x 10^7 cfu/cm^2 of effective filtration area.

During the challenge test the entire filter effluent was passed through a 0.2 µm-rated (*Brevundimonas diminuta* challenge) or 0.1 µm-rated (*Acholeplasma laidlawii* challenge) analysis disc on the downstream side of the test filter assembly. The filter disc was incubated on agar. The disc was then 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:

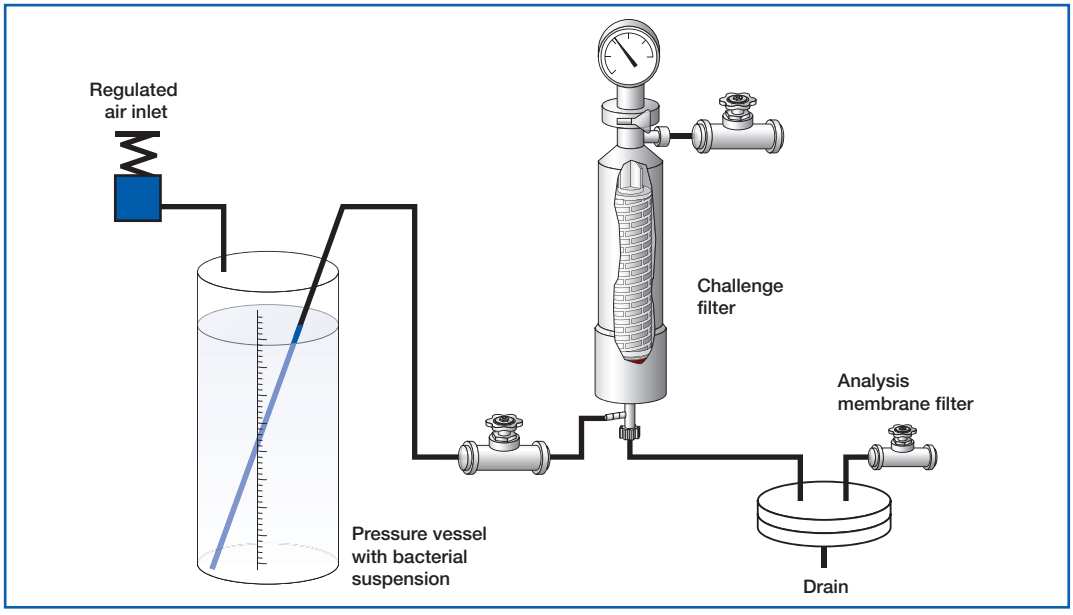
$$T_R = \frac{\text{Total number of bacteria influent to the filter}}{\text{Number of colonies recorded on the downstream analysis disc}}$$

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

> Total number of organisms influent to the filter (e.g., > 1 x 10^7)

On completion of the challenge test the filter assemblies were sanitized, either by autoclaving (filters having undergone *Brevundimonas diminuta* challenge) or by chemical sanitization (filters having undergone *Acholeplasma laidlawii* challenge), water-flushed and Forward Flow tested as described previously.

Figure 2 Microbial Challenge Apparatus



2.3 Results

The Forward Flow and *Brevundimonas diminuta* retention results are shown in Table 4: Results of Forward Flow and *Brevundimonas diminuta* Retention for Typical Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4. 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/cm^2 of filtration area using *Brevundimonas diminuta*.

Table 4 Results of Forward Flow and *Brevundimonas diminuta* Retention for Typical Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4

Pall Cartridge Serial Number	Forward Flow* (mL/min)	Sterile Effluent	Titer Reduction
IL8350156	20.1	Yes	> 3.75×10^{11}
IL8350234	21.0	Yes	> 3.70×10^{11}
IL8350211	21.4	Yes	> 3.27×10^{11}
IL8350346	21.9	Yes	> 3.24×10^{11}
IL8350014	22.1	Yes	> 3.14×10^{11}
IM1597338	22.8	Yes	> 2.35×10^{11}
IM1597011	23.0	Yes	> 3.19×10^{11}
IM1597022	23.0	Yes	> 2.57×10^{11}
IL8352099	23.6	Yes	> 3.80×10^{11}
IM1597255	23.8	Yes	> 3.09×10^{11}
IL8350338	24.0	Yes	> 4.44×10^{11}
IL8352189	24.1	Yes	> 3.52×10^{11}
IM1597276	24.1	Yes	> 3.14×10^{11}
IL8352329	25.5	Yes	> 3.70×10^{11}
IL8350282	25.8	Yes	> 2.82×10^{11}
IM1597161	25.8	Yes	> 3.62×10^{11}
IL8352237	26.1	Yes	> 3.79×10^{11}
IM1597119	27.5	Yes	> 3.29×10^{11}
IL8350076	27.7	Yes	> 3.59×10^{11}
IL8352376	28.0	Yes	> 3.20×10^{11}
IL8352138	28.6	Yes	> 3.84×10^{11}
IL8352307	28.9	Yes	> 3.44×10^{11}
IL8352042	30.0	Yes	> 2.90×10^{11}
IM1597075	33.7	Yes	> 3.32×10^{11}

* Forward Flow values at 4475 mbar (65 psi) air test pressure, wet with water, at 20 °C ± 5 °C, maximum allowable limit value of 32.0 mL/min.

The Forward Flow and *Acholeplasma laidlawii* retention results are shown in Table 5. The highest of the three Forward Flow values (pre-autoclaving, post-autoclaving and post-challenge) is presented and the data are arranged in order of increasing Forward Flow value.

Almost all of the filter cartridges tested gave sterile effluent when challenged with > 1×10^7 cfu/cm^2 of filtration area using *Acholeplasma laidlawii*. One filter showed penetration of *Acholeplasma laidlawii* on a very low level (1 colony).

Table 5 Results of Forward Flow and *Acholeplasma laidlawii* Retention for Typical Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4

Pall Cartridge Serial Number	Forward Flow* (mL/min)	Sterile Effluent	Titer Reduction
IL8350136	22.0	Yes	> 3.6×10^{11}
IL8352170	22.7	Yes	> 5.4×10^{11}
IL8352306	22.8	Yes	> 5.4×10^{11}
IL8352320	22.9	Yes	> 5.4×10^{11}
IL8352392	23.0	Yes	> 5.4×10^{11}
IL8350218	23.6	Yes	> 3.6×10^{11}
IL8350085	24.2	Yes	> 3.6×10^{11}
IM1597227	24.2	Yes	> 1.2×10^{12}
IL8350202	24.3	Yes	> 3.6×10^{11}
IM1597345	24.3	Yes	> 1.2×10^{12}
IM1597176	24.5	no	1.2×10^{12}
IL8352019	24.6	Yes	> 3.9×10^{11}
IL8352120	24.8	Yes	> 3.9×10^{11}
IL8350345	25.2	Yes	> 3.6×10^{11}
IL8350319	25.3	Yes	> 3.6×10^{11}
IM1597031	25.3	Yes	> 1.2×10^{12}
IM1597120	25.4	Yes	> 1.2×10^{12}
IM1597096	25.8	Yes	> 1.2×10^{12}
IM1597048	26.2	Yes	> 1.2×10^{12}
IL8350009	26.3	Yes	> 3.6×10^{11}
IL8352076	26.3	Yes	> 3.9×10^{11}
IM1597268	26.3	Yes	> 1.2×10^{12}
IL8352221	26.6	Yes	> 3.9×10^{11}
IL8350276	28.4	Yes	> 3.6×10^{11}

* Forward Flow values at 4475 mbar (65 psi) air test pressure, wet with water, at 20 °C ± 5 °C, maximum allowable limit value of 32.0 mL/min.

2.4 Conclusions

All of the Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) tested provided sterile effluent when subjected to aqueous microbial challenge tests using *Brevundimonas diminuta* at a challenge level of > 1×10^7 cfu/cm^2.

Almost all of the Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) tested provided sterile effluent when subjected to aqueous microbial challenge tests using *Acholeplasma laidlawii*. Only one cartridge was found to show penetration of *Acholeplasma laidlawii* on a extremely low level (1 colony).

Forward Flow integrity test parameters have been set for Fluorodyne EX Grade EDT filter cartridges based on the above results of the microbial challenge tests and additional considerations and parameters and are shown in Table 6.

Table 6 Forward Flow Integrity Test Parameters for Fluorodyne EX Grade EDT Filter Cartridges, Part Number AB1UEDT7PH4*

Test pressure	4475 mbar (65 psi)
Wetting liquid	Water
Temperature	20 °C ± 5 °C
Test gas	Air
Maximum allowable Forward Flow limit**	32.0 mL/min

* See Section 2.2: Summary of Methods for test procedure.

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

3. Resistance to In Situ Steam and Autoclaving of 254 mm (10 in.) Fluorodyne EX Grade EDT Filter Cartridges

3.1 Introduction

The purpose of these tests was to determine the effects of repeated exposure to in situ steam and autoclaving cycles on filter integrity and water wettability using standard Fluorodyne EX Grade EDT filter cartridges in AB style. The tests were used to qualify the steam exposure claims for Fluorodyne EX filter cartridges and confirm that filters maintain their microbial retention capabilities during steaming.

3.2 Summary of Methods

3.2.1 In Situ Steaming at 125 °C

Typical Fluorodyne EX Grade EDT filter cartridges from three (3) different manufacturing batches (part number AB1UEDT7PH4) were used for the tests.

The test sequence was as follows:

1. Flushing with DI water for 10 minutes at 4 L/min
2. Forward Flow integrity test to confirm their integrity prior to steaming
3. Drying of the filters at 40 °C
4. Subjecting the dry filters to two (2) one-hour in situ steam cycles at 125 °C
5. Flushing with water for 10 minutes at 4 L/min
6. Forward Flow integrity test to confirm integrity and water wettability post dry steaming and prior to further steaming tests
7. Subjecting the wet filters to eight (8) additional one-hour in situ steam cycles at 125 °C with a water flush prior to each steam cycle
8. Flushing with water for 10 minutes at 4 L/min
9. Forward Flow integrity test to confirm integrity and water wettability post wet steaming and prior to further steaming tests
10. Subjecting the wet filters to further ten (10) one-hour in situ steam cycles at 125 °C with a water flush prior to each steam cycle
11. Forward Flow integrity test to confirm integrity and water wettability post wet steaming.

During the initial stages of the wet steam cycles, the wet filter membrane caused the differential pressure to increase across the filter as steam was introduced. The steam inlet valve was controlled so that the differential pressure across the wetted filter did not exceed 0.3 bar (4.35 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.

3.2.2 In Situ Steaming at 135 °C Including Microbial Challenge Tests Post-Steaming

Typical Fluorodyne EX Grade EDT filter cartridges from three (3) different manufacturing batches (part number AB1UEDT7PH4) were used for the tests.

The test sequence was as follows:

1. Flushing with DI water for 10 minutes at 4 L/min
2. Forward Flow integrity test to confirm their integrity prior to steaming
3. Drying of the filters at 40 °C
4. Subjecting the dry filters to two (2) one-hour in situ steam cycles at 135 °C
5. Flushing with water for 10 minutes at 4 L/min
6. Forward Flow integrity test to confirm integrity and water wettability post dry steaming and prior to further steaming tests
7. Subjecting the wet filters to eight (8) additional one-hour in situ steam cycles at 135 °C with a water flush prior to each steam cycle
8. Flushing with water for 10 minutes at 4 L/min
9. Forward Flow integrity test to confirm integrity and water wettability after wet steaming
10. Microbial challenge tests with *Brevundimonas diminuta* following the methods described in Section 2.2: Summary of Methods of this report

During the initial stages of the wet steam cycles, the wet filter membrane caused the differential pressure to increase across the filter as steam was introduced. The steam inlet valve was controlled so that the differential pressure across the wetted filter did not exceed 0.3 bar (4.35 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.

3.2.3 Autoclave Resistance at 135 °C

Typical Fluorodyne EX Grade EDT filter cartridges from three (3) different manufacturing batches (part number AB1UEDT7PH4) were used for the tests.

The test sequence was as follows:

1. Subjecting the dry filters to five (5) one-hour autoclave cycles at 135 °C
2. Flushing with water for 10 minutes at 4 L/min

3. Forward Flow integrity test to confirm integrity and water wettability post dry autoclaving and prior to further autoclaving tests

4. Drying of the filters at 40 °C

5. Subjecting the dry filters to five (5) additional one-hour autoclave cycles at 135 °C

6. Flushing with water for 10 minutes at 4 L/min

7. Forward Flow integrity test to confirm integrity and water wettability post dry autoclaving

3.3 Results

3.3.1 In Situ Steaming at 125 °C

The Forward Flow integrity test results for all tested Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) after exposure to in situ steam cycles at 125 °C are shown in Table 7. All of the filter cartridges retained integrity and full water wettability under the wetting conditions applied (10 minutes at 4 L/min, no backpressure) following exposure to two (2) 1-hour cycles at 125 °C when being dry prior to steaming, and 18 x 1-hour cycles at 125 °C when being wet prior to steaming.

Table 7 Effects of In Situ Steam Exposure at 125 °C on Filter Integrity and Wettability for Fluorodyne EX Grade EDT Filter Cartridges in AB1UEDT7PH4 Style

Forward Flow* Test Results after Exposure to 20 In Situ Steam Cycles at 125 °C

Pall Cartridge Serial Number	Integrity confirmed prior to test start and during the course of the testing	FF** (mL/min) Post-steaming	Integrity Result Post-steaming
IL8350073	Yes	23.7	Pass
IL8350116	Yes	22.8	Pass
IL8350137	Yes	21.6	Pass
IL8350380	Yes	22.4	Pass
IL8352084	Yes	23.6	Pass
IL8352196	Yes	20.8	Pass
IL8352303	Yes	20.6	Pass
IL8352405	Yes	21.4	Pass
IM1597027	Yes	23.3	Pass
IM1597034	Yes	25.0	Pass
IM1597113	Yes	23.0	Pass
IM1597146	Yes	23.2	Pass
IM1597207	Yes	22.3	Pass
IM1597218	Yes	26.5	Pass
IM1597322	Yes	23.7	Pass
IM1597334	Yes	23.3	Pass

* Wetted by Water Flushing for 10 Minutes at 4 L/min.
** Forward Flow values determined at 4475 mbar (65 psi) air test pressure, wet with water at 20 °C ± 5 °C, maximum allowable limit of 32.0 mL/min.

3.3.2 In Situ Steaming at 135 °C Including Microbial Challenge Tests

The Forward Flow integrity test results for all tested Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) after exposure to in situ steam cycles at 135 °C are shown in Table 8. All of the filter cartridges retained integrity and full water wettability under the wetting conditions applied (10 minutes at 4 L/min, no backpressure) following exposure to 2 (two) x 1-hour cycles at 135 °C when being dry prior to steaming, and 8 x 1 hour cycles at 135 °C when being wet prior to steaming.

Table 8 Effects of In Situ Steam Exposure at 135 °C on Filter Integrity and Wettability for Fluorodyne EX Grade EDT Filter Cartridges in AB1UEDT7PH4 Style

Forward Flow* Test Results after Exposure to 10 In Situ Steam Cycles at 135 °C

Pall Cartridge Serial Number	Integrity confirmed prior to test start and during the course of the testing	FF** (mL/min) Post-steaming	Assessment of FF result
IL8350002	Yes	22.4	Pass
IL8350149	Yes	22.0	Pass
IL8350219	Yes	20.6	Pass
IL8350336	Yes	21.9	Pass
IL8352009	Yes	22.5	Pass
IL8352222	Yes	20.3	Pass
IL8352156	Yes	20.6	Pass
IL8352315	Yes	19.1	Pass
IM1597008	Yes	26.6	Pass
IM1597109	Yes	23.5	Pass
IM1597233	Yes	23.2	Pass
IM1597342	Yes	23.2	Pass

* Wetted by Water Flushing for 10 Minutes 4 L/min
** Forward Flow values determined at 4475 mbar (65 psi) air test pressure, wet with water at 20 °C ± 5 °C, maximum allowable limit of 32.0 mL/min.

The results of the microbial challenge tests post exposure to 10 x 1-hour cycles at 135 °C are shown in Table 9. All of the cartridges provided a sterile filtrate when challenged with *Brevundimonas diminuta* at a challenge level of > 1 x 10^7 cfu/cm^2.

Table 9 Effects of In Situ Steam Exposure at 135 °C on Microbial Retention Capabilities of Fluorodyne EX Filter Cartridges in AB1UEDT7PH4 Style*

Pall Cartridge Serial Number	Forward Flow** post Challenge (mL/min)	Sterile Effluent	Titer Reduction
IL8350002	19.5	Yes	> 5.32×10^{11}
IL8350149	18.7	Yes	> 6.45×10^{11}
IL8350219	18.2	Yes	> 6.82×10^{11}
IL8350336	18.6	Yes	> 4.94×10^{11}
IL8352009	19.5	Yes	> 3.95×10^{11}
IL8352222	18.5	Yes	> 4.37×10^{11}
IL8352156	17.4	Yes	> 3.97×10^{11}
IL8352315	17.6	Yes	> 4.05×10^{11}
IM1597008	20.4	Yes	> 4.12×10^{11}
IM1597109	20.1	Yes	> 4.65×10^{11}
IM1597233	20.9	Yes	> 4.50×10^{11}
IM1597342	21.4	Yes	> 4.40×10^{11}

* Wetted by Water Flushing for 10 Minutes at 10 L/min.
** Forward Flow values determined at 4475 mbar (65 psi) air test pressure, wet with water at 20 °C ± 5 °C, maximum allowable limit of 32.0 mL/min

3.3.3 Autoclave Resistance at 135 °C

The Forward Flow Integrity test results before and after autoclaving for six Fluorodyne EX Grade EDT cartridges, (part number AB1UEDT7PH4), which have been dry prior to autoclaving at 135 °C, are shown in Table 10. All filter cartridges retained integrity and water wettability under the wetting conditions applied (10 minutes water flush at 4 L/min, no backpressure) following exposure to 10 x 1-hour cycles of autoclaving at 135 °C having been dry prior to autoclaving.

Table 10 Effects of Autoclave Exposure at 135 °C on Filter Integrity for Fluorodyne EX Grade EDT Filter Cartridges in AB1UEDT7PH4 Style*

	Forward Flow (mL/min) Test Results after Exposure to 5 and 10 Autoclave Cycles at 135 °C**			
Pall Cartridge Serial Number	**FF (mL/min) after 5 Autoclaving Cycles**	**Assessment of FF Result**	**FF (mL/min) after 10 Autoclaving Cycles**	**Assessment of FF Result**
IL8350200	21.2	Pass	21.6	Pass
IL8350366	21.0	Pass	21.5	Pass
IL8352304	19.7	Pass	21.8	Pass
IL8352379	20.6	Pass	20.7	Pass
IM1597101	21.7	Pass	22.9	Pass
IM1597247	21.8	Pass	23.6	Pass

* Wetted by Water Flushing for 10 Minutes at 4 L/min
** Forward Flow values determined at 4475 mbar (65 psi) air test pressure, wet with water at 20 °C ± 5 °C, maximum allowable limit of 32.0 mL/min

3.4 Conclusions

Fluorodyne EX Grade EDT filter cartridges have been demonstrated to maintain their microbial retention capabilities after multiple in situ steam cycles, when steamed dry and also when pre-wet with water prior to steaming. Application of suitable wetting conditions (10 minutes water flush at 4 L/min, no backpressure required) will ensure that the filters will be fully wet for integrity testing both before and after exposure to wet or dry in situ steaming cycles.

The data presented in this section support the following product claims for in situ steaming or autoclaving of Fluorodyne EX Grade EDT filter cartridges in AB style:

Table 11 Product Claims for Steam Resistance (In Situ Steaming and Autoclaving) Fluorodyne EX Grade EDT Filter Cartridges

Pall Filter Part Number	Steam Exposure Conditions	Maximum Recommended Steam Life Claim
AB1UEDT7PH4	Steaming cycles at 125 °C	10 x 1-hour cycle
AB1UEDT7PH4	Steaming cycles at 135 °C	5 x 1-hour cycle

The claims in Table 11 are supported by data with a 100 % safety margin. Filters should be qualified in actual conditions of use.

4. Determination of Water Flow Characteristics

4.1 Introduction

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

4.2 Summary of Methods

The tests were performed on twelve (12) standard Fluorodyne EX Grade EDT filter cartridges in AB style, part number AB1UEDT7PH4. The filter cartridges were sampled from three (3) different manufacturing batches.

Pre-filtered deionized (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.

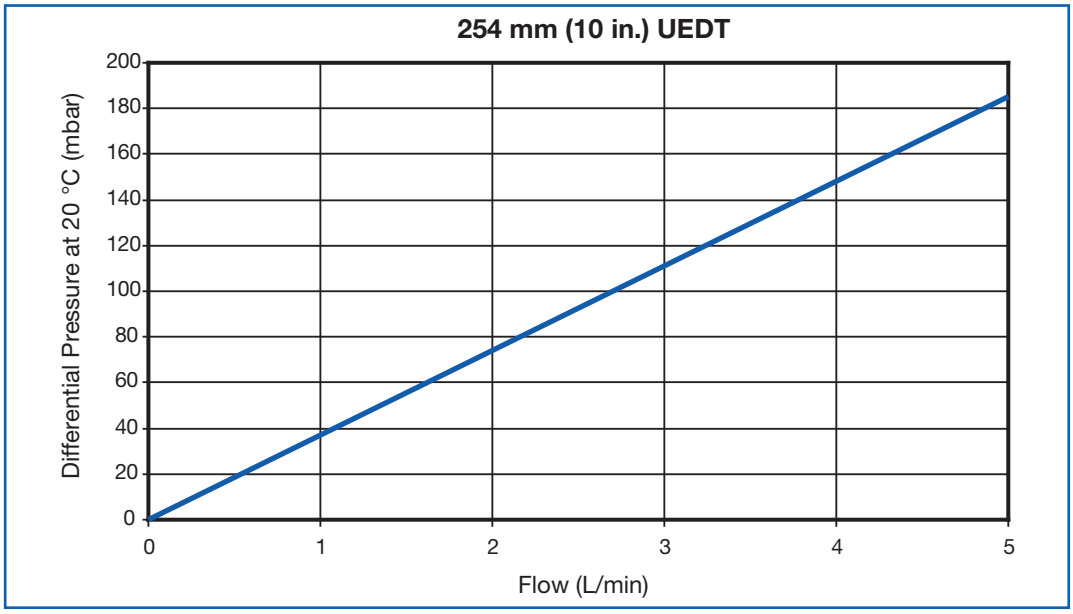
Further flow measurements were taken with the test rig with no filter cartridge or capsule installed, so that the pipe work/housing losses could be measured and then subtracted from the filter assembly results.

The results were corrected for a standard temperature of 20 °C.

4.3 Results

Figure 3 shows the water flow characteristic for a typical Fluorodyne EX Grade EDT filter cartridge, part number AB1UEDT7PH4. The values in the graph represent average values taken from 12 different filter cartridges.

Figure 3 Water Flow/Differential Pressure Characteristics of a Fluorodyne EX Grade EDT Filter Cartridge, Part Number AB1UEDT7PH4



4.4 Conclusions

Water flow rates at set differential pressures have been determined.

The typical clean water flow at 20 °C for a 254 mm (10 in.) Fluorodyne EX Grade EDT filter cartridge (part number AB1UEDT7PH4) at 100 mbar (1.45 psi) pressure drop is 2.7 L/min.

These data can be used to assist users in sizing filter systems employing Fluorodyne EX Grade EDT 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 Grade EDT filter cartridges using water. Water is considered a suitable "worst case" model solvent for a majority of aqueous solutions.

5.2 Summary of Methods

Standard Fluorodyne EX Grade EDT filter cartridges in AB style (part number AB1UEDT7PH4) were used for the tests.

5.2.1 Filter Extract Analytical Techniques: Total Non-Volatile Residue (NVR), Inductively Coupled Plasma (ICP) Spectroscopy, Total Organic Carbon (TOC), Fourier Transform Infrared Spectroscopy (FTIR)

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 loosely wrapped in aluminum foil, while the inlet and the outlet ports of the capsules were loosely covered with aluminum foil with the vent/drain valves open. The filters were then autoclaved for one hour at 125 °C ± 5 °C, using a slow exhaust cycle. Visible droplets of water remaining on the filter elements were allowed to evaporate at room temperature before the extraction was performed.

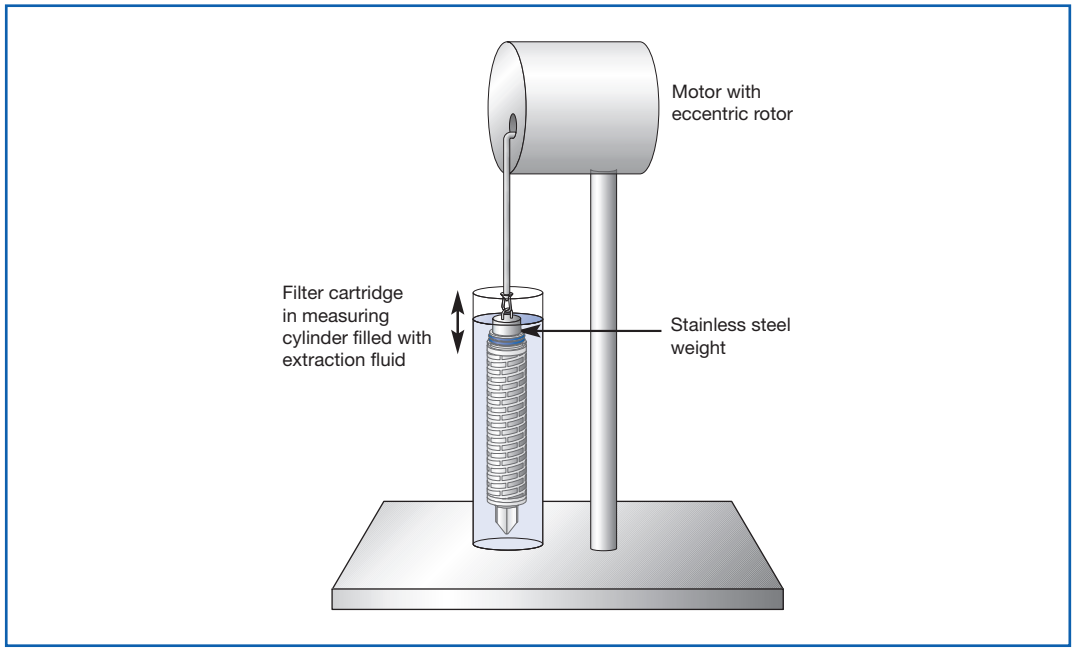
Extraction Procedure of Filter Samples

Dynamic extraction tests were performed in a known volume of deionized water at ambient temperature. The test filters were immersed in the extraction fluid in a clean measuring cylinder, as shown in Figure 4. For twenty four (24) hours the filter was gently moved up and down. This movement created flow through the filter membrane as a result of the pressure head that was created each time the element was partially lifted out of the liquid.

Some filter cartridges were submitted to a second (consecutive) dynamic extraction cycle under the same extraction conditions as described above.

Blank samples were determined as appropriate for method and result controls.

Figure 4 Filter Extraction Apparatus



Preparation of Samples for Analysis

Determination of NVR

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

Analysis by ICP

Following the extraction period, a sample volume of the extraction liquid was taken and analyzed by ICP for various inorganic ions.

Analysis by TOC

Following the extraction period, a sample volume of the extraction liquid was taken and analyzed for TOC. The measurement serve to provide a link to the TOC rinse-up studies described in Section 5.2.2: TOC Rinse-Up.

Analysis by FTIR

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

5.2.2 TOC Rinse-Up

This study was performed to characterize the TOC rinse-up behavior of Fluorodyne EX Grade EDT filter cartridges, part number AB1UEDT7PH4, using Ultrapure Water (UPW, resistivity 18 mega Ohm). Four (4) standard AB1UEDT7PH4 cartridges from two (2) different manufacturing batches were used for these tests. The filters were installed in a stainless steel housing and flushed with Ultrapure Water (UPW) at a flow rate of 1 L/min for 20 minutes. Samples were collected at various time intervals. Blank water samples were also collected for the system without the filter under the same flushing conditions to establish a baseline and a system cleanliness check. All samples were analyzed for TOC.

5.3 Results

5.3.1 Results of NVR Determination and TOC

Table 12: Non-volatile Aqueous (DI water) Extractables Obtained Using Fluorodyne EX Grade EDT AB1UEDT7PH4 Filter Cartridges after Autoclaving at 125 °C ± 5 °C shows the levels of aqueous NVR obtained from the first extraction of twenty one (21) Fluorodyne EX Grade EDT filter cartridges from five (5) production batches that were tested. The values ranged from 23.9 mg to 59.7 mg, resulting in an average NVR per Fluorodyne EX Grade EDT filter cartridge, part number AB1UEDT7PH4, of 34.6 mg with a standard deviation of 9.6 mg.

Table 12 also shows the results of the second (consecutive) extraction of nine (9) Fluorodyne EX Grade EDT filter cartridges from five (5) production batches.

The TOC measurement result of the two extract samples analyzed for TOC are given in a footnote.

Table 12 Non-volatile Aqueous (DI water) Extractables Obtained Using Fluorodyne EX Grade EDT AB1UEDT7PH4 Filter Cartridges after Autoclaving at 125 °C ± 5 °C*

Pall Cartridge Serial Number	Non-Volatile Residue (mg) First Extraction	Non-Volatile Residue (mg) Second Extraction
IK9456397	33.0	–
IK9456317	31.0	–
IK9456331	30.1	–
IK9456403	28.0	–
IK9456412	23.9	–
IK9456340	33.2	–
IK9456464	34.1	–
IK9456374	26.0	–
IK9456334	31.1	8.4
IK9456418	33.4	–
IK9456295	29.9	7.0
IK9456353	28.5	–
IK9456387	41.1	6.5
IK9456481	29.9	–
IK9456360	27.6	5.9
IK9456478	35.6	–
IL0511089	25.2	8.7
IL0511043	48.4	20.3
IL8350015	53.6	15.0**
IL8352039	59.7***	19.6
IM1597015	48.8	10.8

* 24-Hours Extraction Time at Ambient Temperature
** TOC = 10.5 ppm – NVR in this sample 12.5 mg/Liter
*** TOC = 25.2 ppm – NVR in this sample 39.8 mg/Liter

5.3.2 Results of ICP Analysis

Table 13: ICP Analysis Results of the Aqueous Extracts Obtained using Fluorodyne EX Grade EDT Filter Cartridges after Autoclaving at 125 °C ± 5 °C (24 Hours Extraction Time at Ambient Temperature) shows the ICP results obtained from the first extraction and second (consecutive) extraction of two (2) Fluorodyne EX Grade EDT filter cartridges, part number AB1UEDT7PH4, from two (2) production batches that were tested, and of an Ultrapure Water blank sample.

Table 13 ICP Analysis Results of the Aqueous Extracts Obtained using Fluorodyne EX Grade EDT Filter Cartridges after Autoclaving at 125 °C ± 5 °C (24 Hours Extraction Time at Ambient Temperature)

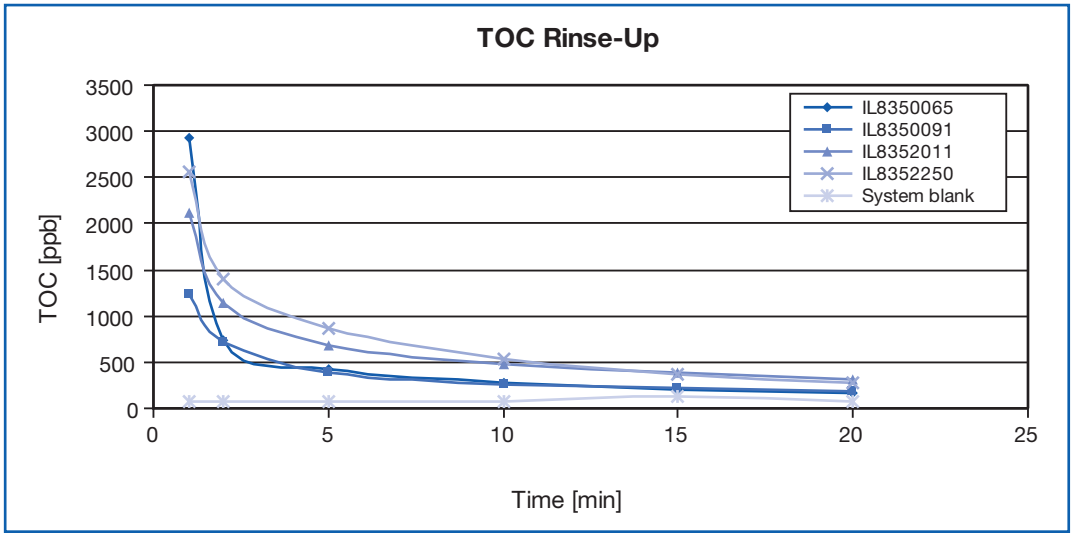
Sample Identity	Al (µg/L)	Fe (µg/L)	Mn (µg/L)	Ni (µg/L)	Cu (µg/L)	Zn (µg/L)	Cd (µg/L)	Pb (µg/L)
Ultrapure Water Blank	< 4	< 4	< 0.2	< 0.1	< 10	< 1	< 0.01	< 0.2
IL8350015								
1st Extract	< 4	< 4	< 0.2	0.23	< 10	< 1	< 0.01	< 0.2
2nd Extract	< 4	< 4	< 0.2	< 0.1	< 10	< 1	< 0.01	< 0.2
IL8352039								
1st Extract	< 4	< 4	< 0.2	< 0.1	< 10	< 1	< 0.01	< 0.2
2nd Extract	< 4	< 4	< 0.2	< 0.1	< 10	< 1	< 0.01	< 0.2

All values stated as "less than" are listed as less than the detection limit for the specific element (e.g.,< 4 µg/L).

5.3.3 Results of TOC Rinse-Up Study

The results of the TOC rinse-up study with Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) and the system blank water samples are shown in Figure 5. The TOC content in the filtrate of all filters tested was below 500 ppb after 20 minutes (equivalent of 20 liters) of flushing.

Figure 5 Results of TOC Rinse-Up of Four (4) Fluorodyne EX Grade EDT Filters at a Flush Rate of 1 L/min



5.3.4 Results of FTIR Analysis

Typical infrared spectra of the aqueous NVRs from Fluorodyne EX Grade EDT filter cartridges (part number AB1UEDT7PH4) are shown in Figures 6 and 7. Figure 6 shows the infrared spectrum of a first extract of a filter cartridge, Figure 7 the infrared spectrum of the second (consecutive) extract of that cartridge.

Figure 6 Typical Infrared Spectrum of the Aqueous NVR from Fluorodyne EX Grade EDT Filters of the First Extract

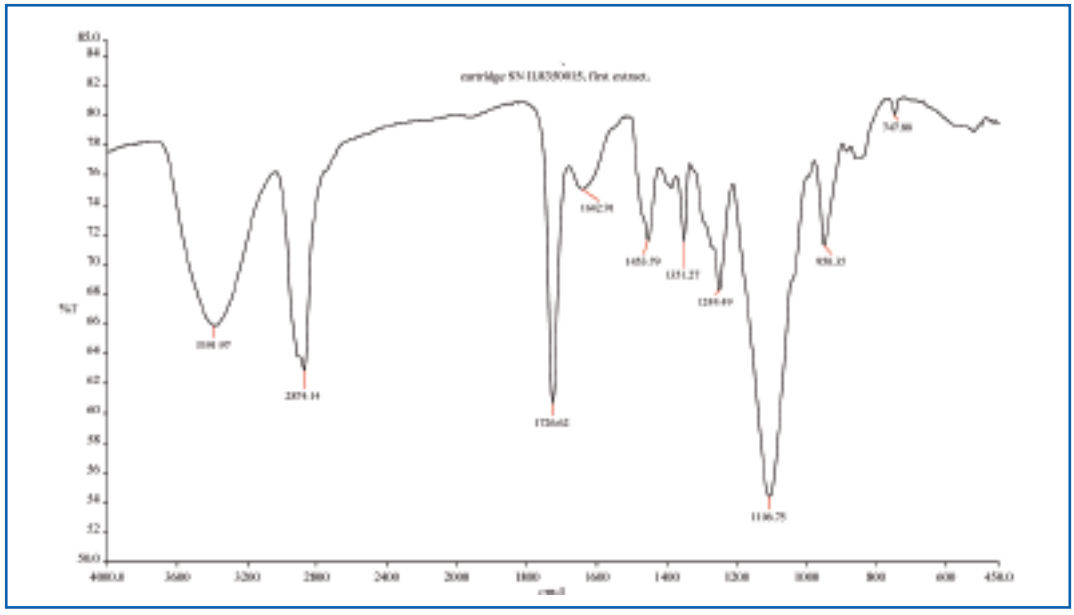
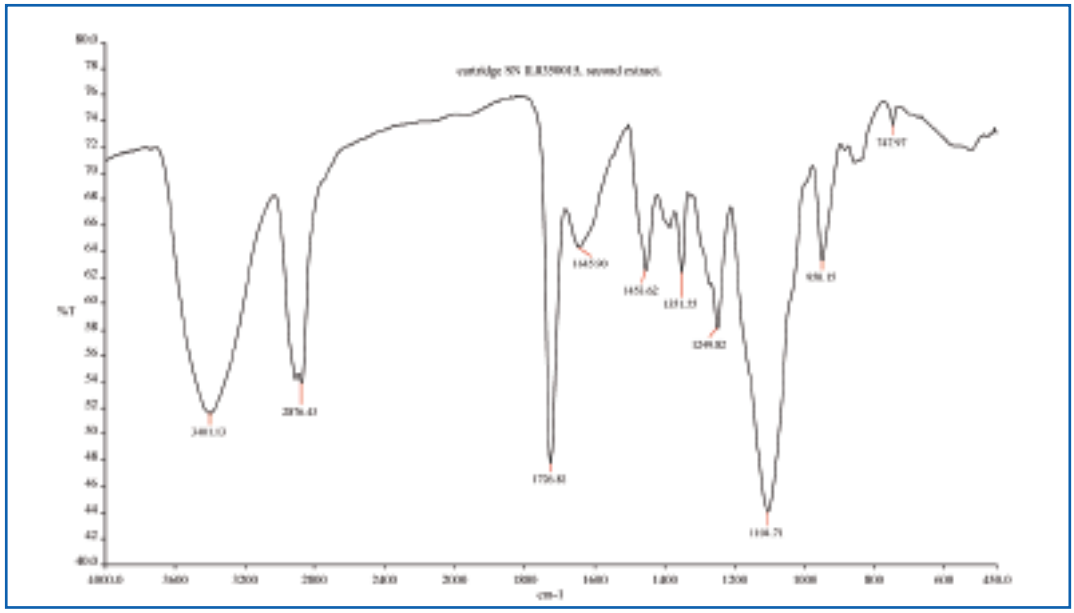


Figure 7 Typical Infrared Spectrum of the Aqueous NVR from Fluorodyne EX Grade EDT Filters of the Second (Consecutive) Extract



Equivalent spectra were obtained for all Fluorodyne EX Grade EDT filter cartridges that were tested.

5.4 Conclusions

5.4.1 NVR, ICP, and TOC Analysis

The average amount of non-volatile residue (NVR) extracted from Fluorodyne EX Grade EDT filter cartridges in AB1 style has been determined using water as the extraction fluid. For the 254 mm (10 in.) filter cartridges tested (part number AB1UEDT7PH4) the values for the first extraction ranged from 23.9 mg to 59.7 mg, resulting in an average NVR of 34.6 mg with a standard deviation of 9.6 mg.

The NVR values of the second (consecutive) extraction were always significantly lower than those obtained in the first extraction and ranged from 5.9 mg to 20.3 mg.

The presence of the various inorganic ions analyzed by ICP were extremely low. The results of almost all extract samples analyzed were under the limit of detection and thus equal of that of the Ultrapure Water blank with the exception of Ni (0.23 µg/L) in the first extract of one of the two cartridges tested. In the second (consecutive) extract, the content of Ni was below detection limit (< 0.1 µg/L).

The TOC content of the first extract of one filter cartridge was determined as 25.2 ppm, while the second extract of another filter cartridge was determined as 10.5 ppm. The NVR per Liter in these samples amounted to 39.8 mg/Liter and 12.5 mg/Liter.

The lower NVR, inorganic ion and TOC content in the second (consecutive) extracts demonstrates the depletion of total soluble material available to the solvent in the finite test time and indicates that exposures greater than 48 hours will not result in a significant increase in the quantity of extractables.

5.4.2 FTIR Analysis

The FTIR spectrum of the extract of all filters tested indicates the presence of extractables typical of polyethersulfone resins and the copolymer used to render the polyethersulfone membrane hydrophilic. They also indicate the presence of the acrylate polymer used to render the polyvinylidene fluoride membrane hydrophilic. Water extractables of polypropylene components are extremely low and were therefore not detected in this test. The FTIR spectrum of the second (consecutive) extract of a filter cartridge was equivalent to the FTIR spectrum of the first extract. This indicates that prolonged exposure to the solvent does not lead to a change in the extractables profile.

5.4.3 TOC Rinse-Up

The TOC content in the filtrate samples of all Fluorodyne EX Grade EDT filter cartridges in AB1 style, part number AB1UEDT7PH4, exponentially decreased during flushing with Ultrapure Water and was below 500 ppb (0.5 ppm) after 20 minutes (equivalent of 20 liters) of flushing.

The content of non-volatile residue (NVR) in the filtrate of Fluorodyne EX Grade EDT filter cartridges after 20 liters of water flush will therefore be extremely low, as indicated by the NVR and TOC results discussed in Section 5.4.1: NVR, ICP, and TOC Analysis of this report.

Actual service in pharmaceutical applications will impose different conditions, such as different steaming conditions, exposure times, temperature, liquid types, and filter system configuration. 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 Grade EDT cartridges and capsules. The materials of construction of the filters are detailed in Table 14.

Table 14 Materials of Construction

Membranes	**Upstream layer:** Pall hydrophilic polyethersulfone (PES) membrane **Downstream layers:** Pall hydrophilic polyvinylidene fluoride (PVDF) membrane
Membrane support and drainage layers	Polypropylene
Core and endcaps	Polypropylene
Filter cage	Polypropylene (in AB style filter cartridges filled with titanium dioxide)
O-rings	Silicone elastomer for H4 option

Fluorodyne EX Grade EDT filter cartridges do not contain materials of construction that are considered specified TSE (and BSE) risk materials according to current legislation and guidelines in Europe and the United States of America:

- The *European CPMP* Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products. (EMEA/410/01 Rev. 2, applicable from 1st July 2004)
- The *U.S. Code of Federal Regulations,* Title 9 Part 94.18, which sets forth restrictions on the source of origin of products obtained from ruminants.
- The *U.S. Code of Federal Regulations,* Title 21 Part 189.5 Subpart B, which defines specified risk materials obtained from cattle.

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 Pharmacopoeia (USP) Chapter <88>.

The testing procedures described in the USP include:

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

The four (4) 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 for 72 hours, 70 °C for 24 hours, or 121 °C for 1 hour. The most stringent condition not resulting in physical changes in the plastic is recommended; therefore the filter materials were extracted at 121 °C.

6.2.1 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 1 in 20 Solution of Alcohol in Sodium Chloride Injection were injected intravenously. Vegetable oil extract and Polyethylene Glycol 400 extract were injected intraperitoneally.

6.2.2 Intracutaneous Tests

An Intracutaneous Test was performed to evaluate the potential of a single injection of an extract to produce tissue irritation. All four (4) of the extracts listed above were used for these tests.

6.2.3 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 Grade EDT filter cartridges 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 Grade EDT filter cartridges passed all of the tests specified.

6.4 Conclusions

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

Copies of the reports are available by contacting Pall Corporation.

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