PALL Life Sciences

Validation Guide

USTR 1666(2)

Novasip™ Filters

Filtration. Separation. Solution.SM

Contents

Part I. Validation Overview

1.1 Introduction

This report contains validation data applicable to Novasip filters. Novasip filters are available in a number of Pall membranes and those reviewed in these studies include Fluorodyne® II, Emflon® PFR and Ultipor® N66 filter membranes. This document is designed to assist the filter user by demonstrating how Novasip filters meet the validation requirements of regulatory authorities within the pharmaceutical industry.

The test program covered three main areas:

(i) Performance of the Novasip filter outer shell and valve components, including:

- Pressure tests
- Vacuum tests
- Creep Resistance
- Cyclic Pressure Pulsing

(ii) Performance of the filter elements, including:

- Retention of *Brevundimonas diminuta* (ATCC 19146) by 0.2 µm rated filters in liquid challenge tests
- Steam Sterilization - Steam In Place and autoclave tests
- Extractables tests
- Biological Reactivity Tests - USP Class VI-121 °C Plastics
- Fluid Flow/Pressure Drop Characteristics
- Filter Assembly Differential Pressures - in use and during integrity testing

(iii) Protection afforded the filter during transportation

1.2 Summary of Conclusions

1.2.1 Steam Sterilization Tests

Novasip filter assemblies have been shown to retain integrity after repeated steam in place (SIP) or autoclaving for 30 min steam cycles at 125 °C and 142 °C, as follows:

- 50 hours (100 x 30 min cycles) at 125 °C
- 4 hours (8 x 30 min cycles) at 142 °C

The maximum cumulative steam exposure for Novasip filters is dependent on the filter cartridge incorporated.

Filter cartridge steam exposure limits are as follows:

- Emflon PFR - 50 hours (100 x 30 min cycles) at 125 °C
  2.5 hours (5 x 30 min cycles) at 142 °C
- Fluorodyne II DFL - 30 hours (60 x 30 min cycles) at 125 °C
  2 hours (4 x 30 min cycles) at 142 °C
- Ultipor N66 NF - 16 hours (32 x 30 min cycles) at 125 °C
  2 hours (4 x 30 min cycles) at 142 °C

1.2.2 Pressure Tests

Novasip filters have a maximum recommended operating pressure of 6.5 bar (94.2 psi) and have been shown (at ambient temperature) to withstand in excess of 30 bar (450 psi, before the Tri-Clover* compatible gasket seal arrangement in the connector assembly fails due to extrusion. On filters that have had the vent and drain ports suitably plugged, the capsule has withstood pressures up to 53 bar (800 psi).

1.2.3 Vacuum Tests

Pall recommend that steam sterilization of filter products be conducted as described in Pall publication 'Steam Sterilization of Pall Filter Assemblies' and do not recommend conducting steam sterilization under conditions that can result in steam collapse. However, testing has been successfully undertaken to demonstrate that Novasip filters can withstand conditions of 1 bar d, from out to in, at 125 °C without collapse.

1.2.4 Creep Tests

Novasip filters that had been steamed at 125 °C for 100 x 30 minute cycles were pressurized to 6.5 bar g (94.2 psi). The maximum strain measured on the bowl was very low at 0.25%. This compares with a material strain at break, in test pieces, of 6% - indicating a high safety margin.

1.2.5 Cyclic Pressure Pulsing

Novasip filters that had been steamed at 125 °C for 100 x 30 minute cycles were subjected to pressure pulses of 6.5 bar (94.2 psi) at a constant temperature of 40 °C. The filters withstood 50,000 cycles without leaking.

1.2.6 Bacterial Removal and Integrity Test Parameters

Novasip filters incorporating Fluorodyne II DFL, Emflon PFR and Ultipor N66 NF grade filter membranes, were demonstrated to meet the requirements of a 0.2 µm sterilizing grade filter, by liquid challenge tests using *Brevundimonas diminuta* (ATCC 19146).

Forward Flow integrity test parameters and Water Intrusion test parameters, were set as follows;

Table 1:
Novasip Forward Flow Integrity Test Parameters

Membrane Type	Fluorodyne II DFL Grade	Emflon PFR Grade	Ultipor N66 NF Grade
Part Number	C3DFLP1	C3PFRP1	C3NFP1
Test Pressure	2760 mbar (40 psi)	1035 mbar (15.0 psi)	2760 mbar (40 psi)
Wetting Liquid	Water	60/40 IPA/Water	Water
Temperature	20 °C ± 5 °C	20 °C ± 5 °C	20 °C ± 5 °C
Test Gas	Air	Air	Air
Maximum Allowable Flow Limit	3.4 mL/min	4.5 mL/min	5.3 mL/min

Table 2:

Novasip Water Intrusion Test Parameters

Membrane Type	Emflon PFR Grade
Part Number	C3PFRP1
Air Test Pressure	2.5 bar (36 psi)
Temperature	20 °C ± 2 °C
Acceptable Limit	0.1 mL/min

1.2.7 Flow Characteristics

Novasip filter assemblies incorporating Pall membrane filters were found to have typical flow rates as shown in Table 3:

Table 3:

Membrane Type	Fluorodyne II DFL grade	Ultipor N66 NF Grade
Part Number	C3DFLP1	C3NFP1
Test Fluid	Water	Water
Temperature	20 °C ± 5 °C	20 °C ± 5 °C
Flow Rate	17 liters/min	10 liters/min
Differential Pressure	1 bar (14.5 psi)	1 bar (14.5 psi)

Membrane Type	Emflon PFR Grade				
Part Number	C3PFRP1				
Test Fluid	Air				
Temperature	20 °C ± 5 °C				
Line Pressure	1 bar g (14.5 psi)	2 bar g (29 psi)	3 bar g (43.5 psi)	4 bar g (58 psi)	Vent Use
Differential Pressure	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)
Flow Rate	13 Nm^3/hr	17 Nm^3/hr	20 Nm^3/hr	24 Nm^3/hr	9 Nm^3/hr

1.2.8 Maximum Temperature and Pressure Ratings

Novasip filters incorporating Pall membrane filter cartridges were found to retain integrity after exposure to the following conditions:

Table 4

Maximum Operating Pressure/Temperature	
Maximum Line Pressure	6.5 bar g (94 psi)
Maximum Operating Temperature	40 °C
Maximum Differential Pressure at Temperature in Flow Direction	
Forward Direction up to 40 °C	5.3 bar (77 psi)
Forward Direction During Steam in Place	300 mbar (43.5 psi)

1.2.9 Biological Reactivity Tests

Novasip filter assemblies were found to meet the requirements of the current United States Pharmacopoeia for Class VI-121 °C Plastics *in vivo* - Systemic toxicity, Implantation and Intracutaneous tests.

1.2.10 Extractables

Novasip filter assemblies gave low, aqueous, non-volatile residues, at 20 °C in laboratory tests.

- Ultipor N66 NF grade, C3NFP1 has typical aqueous soluble extractables of less than 10 mg per assembly at 20 °C

- Fluorodyne II DFL grade, C3DFLP1 has typical aqueous soluble extractables of less than 5 mg per assembly at 20 °C
- Emflon PFR grade, C3PFRP1 has typical aqueous soluble extractables of less than 5 mg per assembly at 20 °C

1.2.11 Quality Control Tests

Each batch of sterilizing grade filters meets quality control requirements, as summarized on the Certificate of Test for pharmaceutical grade filters.

Part II. Steam and Pressure Rating of Novasip filters

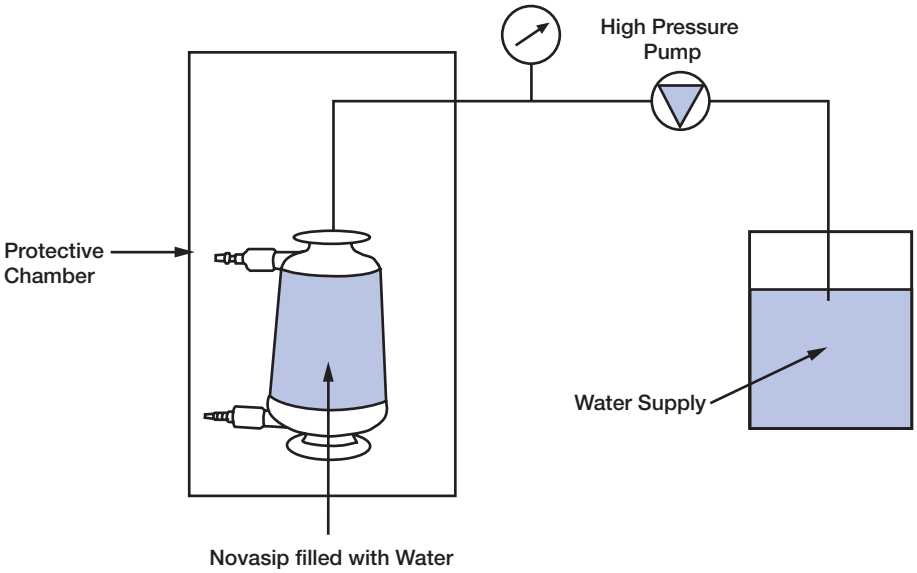
2.1 Pressure Testing

Pressure testing was performed on Novasip filters, to demonstrate their ability to withstand differential pressures (in to out) in excess of the 6.5 bar d maximum rating of the product, even after exposure to extensive steam sterilization conditions.

The test filters having been subjected to their full steam life (100 x 30 mins Steam In Place at up to 125 °C). Each filter was filled with water and then slowly pressurized to 40 °C. The pressure was increased in increments of approximately 3.4 bar (50 psi) and held at pressure for approximately 30 seconds between rises. The tests were terminated when leaks were noticed or the system reached its maximum pressure.

Figure 1

Pressure Testing



A detailed description of the test procedure is available from Pall on request.

2.1.1 Results

Novasip filters (at 40 °C) withstood in excess of 30 bar (450 psi) before the Tri-Clover compatible gasket seal arrangement in the connector assembly failed due to extrusion. On filters that had the vent and drain ports suitably plugged, the capsule withstood pressures up to 53 bar (800 psi).

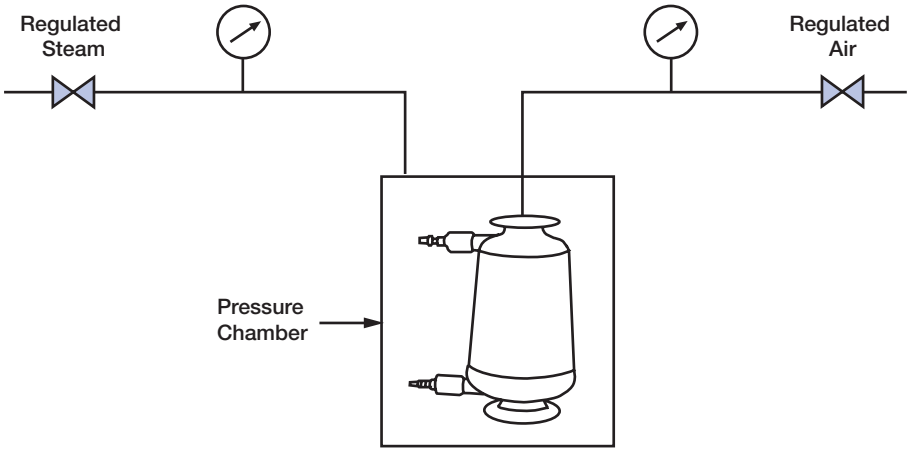
In addition units were subjected to 4 bar internal pressure, at both 125 °C and 142 °C and no damage was evident after 5 minutes exposure without failure.

2.2 Vacuum Testing

Although, Pall does not recommend conducting steam sterilization under conditions that can result in steam collapse, testing was undertaken to demonstrate that Novasip filters can withstand conditions of 1 bar d, from out to in, without collapse of the filter.

Figure 2

Vacuum Testing



Vacuum testing was performed on Novasip filters by creating a one bar differential pressure by regulating the pressure inside the capsule with air, whilst the outside of the capsule was enclosed in a 125 °C steam environment to give an external pressure of 1.3 bar g. Starting the test with equal external and internal pressures, the internal pressure was slowly reduced to give the 1 bar d, and held for a minimum period of five minutes. The internal pressure was then slowly increased until the pressures were equal once again. The filter capsule was then inspected for any visible distortion.

A detailed description of the test procedure is available from Pall on request.

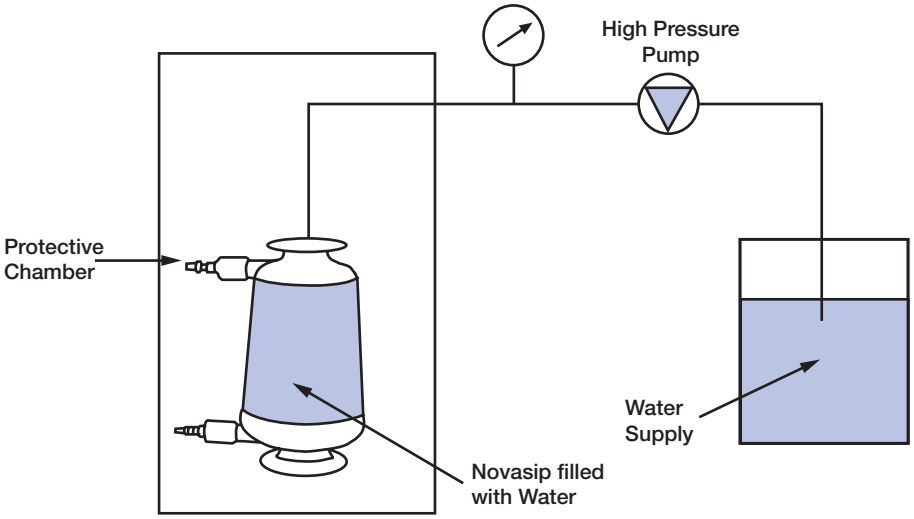
2.2.1 Results

Novasip filters withstood conditions of 1 bar d from, out to in, without collapse.

2.3 Creep Testing

To demonstrate the stability of the Novasip capsule bodies over extended use, creep testing was performed on Novasip filters that have been subjected to their full steam life (100 x 30 mins steam in place at up to 125 °C. Each filter was filled with water, connected to 6.5 bar pressure supply and then slowly pressurized.

Figure 3
Creep Testing



The diameter of a Novasip filter was measured at the test temperature. The filter was then pressurized and another measurement taken immediately. This measurement was then repeated at regular intervals until the measured value remained constant and then daily thereafter. The strain in the filter was then calculated and plotted against time.

A detailed description of the test procedure is available from Pall on request.

2.3.1 Results

Novasip filters that had been steamed at 125 °C for 100 x 30 minute cycles were pressurized to 6.5 bar g. The maximum strain measured on the bowl was 0.25%. This compares with a material strain at break, in test pieces, of 6%.

Figure 4
Results of Creep Test

2.4 Cyclic Pulse Testing

Cyclic pressure testing was carried out in a similar fashion to creep testing but the pressure was not held constant, but cycled from 6.5/7.0 bar g to zero in regular cycles to a total of 50,000 cycles.

A detailed description of the test procedure is available from Pall on request.

2.4.1 Results

Novasip filters were successfully exposed to 50,000 cycles of 6.5 bar difference, at 40 °C.

Part III. Microbial Validation

3.1 Introduction

Liquid challenge tests using *Brevundimonas* (previously known as *Pseudomonas*) *diminuta* (ATCC 19146) were performed with standard production filters using > 1 x 10^7 colony forming units (CFU) per cm^2 of effective filtration area.

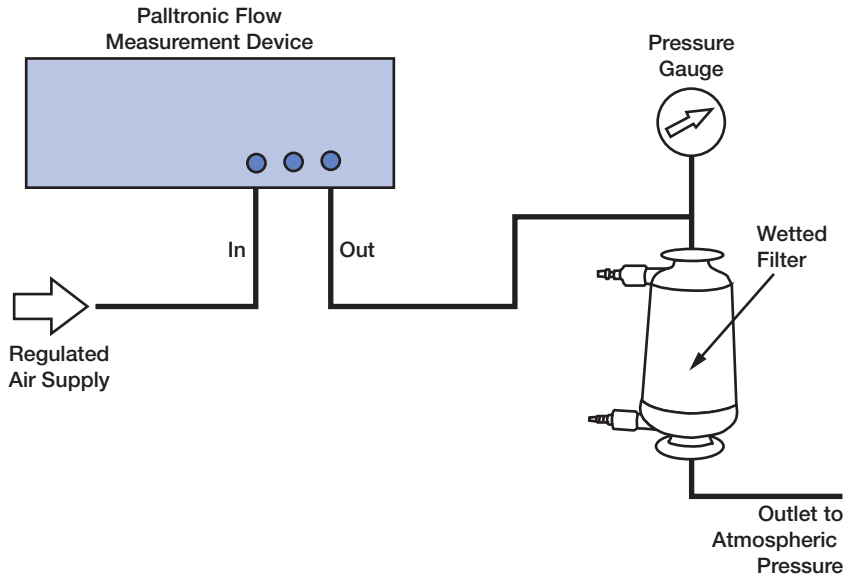
The correlation between microbial retention and a non-destructive integrity test is also an important aspect of the validation of sterilizing grade filters. The aseptic guidelines further state, 'After a filtration process is properly validated for a given product, process and filter, it is important to assure that identical filter replacements (membrane or cartridge) used in production runs will perform in the same manner. One way of achieving this is to correlate filter performance data with filter integrity testing data'.

The integrity test used during this validation study was the Forward Flow integrity test. The integrity test limits for Novasip filters are based on the primary validation for each membrane option in a 254 mm (10 in.) filter configuration. Data for *Brevundimonas diminuta* removal and Forward Flow testing on filter grades used in Novasip filters, was generated to further support the 254 mm (10 in.) validation studies given in Pall publications 'Validation Guide for Pall 0.2 mm Nylon 66 Membrane', 'Emflon PFR Validation Guide' and 'Validation Guide for Pall 0.2 mm Fluorodyne II membrane cartridges'.

In order to perform the Forward Flow test, a filter is wetted with a suitable 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 downstream side (as shown in Figure 5) or on the upstream side, using sensitive flow measurement equipment such as the Palltronic Flowstar filter integrity test device.

Figure 5

Forward Flow Test



In summary, the aims of this stage of the validation were to determine the microbial removal efficiency of Novasip filters in Pall Fluorodyne II, Ultipor N66 and Emflon PFR filter membrane options, in liquid challenge tests.

3.2 Summary of Methods

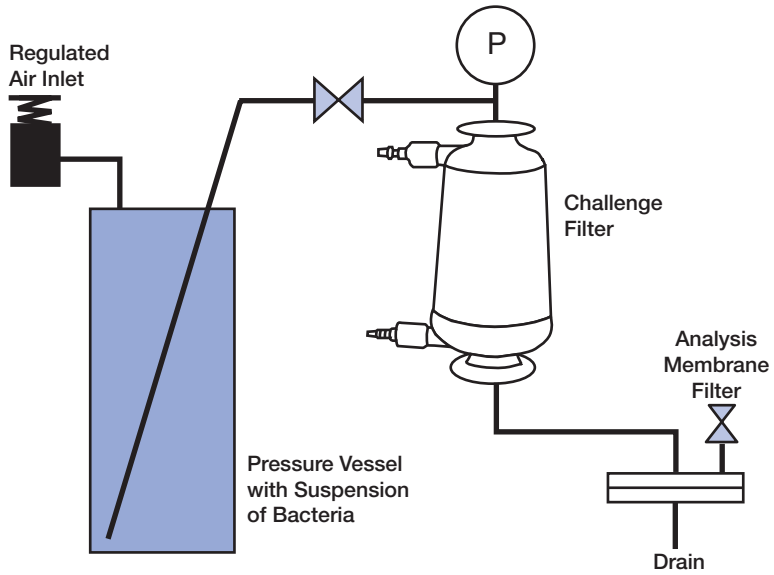
Pall filter cartridges, with a range of Forward Flow values, were selected from standard production lots and subjected to microbial challenge tests using an aqueous suspension of *Brevundimonas diminuta* (ATCC 19146).

Each sample was tested for integrity by the Forward Flow method, prior to being autoclaved at 121 °C for 60 minutes. The filter was then aseptically connected to the pre-sterilized challenge apparatus, as shown in Figure 6.

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. On completion of the challenge a second Forward Flow test was performed.

Figure 6

Bacterial Challenge Apparatus



During the challenge test the entire filter effluent was passed through a 0.2 µm-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 bacteria had passed through the test filter during the challenge.

A detailed description of the test method is available from Pall on request.

3.3 Results

The data obtained from validation studies, into the removal of *Brevundimonas diminuta* in liquid challenge tests, by the different filter membrane options available in Novasip filters, are shown in Tables 5, 6 and 7. The data is presented in order of increasing Forward Flow measurement, with the higher of the pre- and post-challenge Forward Flow values being taken.

Table 5:

B.diminuta Retention for Novasip Fluorodyne II DFL Filters

Filter Serial Number	Forward Flow* (mL/min)	Challenge Level) (cfu/cm^2)	Sterile Effluent
IA3449055	2.0	1.75×10^8	Yes
IA3449024	2.1	1.75×10^8	Yes
IA3449054	2.2	1.75×10^8	Yes
IA3449046	2.4	1.75×10^8	Yes
IA3449096	2.45	1.75×10^8	Yes
IA3449097	2.6	1.75×10^8	Yes
IA1913088	2.8	3.02×10^8	Yes
IA1913025	2.8	3.02×10^8	Yes
IA1913009	2.9	3.02×10^8	Yes
IA1913048	2.9	3.02×10^8	Yes
IA1913002	3.0	3.02×10^8	Yes
IA1913066	4.55	3.02×10^8	No**

** Forward Flow values at 2760 mbar (40 psi) air test pressure, wet with water*
Acceptable Forward Flow limit 3.4 mL/min air flow
*** $T_R = 4.98 \times 10^6$*

Table 6:

B.diminuta Retention for Novasip Ultipor N66 NF Filters

Filter Serial Number	Forward Flow* (mL/min)	Challenge Level) (cfu/cm^2)	Sterile Effluent
IB6205084	0.7	3.4×10^7	Yes
K8006058	0.7	2.5×10^8	Yes
IB5350140	1.1	1.7×10^6	Yes
IB5350059	1.2	1.7×10^7	Yes
K8006025	1.4	2.5×10^8	Yes
IB5350079	1.9	2.7×10^7	Yes
IB5350161	2.1	1.7×10^8	Yes
K8006014	2.5	2.5×10^8	Yes
IB6784078	2.6	1.7×10^7	Yes
K8006040	2.9	2.5×10^8	Yes
K8006019	3.0	2.5×10^8	Yes
IB5350087	4.1	2.8×10^8	Yes
IB5350081	4.3	2.8×10^8	Yes

** Forward Flow values at 2760 mbar (40 psi) air test pressure, wet with water*
Acceptable Forward Flow limit 5.3 mL/min air flow

Table 7

B.diminuta Retention for Novasip Emflon PFR Filters

Filter Serial Number	Forward Flow* (mL/min)	Challenge Level) (cfu/cm^2)	Sterile Effluent
IB5743035	2.2	2.4×10^7	Yes
IB5743059	2.2	2.4×10^7	Yes
IB5743016	2.2	2.4×10^7	Yes
IB5743041	2.3	2.4×10^7	Yes
IB5743013	2.3	2.4×10^7	Yes
IB4024062	2.4	5.3×10^7	Yes
IB5743029	2.5	2.4×10^7	Yes
IB4024091	2.7	5.3×10^7	Yes
IB4024058	2.7	5.3×10^7	Yes
IB4024097	2.8	5.3×10^7	Yes
IB4024099	2.8	5.3×10^7	Yes
B4024015	2.9	5.3×10^7	Yes

** Forward Flow values at 1040 mbar (15 psi) air test pressure, wet with (60/40) IPA/water Acceptable Forward Flow limit 4.5 mL/min air flow*

Part IV. Steam Sterilization

4.1 Introduction

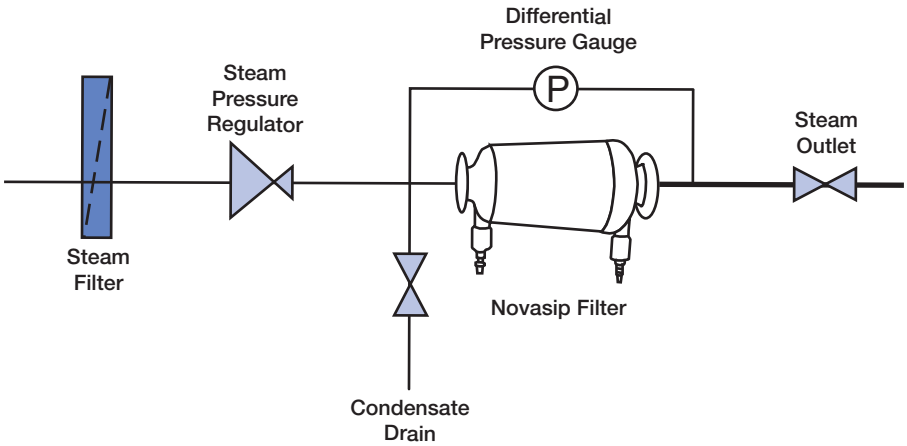
Pall recommend that Novasip filters be used in accordance with procedures given in Pall publication 'Assembly and Installation Procedures for Novasip Filter Assemblies', and that steam sterilization of Novasip filters be conducted as described in Pall publication 'Steam Sterilization of Pall Filter Assemblies'.

4.2 Summary of Methods

Typical Novasip filters were subjected to repeated steam cycles at 125 °C and 142 °C. During the tests, filters were steamed in place and exposed to saturated condensate-free steam. Steam pressure, and flow, were held constant during the sterilization period and after each steam cycle the filters were cooled by passing dry compressed air through them. The differential pressure during the tests was controlled and maintained at < 300 mbar.

Figure 7:

Steaming



Following exposure to steam, Novasip filters were examined for signs of damage, distortion or cracking, and where appropriate the integrity of the filter as measured using the Forward Flow test and in some cases, a bacterial challenge test using *Brevundimonas diminuta* (ATCC 19146) was also performed.

A summary of the steam sterilization test conditions is shown in Table 8.

Table 8:
Steam Sterilization Test Conditions

Steam Temperature	Number of 30 minute Steam Cycles	Measurement of Filter Integrity after Exposure to Steam
125 °C	100	Forward Flow test and liquid bacterial challenge using *B.diminuta*
142 °C	8	Forward Flow test

Further details about the steam sterilization procedure are available from Pall on request.

4.3 Results

Data obtained from steaming studies are shown in Tables 9, 10 and 11. The data is presented in order of increasing Forward Flow measurement.

Data from bacterial challenge tests, on Novasip Emflon PFR filters that have been subjected to 100 x 30 mins Steam In Place cycles at 125 °C, are shown in Table 12.

Table 9:
Forward Flow Results on Steam Sterilized Novasip Fluorodyne II DFL Filters after 20 x 1 Hour Steamings at 140 °C ± 2 °C, followed by 30 Minutes Air Cooling

Filter Serial Number	Forward Flow (mL/min)* Prior to Cyclic Steam In Place	Forward Flow (mL/min)* Post Cyclic Steam In Place
IA1913090	2.6	2.7
IA1913077	2.7	2.5
IA1913105	3.0	2.4

** Acceptable criteria 3.4 mL/min water wet at 2760 mbar (40 psi)*

Table 10:
Forward Flow Results on Novasip Ultipor N66 NF Filters after 4 x 1 Hour Steamings at 140 °C ± 2 °C, followed by 30 Minutes Air Cooling

Filter Serial Number	Forward Flow (mL/min)* Prior to Cyclic Steam In Place	Forward Flow (mL/min)* Post Cyclic Steam In Place
IB5350002	1.5	1.0
IB5350010	1.0	1.3
IB5350038	1.1	1.0
IB5350041	1.1	1.0
IB5350101	1.3	1.1
IB5350177	1.3	1.2

** Acceptable criteria : 5.3 mL/min water wet at 2760 mbar (40 psi)*

Table 11:
Forward Flow Results on Novasip Emflon PFR Filters after 100 Hours Steamings (4 x 25 Hours) at 140 °C ± 2 °C

Filter Serial Number	Forward Flow (mL/min)* Post Cyclic Steam In Place
IB4024017	3.7
IB4024031	3.8
IB4024041	3.5
IB4024054	2.9
IB4024055	2.9
IB4024082	1.2
IB5743008	3.5
IB5743026	3.6
IB5743033	3.8
IB5743037	3.9
IB5743042	4.4

** Acceptable criteria 4.5 mL/min (60:40) IPA/water wet at 1035 mbar (16 psi)*

Table 12:
B.diminuta Retention of Novasip Emflon PFR Filters Part Number C3PFRP1 after Exposure to 100 x 30 Minute Cycles of 140 °C ± 2 °C Steam

Filter Serial Number	Forward Flow* (mL/min)	Challenge Level (cfu/cm^2)	Sterile Effluent
PB4860014	2.2	3.31×10^7	Yes
PB4860005	2.2	1.81×10^7	Yes
PB4860010	2.2	1.66×10^7	Yes
PB4860009	3.5	1.81×10^7	Yes
PB4860002	4.2	1.81×10^7	Yes

** Forward Flow values at 1035 mbar (16 psi) air test pressure, wet with (60/40) IPA/water Acceptable Forward Flow limit 4.5 mL/min air flow*

4.4 Conclusions

Novasip filters can be repeatedly steam sterilized, both by Steam In Place and autoclaving, as appropriate for the filter cartridge incorporated, to a maximum of :

- 50 hours cumulative at 125 °C, or
- 4 hours cumulative at 142 °C

Part V. Extractables

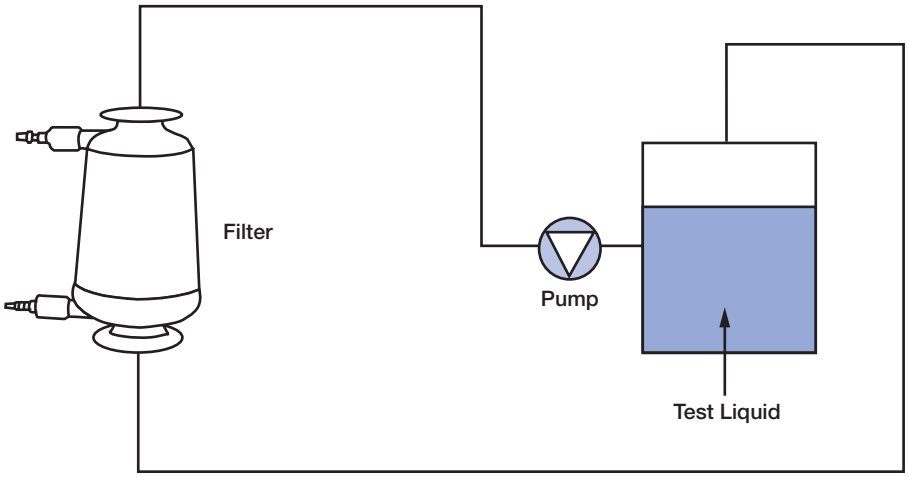
5.1 Introduction

The purpose of these tests was to determine the amount of material which can be extracted from typical Novasip filter assemblies, post steaming (autoclave) by water, at ambient temperature and also to identify the extractables obtained.

5.2 Summary of Methods

Typical production Novasip filters were extracted with 800 mL distilled, deionized water. The water used for the extraction was recirculated through the filter for four hours.

Figure 8:
Extractables Testing



In order to minimize the background residue, a diaphragm pump with PTFE liquid contact parts and tubing was used. The non-volatile residue (NVR) extracted from the Novasip filters was compared with values obtained from control samples of water that had been recirculated through the same extraction system but without the filter installed. Further details of the extraction method are available from Pall on request.

In addition to the determination of NVR, the aqueous extractables from a number of typical production Novasip filters were pooled and then analyzed by Fourier Transform Infra Red spectroscopy (FTIR).

5.3 Results

Table 13 shows the typical quantities of non-volatile residue extracted per Novasip filter, at ambient temperature. The results reported are typical for standard production elements.

Table 13:
*Aqueous Extractables for Novasip Filters**

Filter Part Number	Filter Serial Number	Non-volatile Residue (mg per filter)
C3PFRP1	PILF4711001	1
	PILF4711024	2
	PILF4711011	2
C3NFP1	IB67841007	7
	IB67841004	8
	IB67841010	8
C3DFLP1	IB70351020	1
	IB70351011	1
	IB70351017	1

** Please contact Pall for values with liquids other than water*

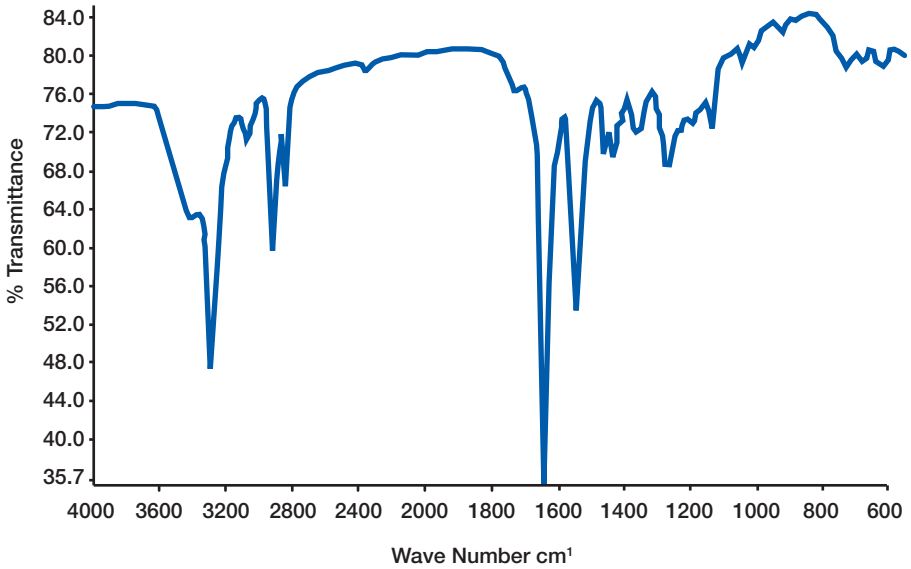
An infra red spectrum of the aqueous extractables, from Novasip filters (part number C3NFP1), was consistent with that of nylon 66, and indicated that the extracted material principally comprised oligimers of nylon associated with the filter membrane.

5.4 Conclusions

The levels of extractables found for Novasip filters are extremely low. The aqueous extractables were identified as originating primarily from the filter membrane selected.

Actual service may impose different conditions, such as different exposure times, temperature, liquid purity, etc. Evaluation under actual process conditions is also recommended.

Figure 9:
Infra Red Spectrum of Aqueous Extractables Obtained from Novasip Filters



Part VI. Biological Reactivity Tests

6.1 Introduction

The purpose of these tests was to evaluate the biological suitability of the materials of construction of Novasip filters in Emflon PFR grade 0.2 µm sterilizing filter medium. The materials of construction are as follows;

Novasip Filter shell:	Polyetherimide mouldings, Natural and unpigmented (clear) and titanium dioxide filled (white)
Filter medium:	Pleated Pall Emflon PFR membrane
Support/Drainage layers:	Polypropylene non-wovens
Core/cage:	Polypropylene mouldings
End caps:	Polypropylene mouldings
Seals:	Silicone elastomeric seals

6.2 Summary of Methods

The tests were performed in accordance with the Biological Reactivity Tests *in vivo* for Class VI-121 °C Plastics as described in the current United States Pharmacopoeia. The tests were conducted by Gibraltar Laboratories, Inc. New Jersey, USA.

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:

- USP Sodium Chloride for Injection

- 1 in 20 Solution of Ethanol in Sodium Chloride Injection
- Polyethylene Glycol 400
- 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 filters 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. Filter extracts in Sodium Chloride Injection and 1 in 20 Solution of Ethanol in Sodium Chloride Injection were injected intravenously. Cottonseed 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 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. The clear (unpigmented) and white (titanium dioxide pigmented) polyetherimide housing components of the Novasip filter were implanted separately.

6.3 Results

Novasip filters incorporating Emflon PFR grade filter medium passed all of the tests specified. Copies of the test reports are shown in Appendix 1.

6.4 Conclusions

Novasip filters, which incorporated Emflon PFR grade filter medium, met the requirements of the USP tests for Class VI-121 °C Plastics *in-vivo*.

Part VII. Flow Characteristics of Novasip Filters

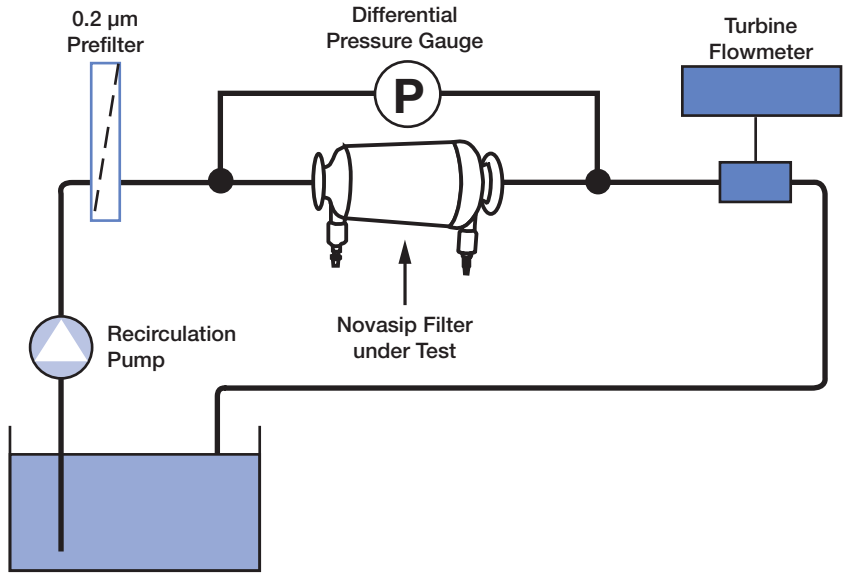
7.1 Introduction

The aim of these tests was to determine the pressure differential characteristics of Novasip filters when subjected to different inlet flow rates with appropriate fluids. For Novasip filters employing hydrophilic filter membranes water was used as the test fluid, and for hydrophobic filter membranes air was used as the test fluid.

7.2 Summary of Methods

7.2.1 Hydrophilic Membrane Options

Figure 10:
Flow Pressure Drop Measurement



The tests were performed on standard production filters. Deionized water was pumped through the test filter in the normal flow direction. Pressure transducers on the upstream and downstream side of the test filter were monitored to calculate the differential pressure at different water flow rates.

All data were corrected to a standard temperature of 20 °C.

Note: The differential pressures quoted are for liquids with a viscosity of 1cP. Differential pressures for liquids at other viscosities can be estimated by multiplying the differential pressure by the viscosity in cP.

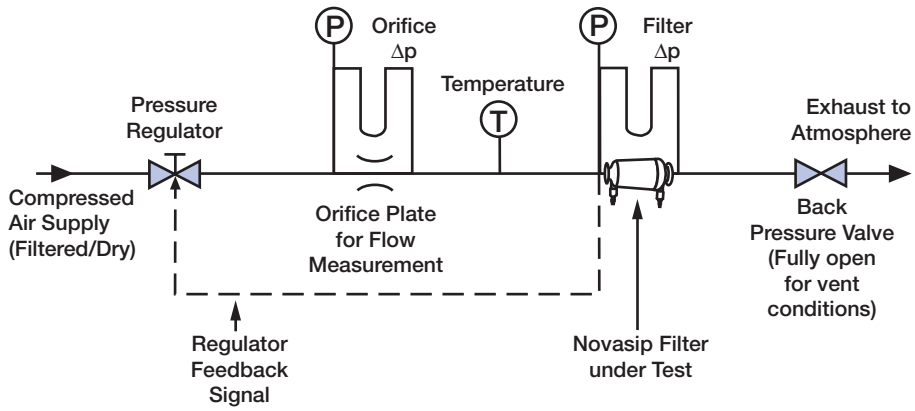
The relationship between water flow and differential pressures was found to be linear up to 2 bard.

Please contact Pall for further details.

7.2.3 Hydrophobic Filter Membrane Options

The tests were performed on standard production filters using air as the test fluid.

Figure 11:
Hydrophobic Filter Membrane Options



All data were corrected to a standard temperature of 20 °C.

Please contact Pall if further details about the test methods are required.

7.3 Results

Novasip filter assemblies incorporating Pall membrane filters were found to have typical flow rates as shown in Table 14 for hydrophilic membrane options, and Table 15 for hydrophobic filter membrane options.

Table 14:

Membrane Type	Fluorodyne II DFL Grade	Ultipor N66 NF Grade
Test Fluid	Water	Water
Temperature	20 °C ± 5 °C	20 °C ± 5 °C
Flow Rate	17 liters/min	10 liters/min
Differential Pressure	1 bar (14.5 psi)	1 bar (14.5 psi)

Table 15:

Membrane Type	Emflon PFR Grade				
Test Fluid	Air				
Temperature	20 °C ± 5 °C				
Line Pressure	1 bar g (14.5 psi)	2 bar g (29 psi)	3 bar g (43.5 psi)	4 bar g (58 psi)	Vent Use
Differential Pressure	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)	30 mbar (0.4 psi)
Flow Rate	13 Nm^3/hr	17 Nm^3/hr	20 Nm^3/hr	24 Nm^3/hr	9 Nm^3/hr

These results are expressed graphically in Figures 12, 13 and 14.

Figure 12:

Typical Water Flow/Pressure Drop Characteristics for Novasip Fluorodyne II DFL Filters C3DFLP1

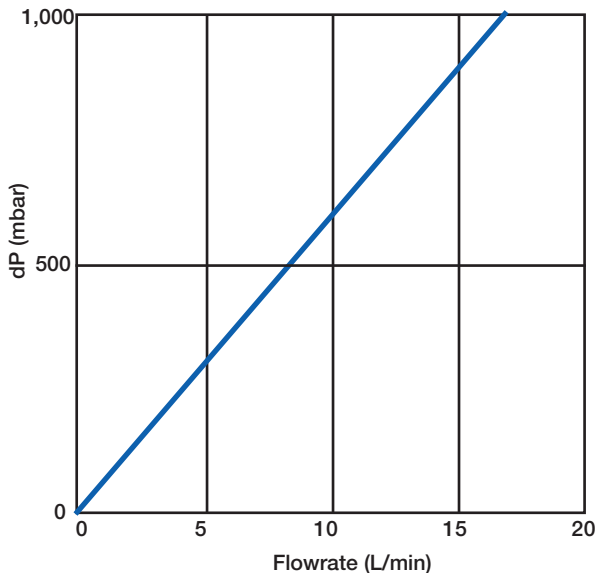


Figure 13:
Typical Water Flow/Pressure Drop Characteristics for Novasip Ultipor N66 Filters C3NFP1

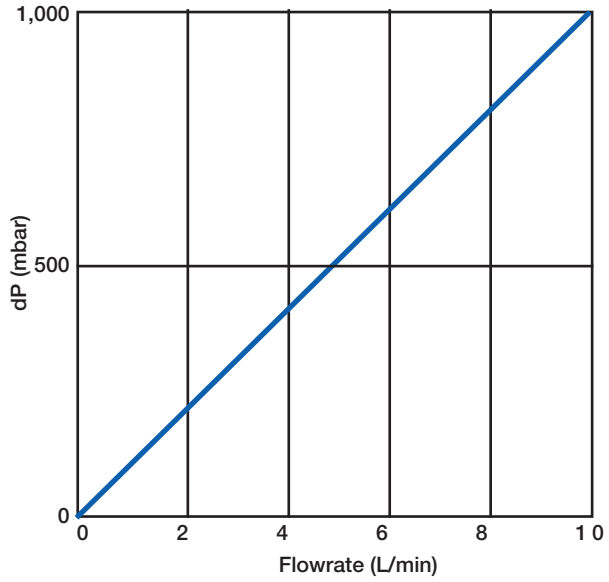


Figure 14a:
Typical Air Flow/Pressure Drop Characteristics for Novasip Emflon PFR Filters C3PFRP1 in the Forward Direction

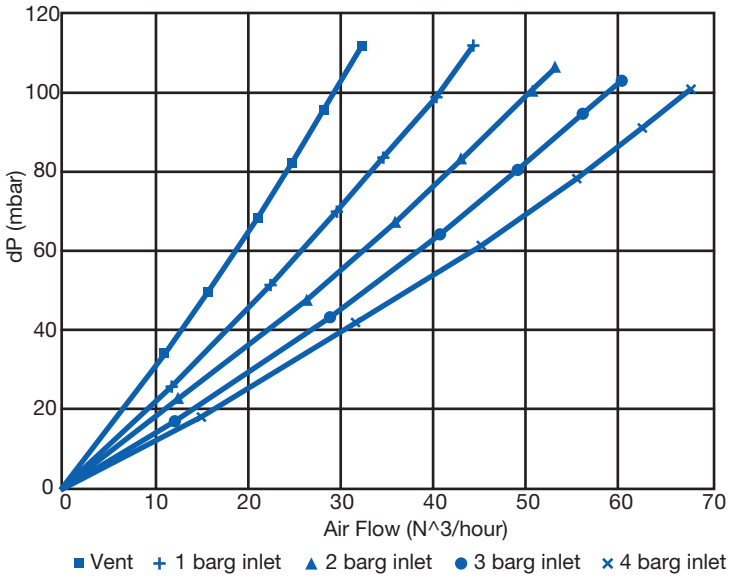
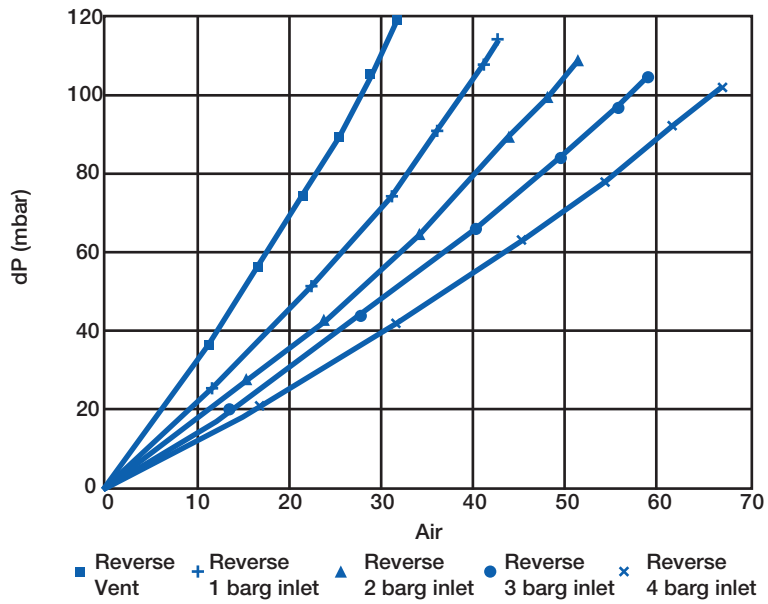


Figure 14b:
Typical Air Flow/Pressure Drop Characteristics for Novasip Emflon PFR Filters C3PFRP1 but in Reverse Direction



Part VIII. Packaging Testing

8.1 Introduction

The design and construction of the Novasip filter packaging was based on Pall's previous experience of protecting its products during transit for delivery to its customers. In addition, Novasip filter packaging was evaluated, to ensure the protection afforded the product was of a sufficient level to prevent damage occurring.

A specialist company in the field of such testing, acting as an independent test house, developed a test plan in association with Pall, to ascertain if the Novasip filter packaging would withstand the rigors of world-wide distribution. This test plan referenced American ASTM and military standards and reflected the specialist's experience with shipments of delicate, high value products.

Tests were conducted to demonstrate the ability of the packaging to protect Novasip filters from damage, under conditions representative of typical transportation and storage.

Novasip filters are supplied boxed singularly, or as multiples of 6 boxed items (wrapped together).
Tests were therefore conducted on boxed items both singly packed and as six items packed together.

In the event that filters are palletized for transportation, vibration tests were also conducted on a single box which had a load applied to its uppermost face, equivalent to the weight of 16 boxed Novasip filters.

8.2 Summary of Methods

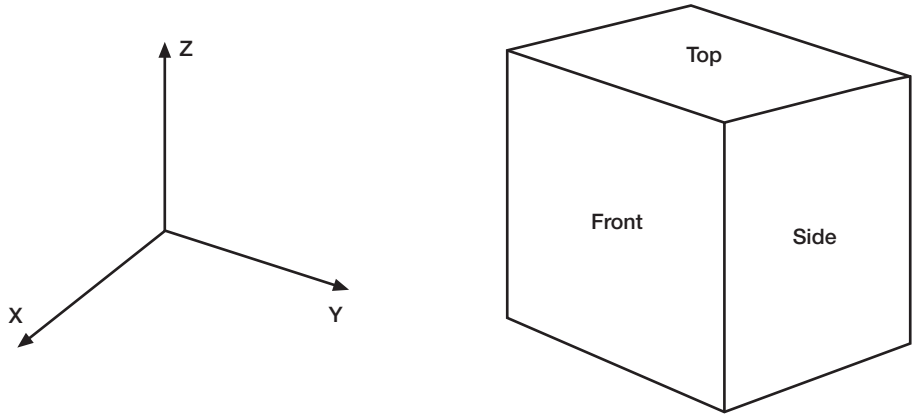
The objective was to perform package testing on a single and two multipack test pieces to recognized package testing criteria in order to give high confidence in the packs capability to protect the product, and that the Novasip filters within the pack should be able to survive the rigors of routine hazards during transit in a normal distribution environment.

Test pieces were subjected to the requirements of the Xyratex Process Document: Packaging

document number: 5625709, Issue Level AA Review Date 24/09/98.

The orientation of each test pieces was designated as follows :-

Figure 15:
Test Piece Orientation



8.2.1 Vibration Testing

Single boxed product, a multipack of 6 single boxes, and a weighted1 multipack of 6 single boxes, were subjected to vibration testing. Measurements were recorded on each of the three axes tests and the resonance frequency determined for each sample axis. (Sine Vibration, 4-200Hz 0.3 g Resonance Search for each of the three axes). Measurements were made using equipment and methodology detailed in Xyratex report (BPCS numbered 35170, for PTL Test Number 1540).

Results

The resonant frequencies were found to be:

- X axis 92 Hz;
- Y axis 109 Hz; and
- Z axis 84 Hz.

8.2.2 Resonance Dwell Testing

The resonance frequency values determined in the vibration testing studies were then used in vibration dwell testing to represent a maximum amplitude situation. Each test piece was exposed to a period of 15 minutes vertical oscillation at the resonant frequency, for each of the three axes.

8.2.3 Random Vibration Testing

A single boxed product, a multipack of 6 single boxes, and a weighted1 multipack of 6 single boxes, were subjected to random vibration test. The random vibration frequency input spectra was generated. This spectrum was created from data captured during real life transportation events to give as real a simulation as possible. Each test piece endured a period of 15 minutes vertical oscillation (High Assurance Transportation test) at the frequency generated by the input spectrum, for each of the three reference axes.

Results

Although some crush damage was evident to the sides of the box when tested with the applied load, in the X and Y directions, no visible physical damage was apparent when the Novasip filters were visually inspected at the conclusion of the vibration testing.

8.2.4 Drop Test

A sample was dropped from a height of 914 mm (36 in.) onto 1 corner, 1 edge and 6 faces onto a solid surface. Impaction shockwave traces were obtained for each face, edge and corner onto which the box was dropped.

Results

A similar impact shockwave traces were obtained for each face, edge and corner which the box was dropped onto.

The maximum impact force encountered by the Novasip filter was 128.13 g for a period of 6.4 ms, when dropped onto its bottom edge.

The Novasip boxes withstood the tests performed aimed at simulating transportation conditions, and although minor damage to the cardboard was witnessed, no visible physical damage occurred to the Novasip product contained within.

In the packaging tests conducted, no visual damage was found to any Novasip filters. Minor corner compression and creasing of the cardboard of an expected nature was found on the multipack.

Details of the test work performed are given in Xyratex report BPCS numbered 35170, for PTL Test Number 1540.

Please contact Pall for further details of the above tests.

8.3 Conclusions

The protection afforded to the Novasip filters by the selected packaging, was sufficient to prevent any physical damage in the tests undertaken, simulating transportation around the world via road, air and/or sea.

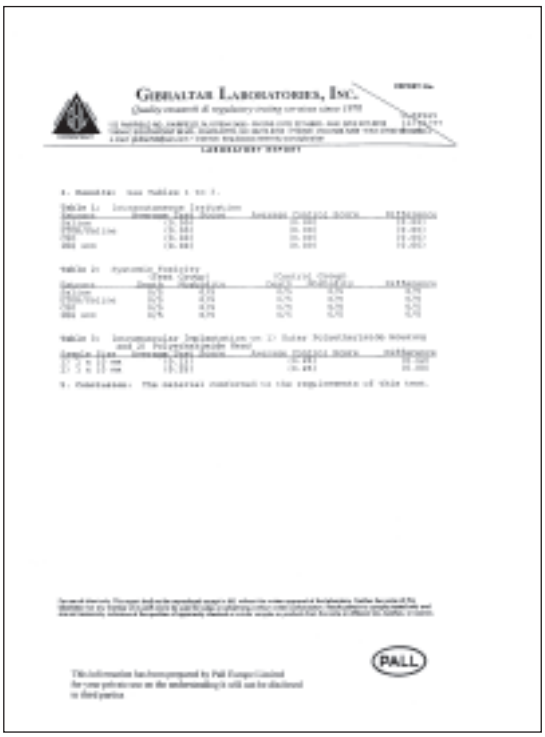
[1] A weight was placed onto one of the multipacks to simulate the stacking of boxes on top of the filter in a worst case situation whilst being transported on a pallet

Appendix 1

Biological Safety Test Report

APPENDIX I
Biological Safety Certificate

GIBRALTAR LABORATORIES, INC.



GIBRALTAR LABORATORIES, INC.

Appendix 2

Materials Safety Data Sheet	
Product Type:	Novasip filter Body
Material Type:	Polyetherimide molding

Physical and Chemical Properties:	
Physical State:	Solid molding
Appearance:	Clear - natural unpigmented White - titanium dioxide filled

Fire Fighting Measures:

Fire Fighting
Approved pressure demand breathing apparatus and protective clothing should be used for all fires. Water spray is the preferred extinguishing medium. This product will melt but will not be carried on the surface of water.

Extinguishing Media
Water spray and foam. Water is the best extinguishing medium. Carbon dioxide and dry chemicals are not generally recommended as their lack of cooling capacity may permit re-ignition.

Hazardous Combustion Products
Hazardous combustion products may include intense heat, dense black smoke, carbon monoxide, carbon dioxide, nitrogen dioxide, hydrogen cyanide and hydrocarbon fragments.

Conditions of Flammability
Requires a continuous flame source to ignite and sustain combustion.

Handling:	Follow good standard pharmaceutical practices.
Storage:	Inert material under normal storage conditions. Store unopened in the original packaging, in dry conditions, away from direct sunlight

Please insure that Novasip filters are installed, and used, in line with recommendations published by Pall.

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The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

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