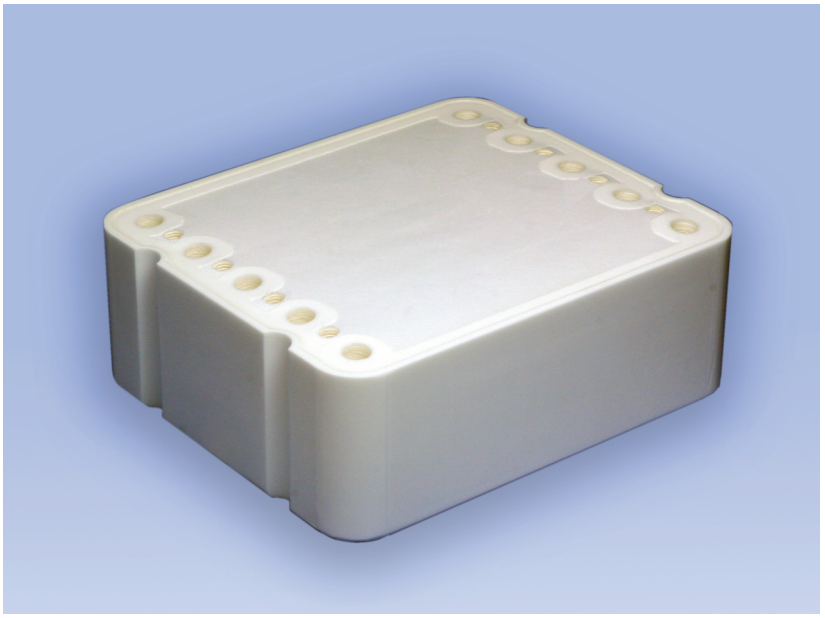
Life Sciences

Validation Guide

USTR 2439

Pall Supor® Membrane Cassette

Centrasette™ Membrane Cassettes
Part No. PSM65F22-S022



*Filtration. Separation. Solution.*SM

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1 Purpose of this Document

This document provides validation support information for Pall Supor® TFF membrane cassettes, and includes summary data to support testing conducted for biological safety, extractables, chemical compatibility, physical and performance attributes, as well as usage conditions (temperature limits, chemical limits, cleaning, flushing, integrity testing, operating methods).

The data contained in this Guide is generated under standard conditions as specified. The methods and information contained in this Guide are designed to provide the user with an acceptable approach for validation of Supor TFF membrane cassettes under actual conditions of use.

Pall Life Sciences offers technical support to customers to develop, troubleshoot, and validate tangential flow filtration procedures.

1.1 Validating Filtration Processes — General Concepts

Tangential flow membrane cassettes play an important role in purifying, concentrating, and separating biopharmaceutical solutions and products. Typical applications include concentrating human plasma fractions, downstream processing of enzyme and protein solutions, and harvesting mammalian or bacterial cells. Hence, the validation of tangential flow filtration processes utilizing membrane cassettes is an essential part of ensuring the manufacture of safe and efficacious products.

The U.S. Food and Drug Administration defines validation as “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes” (Current Good Manufacturing Practice (camp) for Finished Pharmaceuticals, 21 CFR 210.3). With respect to a tangential flow filtration process, validation involves providing assurance that the filtration process operates reproducibly and consistently.

For any given process, a Functional Design Specification must be written based on the requirements of the process and data generated at the pilot scale. For a tangential flow filtration process utilizing the Supor TFF membrane cassette, this will include developing operational protocols within performance limits outlined in this validation guide and based on the individual cassette operating instructions and care and use manuals supplied with cassettes.

A process system can then be designed and built to allow direct scale-up to meet specifications established at pilot or bench scale. Since tangential flow membrane cassettes are incorporated into complex systems, three stages of system validation are followed: Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

1.2 Installation Qualification (IQ)

This checks that the cassettes selected for the process are the ones supplied and installed in the system, and that specified installation procedures such as torque settings have been adhered to. Additionally, it is confirmed that all required documentation has been received (operating instructions, and certificates of conformance) with the cassettes. Refer to the *Membrane Cassettes Care and Use Procedures* (R00640 Rev B) for details.

1.3 Operational Qualification (OQ)

Engineers test and document the range and operational limits of the filtration process with cassettes in place. Operational qualification (OQ) does not have to be conducted in the customer process manufacturing area. Engineers normally simulate worst-case production conditions for these studies, using water or another surrogate process fluid, to deliberately trigger alarm conditions. As part of the operational qualification, engineers also verify and document procedures such as flushing and sanitizing that are associated with the operation of the membrane cassettes.

1.4 Performance Qualification (PQ)

Performance qualification (PQ) involves testing the cassette filtration process during production of the final product under actual operating conditions, including installation, sanitizing, conditioning, concentration, diafiltration,

product recovery, cleaning, etc. Critical elements of performance qualification include verification of chemical compatibility and retention characteristics. Since validating a process ensures the process accomplishes what is intended, performance qualification provides the most meaningful process validation data (which will be confirmed by ongoing performance data collected during system operation) because the data is derived from the process itself, utilizing the intended operating conditions. PQ may not necessarily provide data on the operation of the system at the design limits (alarm conditions), as the process may never reach these.

Manufacturers of regulated products must develop and submit protocols, qualification documents, and validation documents for their specific product to be granted approval to manufacture and market their product.

2 Product Specifications — Supor TFF Membrane Cassettes

To help you prepare IQ documentation, this section provides you with information on the materials of construction, physical characteristics, and basic performance of Supor TFF membrane cassettes.

Membrane cassettes are individually packaged in heat-sealed plastic bags with the following information printed on the cassette edge (Figure 1):

- Company name
- Membrane type
- Pore size
- Cassette format
- Membrane area
- Feed channel format
- Part number
- Serial number

are shipped in a box containing two silicone gaskets in a plastic bag, Certificate of Test, *Membrane Cassettes Care and Use Procedures* (R00640 Rev B) and MSDS documents (where appropriate).

2.1 Part Numbers

Part numbers give specific information about the cassette. For example, the part number PSM65F22 S022 represents a Supor 0.65 µm membrane, 2.0 m^2 (21.5 ft^2) Centrasette™ suspended screen channel cassette.

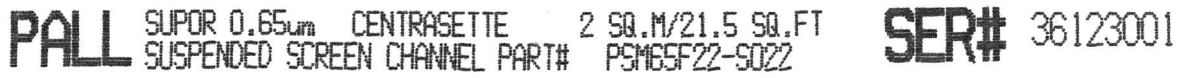

Figure 1: Example of Information Printed on the Side of Cassettes

The Part Number for a cassette can be interpreted to identify specific information about the cassette characteristics..

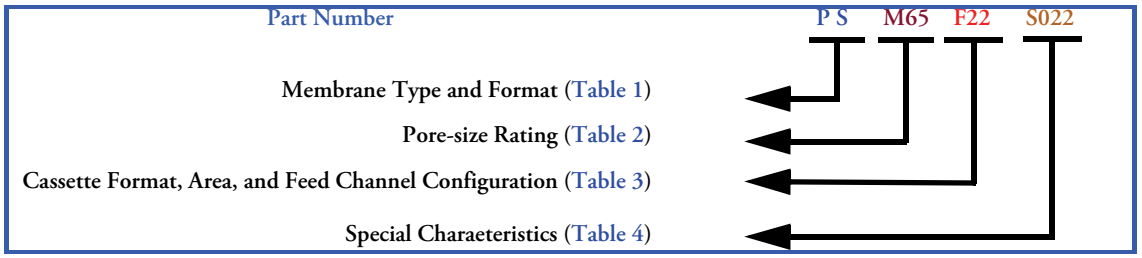

Figure 2: Part Number Code

Table 1: Identification Code for Membrane Type

Part Number (Digits 1 – 2)	Membrane Format
PS	Supor TFF Cassette

Table 2: Identification Codes for Pore Size Rating

Part Number (Digits 3 – 5)	Pore Size
M65	0.65 µm

Table 3: Identification Codes for Cassette Format and Feed Channel Configuration

Part Number (Digits 6 – 8)	Cassette Format, Feed Channel Configuration	Membrane Area (Nominal)	
F22	Suspended Screen Channel	21.5 ft^2	2.0 m^2

(1) Suspended screen cassettes have fine screens in the filtrate channels and fine screens suspended between spacers in the feed channel.

Table 4: Identification Codes (if present) for Special Formats

Part Number (Digits 9 – 12)	Special Characteristics
S022	Urethane encapsulant

2.2 Serial Number

Unique serial numbers enable the tracing of the following cassette information:

- Date of manufacture
- Components used in manufacture
- Water permeability of membrane lot used in construction
- Membrane integrity test results
- KL test values for membrane lot
- Manufacturing plant location
- Name of the technician who manufactured the cassette

From the serial number and production records, components can be traced back to their source.

2.3 Materials of Construction

2.3.1 Membrane

Supor membranes are cast unsupported from polyethersulfone resins. Released lots of membrane are laminated on a highly porous polyolefin backing (substrate) that imparts strength and rigidity to the finished membrane.

2.3.2 Screens

Screens are constructed of polyester.

2.3.3 Spacers

Supor TFF suspended screen channel cassettes incorporate a screen suspended between spacers in the feed/retentate channel. The spacers are constructed of natural HDPE with a nominal thickness of .18 mm (.007 in.)

2.3.4 Encapsulant

The encapsulant is polyurethane with white pigment (TiO_2).

2.3.5 Gaskets

Gaskets are constructed from USP Class VI medical grade, platinum-cured silicone.

Supor F22 cassettes use silicone gaskets with a nominal thickness of 1.6 mm ($^1/_{16}$ in.).

2.4 Dimensions

Pall membrane cassettes are manufactured in a range of formats, and membrane areas (Table 5). This allows the ability to directly scale up or down depending on requirements.

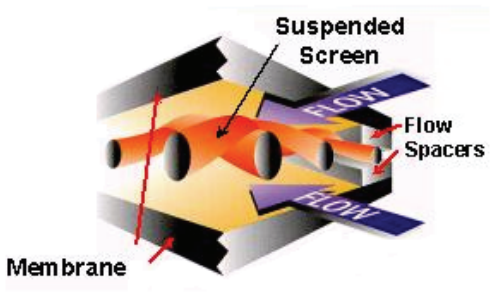

Figure 3: Cassette Suspended Screen Channel Configuration

Table 5: Physical Dimensions of Supor Membrane Cassettes (nominal)

Characteristic		Centrasette
Membrane Area	(m^2)	2.0
	(ft^2)	21.5
Weight (kg) Suspended (2)		1.7
Thickness (cm) suspended		3
Length (cm)		8
Width (cm)		7
Flow path length (cm) (port center to center)		17
Flow path width (cm)		14
Port diameter feed (cm)		1.0
Number of feed ports		5
Port diameter retentate (cm)		1.0
Number of retentate ports		5
Port diameter permeate (cm)		0.6
Number of permeate ports		8

(2) Approximate weight of a cassette as shipped in plastic foil bag (no outer packaging).

2.5 Operating Pressures and Temperatures

Membrane cassettes have operating limits for pressure, temperature, and pH (Table 6).

Table 6: Cassette Operating Limits of Pressure, Temperature, and pH

Membrane	Temperature	Maximum Recommended Operating Pressure		pH Range	
				Continuous at 25 °C	Cleaning at 45 °C
Supor TFF	4 – 25 °C	3 barg (3)	(45 psig) (3)	2 – 14	2 – 13
	25 – 50 °C	2 barg	(30 psig)	2 – 14	2 – 13

(3) Clamping pressure must be set to the recommended level to avoid leaks.

Two Supor TFF cassettes (PSM65F22-S022) were tested at ~1 bar (15 psi) TMP (Transmembrane Pressure) at 45 °C in 0.5 N NaOH for 30 hours (10 cycles of 3 hours). Cassettes met release specifications.

In a separate study, two additional Supor TFF cassettes were tested at 4bar feed pressure and an elevated temperature of 55 °C in water for 6 cycles of 3 hours each. Cassettes were cooled, and then characterized for air Integrity, water flux rate and pressure drop after each cycle. No significant changes to cassette performance was noted. When operating at maximum pressure, cassette holders may need to be set near the upper end of the torque/hydraulic pressure range.

2.6 Water Flux Ranges

Membrane water flux is a measure of the membrane permeability. Water quality, temperature, and pressure affect the water flux rate. At a minimum, the water used to measure flux should be distilled, deionized (DI), 0.2 µm filtered, or preferably, pharmaceutical grade (USP Water for Injection, hereafter called WFI). The presence of biological organisms, organic materials, or minerals in the water may affect water flux results.

2.6.1 Water Flux Specifications for Supor TFF Membranes

Water flux is measured in stirred cells on 47 mm disc membrane samples stamped out from the beginning, and end of each production lot of membrane (Table 7).

Water flow is determined using a 47 mm disc filter holder. Membrane is wetted out in water and inserted in the disc holder. A measured volume of water at a temperature between 29 – 32 °C is added to the filter holder.

Vacuum is applied (24 inches Hg) and the time is measured to draw the water through the membrane. The water flow is calculated and reported in mL/min/cm^2. Membranes used in cassette construction must meet the water flux specifications.

Table 7: Water Flux Specifications For Supor TFF Membranes

Membrane	Water Flux on Disc Membrane		
Pore Size µm	**mL/min/cm^2 @ 24 inches Hg, 30 °C**		**Calculated Average LMH/psi @ 20 °C**
0.65	65	170	4280

2.7 Membrane Characterization — K_L Test

Supor TFF membrane is characterized by performing a K_L (quantitative bubble point) test on samples taken from each roll of membrane. Membrane samples are wetted out in water or water/isopropyl alcohol (IPA). Measurements are performed on a K_L Test Stand which records air flow as a function of applied pressure and determines the K_L point (knee location) from programmed algorithms.

2.8 Membrane Integrity — Forward Flow Test Values

The membrane integrity test measures air forward flow rates at specified pressures to determine the integrity of membranes. The air forward flow is a measure of air diffusion through the liquid in the membrane pores plus air leakage around seals. The test identifies gross defects in the cassette membrane or membrane seals. Membrane integrity forward flow test values are given in Table 8 for the different cassette formats. The same integrity test limit values apply for cassettes flushed out with water or preservative solution (20% glycerin, 0.1% NaN_3, or 0.3 N NaOH).

Use only dry filtered air or nitrogen from cylinders (instrument-quality) when using integrity analyzers incorporating mass flow meters. Fluctuations in house air and nitrogen supplies as well as changes in temperature can cause inconsistent results. Fully wet-out the membrane in a cassette prior to performing the membrane integrity test or high forward flow values may be obtained. The procedures for wetting out cassettes and measuring forward flow are described in *Membrane Cassettes Care and Use Procedures* (R00640 Rev B).

Table 8: Membrane Integrity Test — Forward Flow Limits

Supor TFF Membrane			Maximum Air Forward Flow(4)	
Cassette Format	Rating (µm)	Test Pressure bar (psig)	(sccm/ft^2)	(sccm/m^2)
Centrasette	0.65	0.7 (10)	25	270

(4) Nitrogen can be used in place of air. However, a correction factor on the maximum diffusive flow of 0.84 must be applied if Nitrogen is used as the test gas.

2.9 Recommended Hydraulic Pressure Settings and Torque Values for PSM65F22-S022 Cassettes

Table 9: Recommended Hydraulic Pressure Range for AT Holders

Holder Type	No. Bolts on Holder	Recommended Hydraulic Pressure	
		With Supor TFF Membrane Cassette	
		(psi)	(bar)
Centrasette 5 AT	4	750 – 1125	52 – 78
Centrasette 10 AT	2	1500 – 2250	104 – 155
Centrastak™ AT	2	1500 – 2250	104 – 155

Table 10: Recommended Torque Values for Manual Holders

Holder Type	No. Bolts on Holder	Recommended Torque Range	
		With Supor TFF Membrane Cassette	
		(in-lb.)	(Nm)
Centrasette 5	4	350-550	40-60
Centrasette 10	2	700-1100	80-120
Centrastak	2	350-550	40-60

2.10 Shelf Life of New and Used Cassettes

The recommended shelf life of cassettes is three years from date of manufacture. To achieve satisfactory performance, it is recommended that the cassettes be stored unopened in the original packaging at 4 – 25 °C and protected from direct light.

The useful life of cassettes that are properly conditioned, used, cleaned, stored, and maintained is often more than one year. However, it is not possible to specify a shelf life or useful life of a cassette that has been used or removed from the original packaging. The actual useful life for a cassette will depend on the character and complexity of the product to which it is exposed, composition of process fluids, process temperatures, operating pressures, and cleaning regime. Therefore, customers should validate reuse and the useful life of a cassette in their process. Pall Life Sciences makes no claims of warranty or guarantee of performance related to reuse of cassettes. Consult Pall Life Sciences *T-Series Membrane Cassettes Care and Use Procedures* for recommended storage conditions.

2.11 Chemical Compatibility—Sodium Hydroxide, 0.5 N, 45 – 50 °C

Sodium hydroxide is the most effective and commonly used agent in biological applications for cleaning, sanitizing, and depyrogenating membrane cassettes. To evaluate the chemical resistance of Supor TFF membrane cassettes, a study was performed in which cassettes were first put through a standard pre-conditioning, characterized and then cycled 10 times (3-hour cycle time) in 0.5 N NaOH at 45 – 50 °C. The following function tests were performed on the cassettes: membrane integrity, water flux, and pressure drop.

Results

After ten (10) cycles of 3 hours at 45 – 50 °C, the samples were within specification for membrane integrity, and water flux. Details of the procedure are given in Section 3.3 on page 9. Results from testing are given in Table 12 and Figures 4 and 5.

2.12 Chemical Compatibility — General

Chemical compatibility of membrane cassettes can be described in terms of changes in physical characteristics as a result of continuous contact with a chemical solution for several hours. Changes can affect dimensions, hardness,

swelling, integrity of internal seals, and membrane integrity. Changes can also be described in terms of functional characteristics of the membrane (such as water permeability, retention characteristics).

Table 11 illustrates the compatibility of Supor TFF membrane cassettes at 20 °C (unless otherwise noted) with respect to physical characteristics. Table 11 should be used only as a guide. Cassettes should be tested in the appropriate solvent and product under actual operating conditions and for an appropriate time to determine compatibility for the specific application. Membrane porosity— and consequently both water permeability and retention characteristics —may be affected. Physical changes to the cassette may be permanent or reversible. To determine if changes are permanent, flush and then soak the cassette in water for one to two days and then test the sample again. Changes in water permeability and solute retention may be due to physical changes in the membrane. Changes in solute retention may be a result of conformational changes in the molecules used to measure retention, or a combination of factors.

Table 11: Membrane Chemical Compatibility Chart

Reagent	Compatible ✔
pH Range	2 – 14
Acetic Acid (5%)	✔
Alconox* (1%)	✔
Citric acid (1%)	✔
Ethanol (70%)	✔
Formaldehyde (1%)	✔
Glycerine (50%)	✔
Guanidine HCl (6 M)	✔
Hydrochloric acid (0.1 N)	✔
Hydrogen peroxide (1%)	✔
Phosphoric acid (0.1 N)	✔
Sodium dodecyl sulfate (0.01M)	✔
Sodium hydroxide (0.5 N @ 50 °C)	✔
Sodium hypochlorite (0.05%)	✔
Terg-a-zyme* (1%)	✔
Triton* X-100 (0.002 M)	✔
Urea (25%)	✔

(5) Data for cassette membrane and components at 20 °C, 24-hour exposure, unless otherwise noted. There may be changes in porosity and/or selectivity of membrane.

** Alconox and Terg-a-zyme are trademarks of Alconox, Inc.*

** Triton is a trademark of Dow Chemical Company.*

2.13 Protein Binding Characteristics

Supor TFF membranes have low nonspecific adsorption characteristics. The actual amount of protein or other substances that will adsorb (nonspecifically bind) to the membrane is dependent on the specific characteristics of that substance. Adsorption of a molecule to a membrane can vary to a great extent depending on its environment (i.e., the chemical composition of the solution it is in, as well as the number and concentration of other solutes present). Changes in pH, ionic strength, temperature and concentration have a significant effect on binding properties. Buffer salts, detergents, and organic solvents also influence binding. If adsorption is a concern, then a study can be performed on a disc membrane using the actual sample and buffer to determine the level of nonspecific adsorption.

3 Validation Procedures

This section describes the procedures Pall used to validate specific chemical and physical characteristics of the Supor TFF membrane cassettes.

3.1 Extractables Test

Contact Pall Life Sciences for details on extractables and methods.

3.2 Cassette Flushing Procedures to Remove Storage Agents

Supor TFF membrane cassettes are shipped dry. The cassette has to be flushed well with water prior to use.

3.3 Chemical Compatibility — Sodium Hydroxide, 0.5 N, 45 – 50 °C

To evaluate the chemical resistance of Supor TFF membrane cassettes, a study was performed in which cassettes were first put through a standard pre-conditioning, characterized and then cycled 10 times (3-hour cycle time) in 0.5 N NaOH at 45 °C. For this study 0.65 µm Supor TFF membrane cassettes (PSM65F22-S022) were used. The following function tests were performed on the cassettes: membrane integrity, water flux, and pressure drop.

Summary of Method

1. Install cassette in a Centrasette AT Cassette Holder using $^1/_{16}$ in. gaskets between cassettes. Set clamping force to 1500 psig.
2. Flush with water (DI / 0.2 µm filtered).
3. Characterize each cassette for NWP, Air Integrity and Pressure Drop.
4. Transfer cassettes to a holder for caustic cycling.
5. Perform each cleaning cycle using 0.5 N NaOH, at the following conditions:
   (i) Time = 3 hour
   (ii) Feed Pressure 1.5 bar (20 psi), Retentate Pressure 0.7 bar (10 psi).
   (iii) Temp. = 45 °C
6. At the end of the cycle, drain the system, cool down the cassettes, and then transfer cassettes to the characterization holder.
7. Flush with water (ambient temperature), 5 L/ft^2.
8. Repeat cleaning cycle and flush cycles, steps 4 – 7, for a total of 10 cycles.
9. After the 10th cycle, characterize the cassettes individually for NWP, Air Integrity, and Pressure drop
10. Compare initial and final results for individual and stack cassette conditions.

Results

After 10 cycles of 3 hours at 45 – 50 °C, the samples were within specification for membrane integrity, and water flux.

Table 12: Results from Compatibility Study of Supor TFF Cassettes with 0.5 N NaOH

	Initial Characterization (average values)			Final Characterization (20 cycles) (average values)		
Cassette & Serial No. PSM65F22	NWP (LMH/psi @10psi TMP)	ΔP @ 1.0 L/min/ft^2 (psi)	Air Integrity sccm/ft^2@ 5 psi	NWP (LMH/psi @10psi TMP)	ΔP @ 1.0 L/min/ft^2 (psi)	Air Integrity sccm/ft^2@ 5 psi
86170054	170	6.42	5.1	160	6.5	5.6
86171080	162	5.8	0	162	6.5	0

Figures 4 and 5 show the Water Permeability vs. TMP and ΔP vs. CFF data generated from cycle testing of the PSM65F22 cassettes.

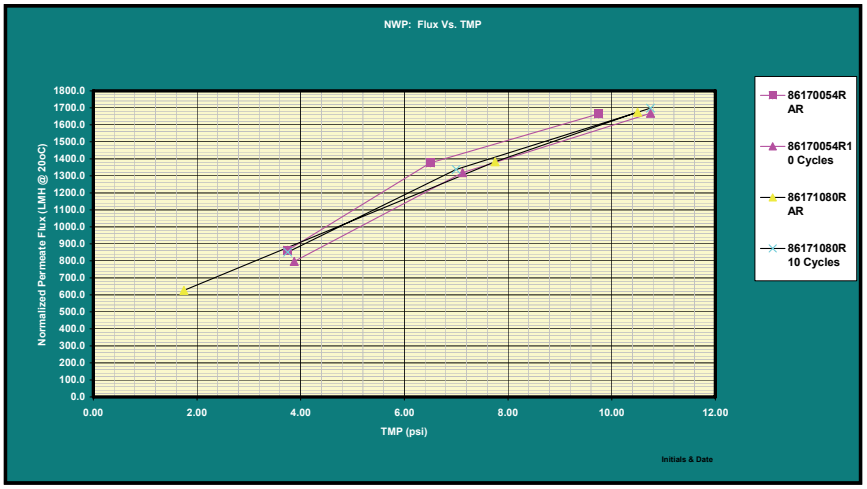

Figure 4: Water Permeability vs. Transmembrane Pressure

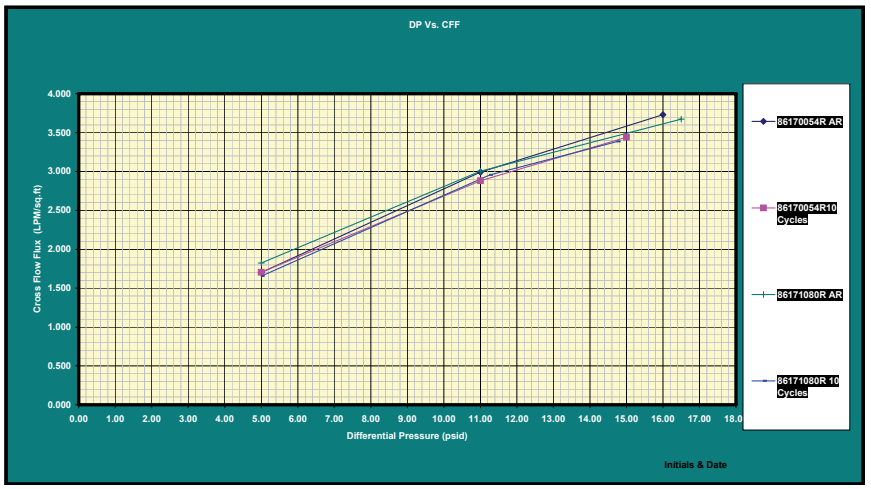

Figure 5: Cross Flow Flux Rate vs. Δ P

3.4 Maximum Pressure and Temperature Compatibility

To evaluate the ability of Supor TFF Cassettes, PSM65F22-S022 to withstand multiple cycles at maximum temperature and pressure, a study was performed where two cassettes were subjected to 6 cycles, 3 hours each at 4 bar feed pressure and 55 °C. Cassettes were evaluated for water flux, pressure drop and air integrity following each cycle. No significant changes in cassette performance were observed.

Summary of Method

Test condition: water at 55-60°C ; 4 bar (58 psi) feed pressure; 6 x 3 hr. cycle time

1. Install each cassette in the test characterization holder separately
2. Characterize each cassette for IT, DP and NWP
3. Install both cassettes in the test holder
4. Open all valves - feed, retentate and filtrate
5. Increase the pump speed and slowly close the retentate valve
   (i) Adjust pump speed, retentate valve and filtrate valve to obtain 4 bar (58 psi) feed pressure
   (ii) Maintain retentate flow between 0.5 and 1.0 L/min/ft2

6. Use a heat exchanger to maintain the temperature at 55 to 60 °C.
   Start the time when the water temperature is 50 °C.
7. Recirculate for 3 hours. Adjust valves to maintain the pressure if necessary.
8. Drain the system, then cool.
9. Remove the cassettes from holder and characterize each cassette separately at ambient temperature.
10. Repeat steps 3 through 9, five additional cycles (Total of 6 x 3-hour cycles)

Results

After 6 cycles of 3 hours in water at 4 bar feed pressure and 55 °C, the test cassettes showed no significant change in water permeability, air integrity or pressure drop.

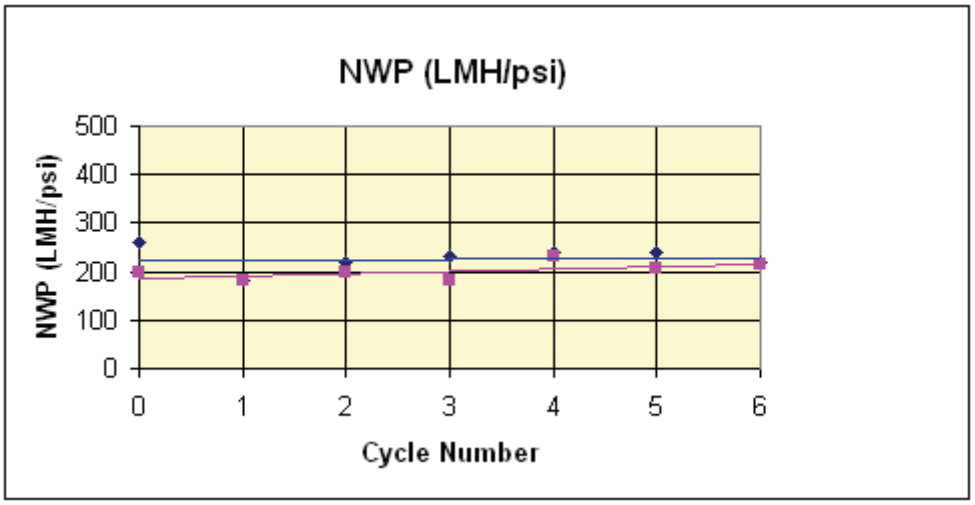

Figure 6: Normalized Water Permeability over 6 cycles at 4 bar, 55 °C in Water

4 Quality Assurance

Membranes and cassettes are produced in conformance with the Pall Corporation manufacturing documentation. Cassette components meet current standards for USP Class VI, 70 °C Biological Reactivity Tests for Plastics.

4.1 Quality Control Measures

Raw materials used in production are logged in for traceability and quarantined upon receipt. After inspection by the Quality Control Department, approved raw materials are issued to the warehouse for storage.

During manufacturing, multiple samples from the beginning, and end of each lot of membrane are tested for quality. Tests include water permeability, KL (bubble point), and thickness measurement.

Quality control inspects each cassette and lot card for completeness. The cassettes are then flushed with a glycerin solution and membrane integrity is tested.

4.1.1 Quality Assurance Certificates

A quality assurance certificate is packaged with each tangential flow cassette.

4.1.2 Labels

Each cassette, sealed in a plastic bag, is inserted into a cardboard cradle, and then packaged in a box. Labels affixed to the cradle, box and bag describe the contents. The label (Figure 7) identifies the cassette format and contains the part number, and the serial number. This information should match the information printed on the side of the cassette.

Figure 7: Packaging Label

4.1.3 Cassette

The following information is printed on the side of each cassette (Figure 8):

1. Company name
2. Membrane type
3. Pore size
4. Cassette format
5. Membrane area
6. Feed channel format
7. Part number
8. Serial number

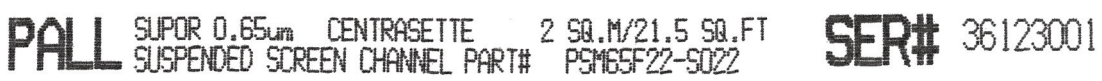

Figure 8: Example of the Information Printed on Supor TFF Cassettes

5 Biological Evaluation and Test Procedures

5.1 Introduction

The purpose of the biological evaluations and tests was to evaluate the biological suitability of the materials of construction of the Supor TFF membrane cassettes. These tests were performed by an outside contract laboratory. Tests performed included the *Biological Reactivity Tests, In Vivo, for Plastics* (hereafter called the *biological reactivity tests*), as described in the *United States Pharmacopeia*, Chapter <88>; as well as the *Hemolysis Test*, and the L929MEM—*Cytotoxicity Test* (hereafter called the *cytotoxicity test*).

5.2 Summary of Test Procedures

The biological reactivity tests described in the United States Pharmacopeia include injection of extracts of plastic materials, as well as implantation of the material itself into animal tissue. Four extracting media are listed which simulate parenteral solutions and body fluids. These include: (1) sodium chloride injection, (2) 1-in-20 solution of alcohol in sodium chloride injection, (3) polyethylene glycol 400, and (4) vegetable oil (sesame or cottonseed oil). Extracts are prepared at one of three standard conditions: 50 °C for 72 hours, 70°C for 24 hours, or 121 °C for one hour. Since Supor TFF membrane cassettes have a recommended operating temperature limit of 50 °C, cassette components were extracted at 70 °C to provide for the most stringent test condition not resulting in physical changes in the plastic itself.

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 extracts were injected intravenously. Vegetable oil extract and polyethylene glycol 400 extract were injected intraperitoneally.

An intracutaneous test was performed to evaluate the potential of a single injection of an extract to produce tissue irritation. The four specified extracts were used.

Implantation was also performed in order to subject the materials of construction to the most stringent conditions included in the United States Pharmacopeia. Each of the components of the filter cassette was implanted separately.

The hemolysis test and cytotoxicity test were conducted to determine the potential toxicity resulting from direct contact of the materials of construction with blood or tissue. The hemolysis test determines the degree of red blood cell lysis caused by contact of the test material. Using cell culture techniques, the cytotoxicity test determines the lysis of cells and the inhibition of cell growth caused by extracts of the test materials.

5.2.1 Results

All Supor TFF membrane cassette components were found to meet the requirements of the USP, In Vivo Class VI-70 °C Plastics. Additionally, test samples meet the requirements of the *hemolysis test* and *cytotoxicity test*.

Tests were conducted by STS *division of Ethox Corp*, 7500 W. Henrietta Road, Rush, NY 14543 and by Toxicon Laboratories, 225 Wildwood Avenue, Woburn Massachusetts 01801.

Details of test reports are available by contacting Pall Life Sciences, Quality Assurance department.

5.3 Summary of Materials of Construction

- Polyethersulfone-Meets FDA 21 CFR, part 177.2440, USP Class VI plastics at 70 °C
- Polyolefin membrane support-Meets 21 CFR, part 176.170, 177.1520, 177.2800, USP Class VI plastics at 70 °C
- Polyester screen-Meets 21 CFR, part 177.1630, USP Class VI plastics at 70 °C
- Polyolefin spacers-Meets 21 CFR, part 177.1520, USP Class VI plastics at 70 °C
- Polyurethane encapsulant-Meets 21 CFR, part 175.103, 175.300, 177.2600, USP Class VI plastics at 70 °C
- Silicone Seals - Meets 21 CFR, part 175.103, 175.300, 177.2600, USP Class VI plastics at 70 °C
- Silicone gaskets-Platinum cured, medical grade, Meets 21 CFR, part 177.2600, USP Class VI plastics at 70 °C
- Spacer in suspended screens-Natural HDPE sheet, USP Class VI

6 Method Details

6.1 Characterization of Extractables

Contact Pall Life Sciences for details on extractables and methods.

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