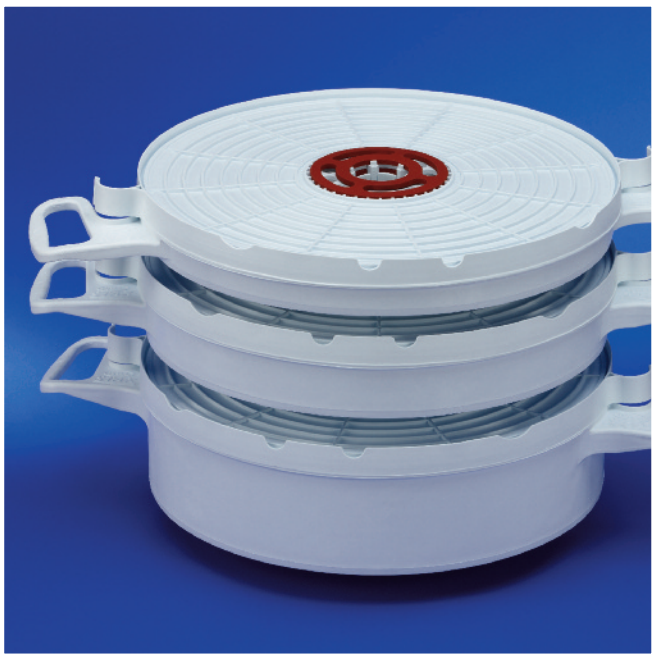
PALL Life Sciences

Validation Guide

USTR 2528a

Stax™ Capsule System



*Filtration. Separation. Solution.*SM

Contents

1. Overview

1.1 Introduction

This guide contains validation data applicable to the Stax™ disposable depth filter capsules and appropriate manifold kits, hereafter referred to as the "Stax capsule system". This system was designed to provide a fully disposable system for Pall Seitz® depth filter sheets. The depth filter sheets are configured in single or double-layer modules using the same sheet support construction as in the established SUPRAdisc™ II 16-inch modules, which ensure high mechanical robustness even under difficult process conditions. The modules are then encapsulated in Stax capsules. The Stax system platform consists of fully disposable Stax capsules, two types of manifold kits (for various connection options), and stainless steel chassis in three different sizes. The design ensures simple and flexible assembly of different Stax capsules. The Stax capsules are available in three sizes (large, medium, and small). The large Stax capsules (SXL) are manufactured with filter areas of 2 m^2 for the single-layer and 1 m^2 for the double-layer module. The medium Stax capsules (SXM) are manufactured with filter areas of 1 m^2 (single-layer module) and 0.5 m^2 (double-layer module), while the small Stax capsules (SXS) are manufactured with filter areas of 0.5 m^2 (single-layer module) and 0.25 m^2 (double-layer module). This modular design provides a high flexibility for the system filter area. The Stax capsule system combines handling comfort with efficiency and reliability. It uses the same design concept as SUPRAcap™ 100 and SUPRAcap 60 capsules, thus completing the range of disposable capsules with excellent scalability for process volumes up to > 20,000 liters.

This report summarizes the tests that were conducted to qualify the performance of the Stax capsule system under a range of standard test conditions.

The qualification program included:

- Determination of water flow characteristics
- Determination of capsule weights and fluid hold-up volumes
- Resistance to autoclave conditions
- Burst pressures at 25 °C and 60 °C
- Creep-rupture testing
- Extractables testing using water and ethanol 96%
- Biological reactivity tests

Materials of construction and performance parameters of the Stax capsule system are described in the Pall brochure "Stax Disposable Depth Filter Systems" (USD2590), which supplements this guide.

The units of pressure quoted in this document are bar and pounds force per square inch (psi).

The following formulas can be used to convert these units of pressure to Pascals (Pa):

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

1.2 Overview of Conclusions

1.2.1 Determination of Water Flow Characteristics (see Section 2)

Water flow rates of different Seitz sheet filter types in all three Stax capsule sizes have been determined at set water flow rates. The results demonstrate that the water flow characteristic of the filter sheets incorporated in the three Stax capsule types does not significantly vary with capsule size, thus demonstrating excellent linear scalability of the Stax capsules from large (SXL) to medium (SXM) to small (SXS) capsule sizes.

1.2.2 Determination of Capsule Weight and Fluid Hold-Up (see Section 3)

The average capsule weights as made and after fluid filtration following the application of suitable air pressures to minimize liquid hold-up volumes have been determined for all three Stax capsule sizes from large (SXL) to small (SXS) with a range of different Seitz sheet filter types. The results can assist with determining the weight of a given Stax capsule system, and indicate the typical fluid hold-up volume in the Stax system after product filtration following a suitable blow-down procedure with pressurized air.

1.2.3 Resistance to Autoclave Conditions (see Section 4)

Stax depth filter capsules have demonstrated the ability to withstand at least two (2) autoclave cycles at 125 °C. The tests performed demonstrate that the SUPRAdisc II 16-inch filter modules incorporated in the Stax capsules maintain their structural integrity. Tests also showed that the capsule shells maintain their structural integrity and operating safety margin after two (2) autoclave cycles (see also Section 5, Burst Testing and Section 6, Creep-Rupture Testing). The data presented in this report support the product claims shown in Table 1: Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS***.

Table 1

*Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS****

Pall Filter	Autoclave Conditions	Maximum Recommended Autoclave Claim
SXL***, SXM***, SXS***	Autoclaving at 125 °C	1 x 1-hour cycle

*The claim in Table 1: Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS*** is supported by data with a 100 % safety margin. A second autoclaving cycle might be performed for sanitization purpose post use prior to disposal. Pall autoclave resistance testing is conducted under laboratory conditions intended to demonstrate robustness under typical user autoclaving conditions. Pall recommends that structural integrity be confirmed under user autoclave conditions during process qualification validation.*

1.2.4 Burst Pressures at 25 °C and 60 °C (see Section 5)

Stax depth filter capsules have demonstrated the ability to withstand the maximum specified operating pressures at 25 °C and at 60 °C with a considerable safety margin after exposure to two (2) cycles of autoclaving at 125 °C. The recorded burst pressures at 25 °C exceeded 8.5 bar, while the recorded burst pressures at 60 °C exceeded 7.3 bar. These data support the maximum operating pressures detailed in Table 2: Maximum Operating Pressures of Stax Depth Filter Capsules.

Table 2

Maximum Operating Pressures of Stax Depth Filter Capsules

Pall Filter Part Number	Maximum Operating Pressure (bar/psi)
SXL***, SXM***, SXS***	3.5 bar (50.8 psi) at up to 25 °C 1.0 bar (14.5 psi) at up to 60 °C

1.2.5 Creep-Rupture Testing (see Section 6)

Stax depth filter capsules have been designed for single cycle use when operated at up to 3.5 bar (50.8 psi) up to 25 °C and 1.0 bar (14.5 psi) at up to 60 °C for 8 hours in continuous use. An extrapolation of the trend lines of the creep-rupture data from large, medium, and small Stax depth filter capsules (part numbers SXL***, SXM***, SXS***) presented in this report predict a creep-rupture of capsules maintained at constant maximum operating pressure (3.5 bar (50.8 psi) at 25 °C; 1 bar (14.5 psi) at

60 °C) in excess of 10,000 hours (416 days), thus demonstrating the very large safety margins that have been incorporated into these pressure claims. Please contact Pall for further advice on longer operating times, if required.

1.2.6 Extractables Testing of Capsule Moldings using Water and Ethanol 96% (see Section 7)

Information on the extractables and rinse-up behavior of the Seitz filter sheets incorporated into Stax capsules can be obtained in the Pall documents USTR 2366 “Pall® P-series Depth Filter Media” and USTR 2404 “Pall® SUPRAdisc HP Depth Filter media”. Recommended rinse-up volume is 50 L/m^2 filter area for single-layer configurations, while 100 L/m^2 filter area is recommended for the HP depth filter sheets (double-layer configuration).

The average amount of non-volatile residue (NVR) extracted from Stax capsule system mold samples (without filter medium) in water at ambient temperature was extremely low and ranged from 0.4 mg to 1.0 mg per extracted sample. The NVR value of the second (consecutive) water extraction was lower than that obtained in the first extraction and amounted to 0.3 mg per sample. The average amount of NVR extracted from Stax capsule system mold samples (without filter medium) in ethanol 96% at ambient temperature ranged from 1.0 mg to 2.1 mg per extracted mold sample. The NVR value of the second (consecutive) ethanol 96% extraction was also significantly lower than that obtained in the first extraction of that sample and amounted to 0.9 mg.

The FTIR spectrum of the 96% ethanol non-volatile residues of all mold samples tested indicates the presence of polypropylene. The FTIR spectrum of the second (consecutive) extract of a mold sample tested 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.

The area-ratio based calculations for the Stax capsule system moldings highlight the typical amount of NVR which can be extracted from the actual molded parts.

The presence of the various inorganic ions analyzed by Inductively Coupled Plasma (ICP) Spectroscopy was extremely low. The results of almost all extract samples analyzed were under the limit of detection or in the range of the level in the ultrapure water blank. Slightly increased values were found for Ni in the first extracts of the three samples (0.161 – 0.255 µg/L); in the second (consecutive) extract, the content of Ni was below detection limit (< 0.1 µg/L). Increased values were also found for Zn in the first extracts of the three samples (3.67 – 5.79 µg/L); in the second consecutive) extract, the content of Zn (1.17 µg/L) was near the value of the ultrapure water blank (1.05 µg/L).

The Total Organic Carbon (TOC) content of all extracts (340 – 394 ppb) was greater than the water blank (133 ppb). The second (consecutive) extract showed a lower TOC value (294 ppb) than the first extract of that mold sample (394 ppb).

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

The extraction tests for the Stax capsule system moldings have demonstrated depletion of the total soluble material in a second extraction. This indicates that suitable flushing regimes, such as the required flushing for the incorporated filter sheets (50 L/m^2 filter area for single-layer configurations, 100 L/m^2 filter area for

double-layer configuration), will remove the extractables from the Stax capsule system moldings below detection level. Process-specific evaluation for specific Stax capsule systems is recommended.

1.2.7 Biological Reactivity Tests of Stax Capsules (see Section 8)

The materials of construction used in the Stax capsule system 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. They also met Hemolysis Tests (Saline Extraction Method) and MEM Elution Cytotoxicity Tests (method references see Section 8.2).

Information on the Biological Reactivity Tests of the incorporated Seitz filter sheets can be obtained in the Pall documents USTR 2366 “Pall® P-series Depth Filter Media” and USTR 2404 “Pall® SUPRAdisc HP Depth Filter media”.

2. Determination of Water Flow Characteristics

2.1 Introduction

The purpose of these tests was to determine the differential pressure across the range of Stax capsules sizes incorporating various types of filter sheets at set water fluxes. The tests served to confirm the linear scalability of the capsule design.

2.2 Summary of Methods

The three available Stax capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS) equipped with a range of different sheet filter types were used for the tests. The sheet filter types were chosen to represent the full range of water permeability of Seitz filter sheets in P-grade in single and double-layer configuration, and one grade of the Bio-series. Each sheet type was tested while incorporated in three large (SXL), three medium (SXM) and three small (SXS) capsules, thus representing triple samples per module size and sheet type.

P-grade single-layer sheets used for determination of water flow characteristics:

- K900P (high water permeability)
- K100P (medium water permeability)
- EKSP (low water permeability)

P-grade double-layer sheets used for determination of water flow characteristics:

- PDK5 (high water permeability)
- PDD1 (low water permeability)

Sheets from the Bio-series used for the determination of water flow characteristics:

- Bio 10 (low water permeability)

Pre-filtered water was pumped through the filter capsules in the normal flow direction (out to in) using an automated test rig. After an initial water flush at a flux of 750 $L/m^2 \cdot h$ for 5 minutes, the flow was ramped up and pressure readings from transducers on the upstream and downstream sides of the test assembly were monitored to calculate the differential pressure at set water fluxes (50, 100, 200, 300, 400, 500, 600, and 750 $L/m^2 \cdot h$). The test was repeated three times for each module sample tested.

Further flow measurements were taken with the test rig with no capsule installed, to assess whether the piping pressure losses were negligible or required subtraction from the filter assembly results.

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

2.3 Results

The graphs in Figures 1 – 7 show the water flow characteristic of the samples tested. Each of the graphs in Figures 1 – 6 combines the water flow test results of one of the six sheet filter types tested (K900P, K100P, EKSP, PDK5, PDD1, Bio 10) incorporated in the three different capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS). Each line represents the average of the three test replicates per capsule sample tested. Figure 7 shows the average water flow test results of the six sheet filter types tested in the Stax Depth Filter Capsules.

Figure 1

Water Flow Test Results of Sheet Type K900P in SXL, SXM, and SXS Capsules

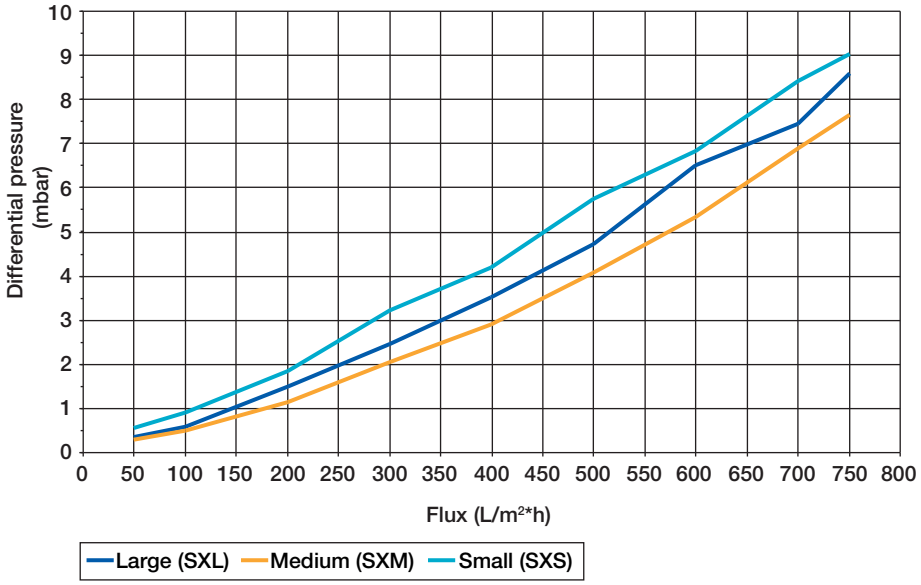


Figure 2

Water Flow Test Results of Sheet Type K100P in SXL, SXM, and SXS Capsules

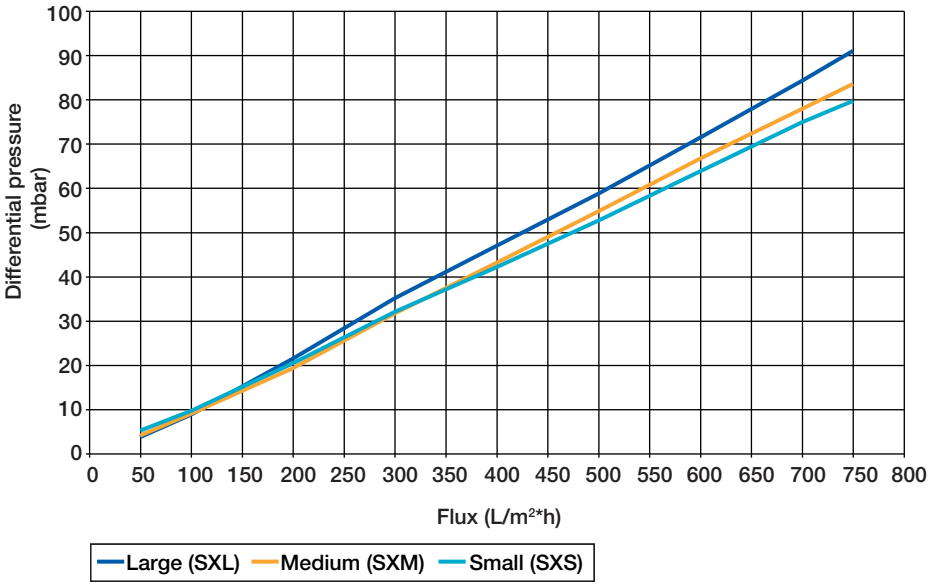


Figure 3

Water Flow Test Results of Sheet Type EKSP in SXL, SXM, and SXS Capsules

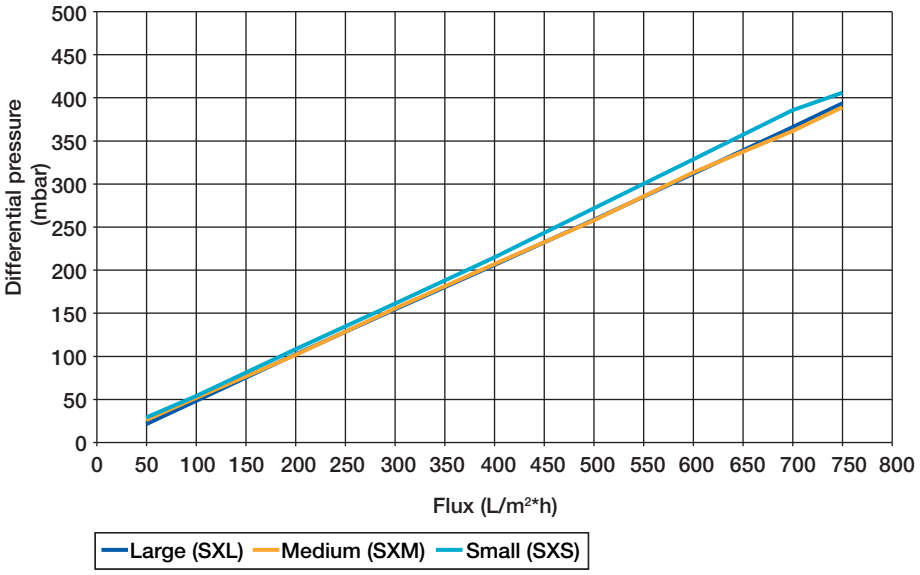


Figure 4

Water Flow Test Results of Sheet Type PDK5 in SXL, SXM, and SXS Capsules

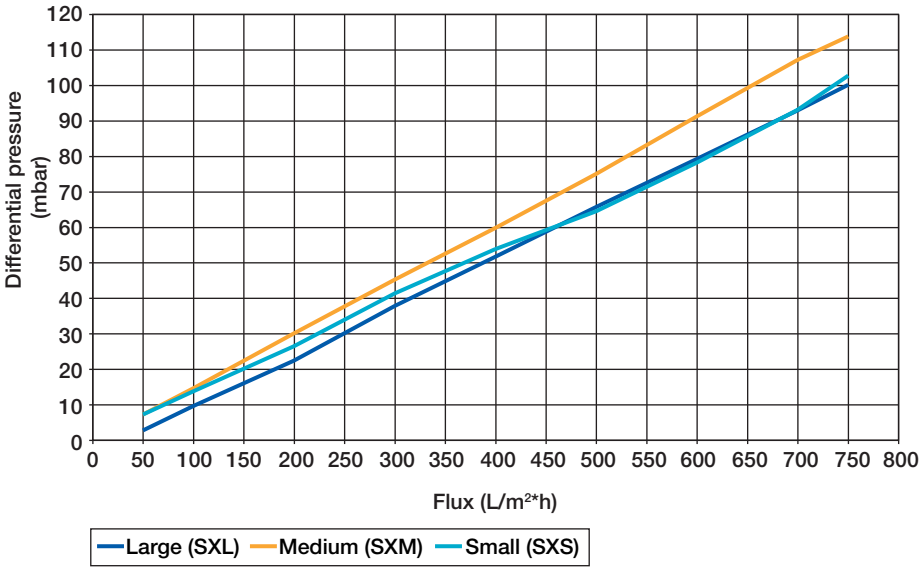


Figure 5

Water Flow Test Results of Sheet Type PDD1 in SXL, SXM, and SXS Capsules

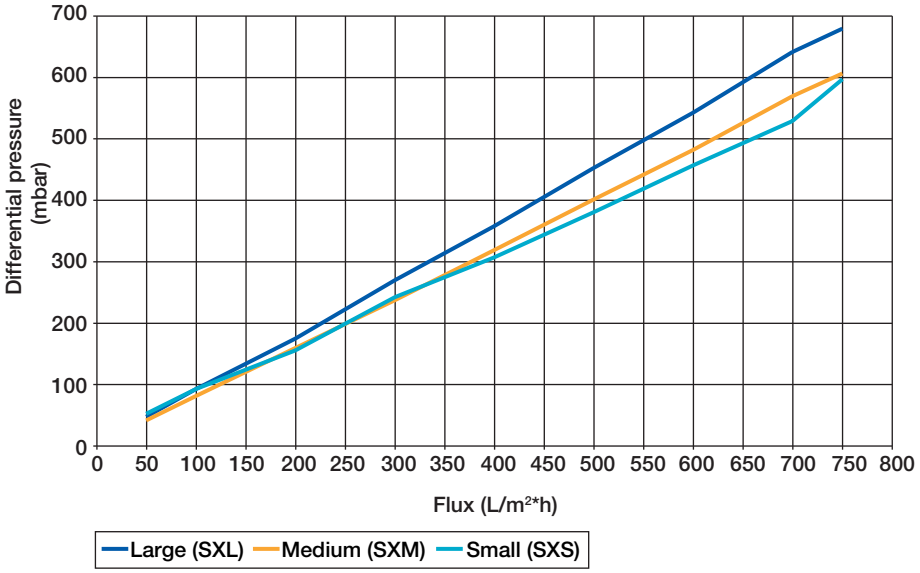


Figure 6

Water Flow Test Results of Sheet Type Bio 10 in SXL, SXM, and SXS Capsules

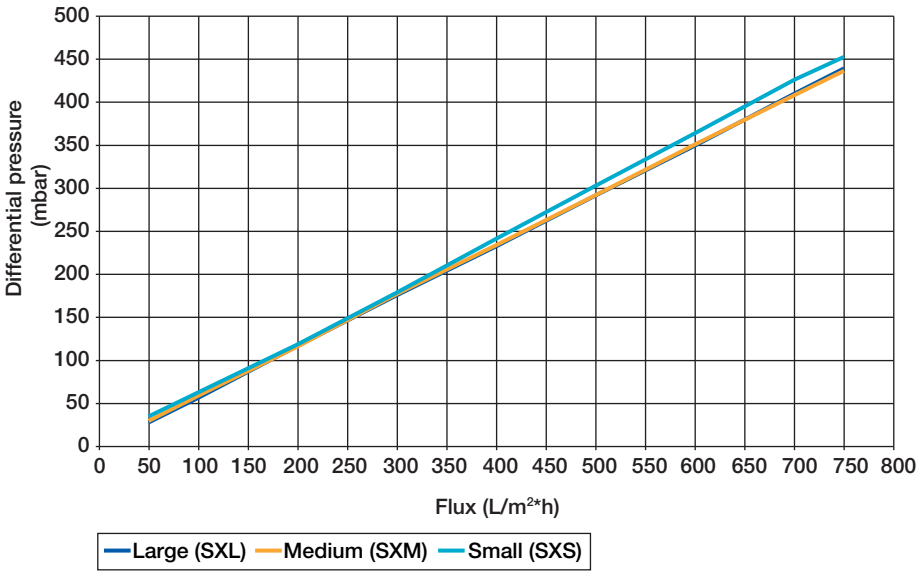
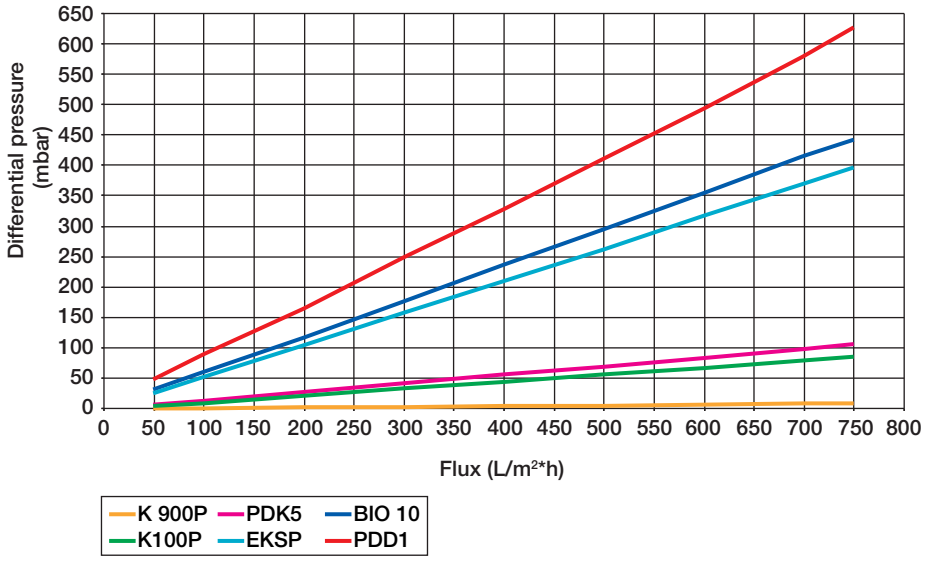


Figure 7

Average Water Flow Test Results of All Sheets Types Tested in SX Capsules



2.4 Conclusions

Water flow rates of different Seitz sheet filter types in all three Stax capsule sizes have been determined at set water flow rates. The results demonstrate that the water flow characteristic of the filter sheets incorporated in the three Stax capsule types does not significantly vary with capsule size, thus demonstrating excellent linear scalability of the Stax capsules from large (SXL) to medium (SXM) to small (SXS) capsule sizes.

3. Determination of Capsule Weight and Fluid Hold-Up Volume

3.1 Introduction

The purpose of these tests was to determine the weight of Stax capsules incorporating various types of filter sheets, dry (as made) and water wet following the application of a defined air pressure to displace and minimize fluid hold-up. The tests serve to indicate the Stax capsule weight as made and with the fluid hold-up volume in the capsules after a product filtration following a suitable blow-down procedure with pressurized air.

3.2 Summary of Methods

The three available Stax capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS) equipped with a range of different sheet filter types were used for the tests. The sheet filter types were chosen to represent the full range of water permeability of Seitz filter sheets in P-grade in single and double-layer configuration, and one grade of the Bio-series. Typically each sheet type was tested incorporated in three large (SXL), three medium (SXM) and three small (SXS) capsules, thus typically representing triple samples per module size and sheet type.

P-grade single-layer sheets used for determination of weight and fluid-hold-up volumes:

- K900P (high water permeability)
- K100P (medium water permeability)
- EKSP (low water permeability)

P-grade double-layer sheets used for determination of weight and fluid-hold-up volume:

- PDK5 (high water permeability)
- PDD1 (low water permeability)

Sheets from the Bio-series used for the determination of weight and fluid hold-up volume:

- Bio 10 (low water permeability)

New dry modules were placed on a suitable electronic scale and their dry weight determined. Pre-filtered water was pumped through the filter capsules in the normal flow direction (out to in) at a flux of up to 750 L/m^2·h for at least 20 minutes, to ensure that the incorporated filter sheets were thoroughly wetted. A defined air pressure was applied on the upstream side for 20 minutes, while the downstream side was allowed to freely drain. The pressure was chosen depending on the sheet filter type incorporated into the capsule and remained below the pressure required to expel the fluid from the largest pore (no blow-through). The pressure decay in the capsule was monitored to control that no blow-through occurred and to confirm the structural integrity of the capsule. After 20 minutes of pressure exposure, the wet capsules were again placed on an electronic scale to determine their wet weight. The fluid hold-up was calculated from the difference between the dry and wet weight.

3.3 Results

The results of the weight determination are shown in Table 3: Average Capsule Weights and Fluid Hold-up Volumes of Stax Capsules Equipped with Various Seitz Depth Filter Types. The values presented are the averages of the individual values obtained for each of the six sheet filter types incorporated into the three Stax capsule sizes.

Table 3

Average Capsule Weights and Fluid Hold-up Volumes of Stax Capsules Equipped with Various Seitz Depth Filter Types

Sheet Type	Capsule Size	Sheet Lot Number	Air Pressure Applied (mbar)	Average Dry Weight (kg)	Average Wet Weight After 20 minutes Air Pressure (kg)	Average Water Hold-up (kg)
K900P	Large	R446	50	7.42	13.55	6.13
K900P	Medium	R446	50	4.85	8.28	3.43
K900P	Small	R446	50	3.50	5.13	1.63
K100P	Large	S287	100	7.85	13.13	5.28
K100P	Medium	S287	100	5.03	7.65	2.62
K100P	Small	S287	100	3.60	5.10	1.50
EKSP	Large	S250	500	8.08	13.6	5.52
EKSP	Medium	S250	500	5.15	7.95	2.80
EKSP	Small	S250	500	3.70	5.20	1.50
PDK5	Large	R446 S287	75	7.12	12.62	5.50
PDK5	Medium	R446 S287	75	4.75	8.02	3.27
PDK5	Small	R446 S287	75	3.48	4.91	1.43
PDD1	Large	S158 S309	600	7.41	12.26	4.85

Table 3 *Continued*

Average Capsule Weights and Fluid Hold-up Volumes of Stax Capsules Equipped with Various Seitz Depth Filter Types

Sheet Type	Capsule Size	Sheet Lot Number	Air Pressure Applied (mbar)	Average Dry Weight (kg)	Average Wet Weight After 20 minutes Air Pressure (kg)	Average Water Hold-up (kg)
PDD1	Medium	S158 S309	600	4.83	7.26	2.43
PDD1	Small	S158 S309	600	3.55	4.85	1.30
Bio 10	Large	R841	500	8.23	12.58	4.35
Bio 10	Medium	R841	500	5.25	7.65	2.40
Bio 10	Small	R841	500	3.75	5.00	1.25

3.4 Conclusions

The average capsule weights as made and after fluid filtration following the application of suitable air pressures to minimize liquid hold-up volumes have been determined for all three Stax capsule sizes from large (SXL) to small (SXS) with a range of different Seitz sheet filter types. The results can assist to determine the weight of a given Stax capsule system, and indicate the typical fluid hold-up volume in the Stax capsule system after product filtration following a suitable blow-down procedure with pressurized air.

4. Resistance to Autoclave (125 °C) Conditions

4.1 Introduction

The purpose of these tests was to determine the effects of exposure to autoclaving cycles on Stax depth filter capsules. The test results serve to demonstrate the ability of Stax depth filter capsules to withstand autoclaving while maintaining the structural integrity of the incorporated filter module and structural integrity and operating safety of the capsule shell (for the latter see also Section 5. Burst Testing and Section 6. Creep-Rupture Testing).

4.2 Summary of Methods

The three available capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS) equipped with two different sheet filter types were used for the tests. The sheet filter types were chosen to represent Seitz filter sheets in P-grade in single and double-layer configuration and to allow assessment of the structural integrity of the incorporated modules by a diffusive air test (pressure decay method). Each sheet type was tested incorporated in several large (SXL), medium (SXM) and small (SXS) capsules and subjected to two or three autoclave cycles.

P-grade single-layer sheets used for determination of resistance to autoclaving:

- EKSP (low water permeability)

P-grade double-layer sheets used for determination of resistance to autoclaving:

- PDD1 (low water permeability)

Pre-filtered water was pumped through the filter capsules in the normal flow direction (out to in) at a flux of 750 L/m^2·h for five (5) minutes. A defined air pressure was applied on the upstream side to assess the structural integrity of the capsules and the incorporated sheet filter modules by monitoring the pressure decay, which is a result of the gas transport across the wetted filter sheets. The integrated module and capsule shell was deemed integral when the applied test pressure had decayed by not more than 10% in one (1) minute test time. The capsules were then autoclaved in cycles of one (1) hour at 125 °C using a suitable autoclave program (fractionated pre-vacuum draw of 3 x -500 mbar). After each autoclave cycle the capsules were water flushed and the structural integrity assessed as described above.

The above test sequence, where the sheet filters were wetted prior to the first autoclave cycle, presents a worst-case scenario for the autoclaving of sheet filters. However, this is not fully representative of typical autoclaving conditions at a customer site. Therefore some tests were also performed where the sheet filters were dry prior to the first autoclave cycle, which is more representative of a typical user process. For these tests the water flush prior to the first autoclave cycle was omitted so that the incorporated module was dry prior to autoclaving. All following steps were performed as described above.

4.3 Results

The test results for the Stax capsules tested are shown in Table 4: Results of Autoclaving Resistance Tests of Large, Medium and Small Stax Depth Filter Capsules Equipped with Single-Layer Filter Sheets after Autoclaving Cycles at 125 °C and Table 5: Results of Autoclaving Resistance Tests of Large, Medium and Small Stax Depth Filter Capsules Equipped with Double-Layer Filter Sheets after Autoclaving Cycles at 125 °C. All capsules were found to having maintained the structural integrity of the incorporated modules after two (2) 1-hour autoclave cycles at 125 °C.

Table 4

Results of Autoclaving Resistance Tests of Large, Medium and Small Stax Depth Filter Capsules Equipped with Single-Layer Filter Sheets after Autoclaving Cycles at 125 °C

Sheet Type	Capsule Size	Sheet Lot Number	Capsule Sample Number	Autoclaving Cycles	Structural Integrity Test Result
EKSP	Large	S250	1	0	Pass
				1	Pass
				2	Pass
				3	Pass
EKSP	Large	S250	2	0	Pass
				1	Pass
				2	Pass
EKSP*	Large	S250	3	1	Pass
				2	Pass
EKSP*	Medium	S626	1	1	Pass
				2	Pass
EKSP*	Medium	S626	2	1	Pass
				2	Pass
EKSP*	Medium	S626	3	1	Pass
				2	Pass
EKSP	Small	S250	1	0	Pass
				1	Pass
				2	Pass
				3	Pass
EKSP	Small	S250	2	0	Pass
				1	Pass
				2	Pass
EKSP	Small	S250	3	0	Pass
				1	Pass
				2	Pass

** Dry prior to the first autoclaving cycle*

Table 5

Results of Autoclaving Resistance Tests of Large, Medium and Small Stax Depth Filter Capsules Equipped with Double-Layer Filter Sheets after Autoclaving Cycles at 125 °C

Sheet Type	Capsule Size	Sheet Lot Number	Capsule Sample Number	Autoclaving Cycles	Structural Integrity Test Result
PDD1*	Large	S158	1	1	Pass
		S309		2	Pass
PDD1*	Large	S158	2	1	Pass
		S309		2	Pass
PDD1*	Large	S158	3	1	Pass
		S309		2	Pass
PDD1*	Medium	S158	1	1	Pass
		S309		2	Pass
PDD1*	Medium	S158	2	1	Pass
		S309		2	Pass
PDD1*	Medium	S158	3	1	Pass
		S309		2	Pass
PDD1	Small	S158	1	0	Pass
		S309		1	Pass
				2	Pass
				3	Pass
PDD1	Small	S158	2	0	Pass
		S309		1	Pass
				2	Pass
				3	Pass
PDD1	Small	S158	3	0	Pass
		S309		1	Pass
				2	Pass

** Dry prior to the first autoclaving cycle*

4.4 Conclusions

Stax depth filter capsules have demonstrated the ability to withstand at least two (2) autoclave cycles at 125 °C. The tests performed demonstrate that the SUPRAdisc II 16-inch filter modules incorporated in the Stax capsules maintain their structural integrity. Tests also showed that the capsule shells maintain their structural integrity and operating safety margin after two (2) autoclave cycles (see also Section 5: Burst Testing and Section 6: Creep-Rupture Testing).

The data presented in this report support the product claims shown in Table 6: Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS***.

Table 6

*Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS****

Pall Filter Part Number	Autoclave Conditions	Maximum Recommended Autoclave Claim
SXL***, SXM***, SXS***	Autoclaving at 125 °C	1 x 1-hour cycle

*The claim in Table 6: Product Claims for Autoclave Resistance of Stax Depth Filter Capsules, Part Numbers SXL***, SXM***, and SXS*** is supported by data with a 100 % safety margin. A second autoclaving cycle might be performed for sanitization purpose post use prior to disposal. Pall autoclave resistance testing is conducted under laboratory conditions intended to demonstrate robustness under typical user autoclaving conditions. Pall recommends that structural integrity be confirmed under user autoclave condition during process qualification validation.*

5. Burst Testing

5.1 Introduction

The purpose of these tests was to demonstrate that Stax depth filter capsules withstand the maximum specified operating pressures at 25 °C (3.5 bar/ 50.8 psi) and at 60 °C (1.0 bar/14.5 psi) while maintaining structural integrity and operating safety with an appropriate safety margin. Burst tests were performed with large, medium, and small Stax depth filter capsules (part numbers SXL***, SXM***, SXS***, respectively) after exposure to two (2) autoclave cycles at 125 °C.

5.2 Summary of Methods

Standard capsules of the three available capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS) from four (4) different media batches were used for the tests. The capsules were equipped with various sheet filter types. The sheet filter types were chosen to represent Seitz filter sheets in P-grade in single and double-layer configuration. Prior to the burst testing samples of the capsules were pre-treated with two (2) autoclave cycles at 125 °C.

Each capsule was burst tested in a fixture to simulate how it is fitted in the stainless steel chassis. The entire assembly was placed in a water bath at 25 °C for a minimum of 1 hour or at 60 – 63 °C for a minimum for 4 hours to ensure that it had equilibrated with the water bath temperature. The capsule was then connected to the pressure source, completely filled with water (fill time about 30-45 seconds) at the respective test temperature until water was observed to escape through the air bleed. The air bleed was secured and the pressure was gradually increased until the filled capsule burst. The burst pressure was recorded.

5.3 Results

The test results of the burst pressure tests are shown in Tables 7 – 9. The average burst pressure of the large capsules was 9.18 bar (133.1 psi) at 25 °C and 7.9 bar (114.6 psi) at 60 °C. The average burst pressure of the medium capsules was 9.53 bar (138.2 psi) at 25 °C and 9.11 bar (132.1 bar) at 60 °C. The average burst pressure of the small capsules was found to be 9.97 bar (144.6 psi) at 25 °C and 8.73 bar (126.6 psi) at 60 °C.

Table 7

Burst Pressure of Large Stax Depth Filter Capsules after Two Autoclaving Cycles at 125 °C

Part Number	Media Batch Number	Serial Number	Test Temperature (°C)	Burst Pressure (bar/psi)
SXLPEKS416SP (containing single-layer sheet of type EKSP)	S250	0002	25	9.10 bar/132.0 psi
		0003	25	9.03 bar/131.0 psi
		0008	25	8.83 bar/128.1 psi
		0009	25	9.79 bar/142.0 psi
		0010	25	8.96 bar/130.0 psi
SXLPDK5408SP (containing double-layer sheet configuration of type PDK5)	R446/S287	0001	25	8.89 bar/128.9 psi
		0002	25	9.17 bar/133.0 psi
		0003	25	10.00 bar/145.0 psi
		0009	25	9.03 bar/131.0 psi
		0010	25	9.79 bar/142.0 psi
SXLPEKS416SP (containing single-layer sheet of type EKSP)	S250	0001	63	7.31 bar/106.0 psi
		0004	63	8.14 bar/118.1 psi
		0005	63	8.20 bar/118.9 psi
		0006	63	8.27 bar/119.9 psi
SXLPDK5408SP (containing double-layer sheet configuration of type PDK5)	R446/S287	0003	63	8.14 bar/118.1 psi
		0004	63	7.58 bar/109.9 psi
		0010	60	7.65 bar/111.0 psi

Table 8

Burst Pressure of Medium Stax Depth Filter Capsules after Two Autoclaving Cycles at 125 °C

Part Number	Media Batch Number	Serial Number	Test Temperature (°C)	Burst Pressure (bar/psi)
SXMB010408SP (containing single-layer sheet of type Bio 10)	R841	0001	25	10.10 bar/146.5 psi
		0002	25	9.24 bar/134.0 psi
		0004	25	9.45 bar/137.1 psi
		0006	25	9.17 bar/133.0 psi
		0010	25	9.58 bar/138.9 psi
SXSPDD1404SP (containing double-layer sheet configuration of type PDD1)	S158/S309	0002	25	9.24 bar/134.0 psi
		0003	25	9.86 bar/143.0 psi
		0004	25	9.86 bar/143.0 psi
		0005	25	9.31 bar/135.0 psi
		0006	25	9.51 bar/137.9 psi
SXMB010408SP (containing single-layer sheet of type Bio 10)	R841	0005	63	8.55 bar/124.0 psi
		0007	63	9.38 bar/136.0 psi
		0008	63	10.10 bar/146.5 psi
		0009	63	8.55 bar/124.0 psi
SXMPDD1404SP (containing double-layer sheet configuration of type PDD1)	S158/S309	0001	63	9.03 bar/131.0 psi
		0007	63	9.86 bar/143.0 psi
		0009	60	9.58 bar/138.9 psi
		0010	60	7.86 bar/114.0 psi

Table 9

Burst Pressure of Small Stax Depth Filter Capsules after Two Autoclaving Cycles at 125 °C

Part Number	Media Batch Number	Serial Number	Test Temperature (°C)	Burst Pressure (bar/psi)
SXSB010404SP (containing single-layer sheet of type Bio 10)	R841	0001	25	10.80 bar/156.6 psi
		0003	25	10.60 bar/153.7 psi
		0004	25	9.45 bar/137.1 psi
		0005	25	9.93 bar/144.0 psi
		0010	25	9.24 bar/134.0 psi
SXSPDD1402SP (containing double-layer sheet configuration of type PDD1)	S158/S309	0001	25	9.24 bar/134.0 psi
		0002	25	10.40 bar/150.8 psi
		0003	25	11.20 bar/162.4 psi
		0006	25	8.55 bar/124.0 psi
		0007	25	10.30 bar/149.4 psi
SXSB010404SP (containing single-layer sheet of type Bio 10)	R841	0002	63	8.20 bar/118.9 psi
		0006	63	8.20 bar/118.9 psi
		0007	60	8.55 bar/124.0 psi
		0009	60	9.31 bar/135.0 psi
SXSPDD1402SP (containing double-layer sheet configuration of type PDD1)	S158/S309	0004	63	8.62 bar/125.0 psi
		0005	63	10.10 bar/146.5 psi
		0009	63	8.14 bar/118.1 psi

5.4 Conclusions

Stax depth filter capsules have demonstrated the ability to withstand the maximum specified operating pressures at 25 °C and at 60 °C with a considerable safety margin after exposure to two (2) autoclave cycles at 125 °C. The recorded burst pressures at 25 °C exceeded 8.5 bar (123.3 psi), while the recorded burst pressures at 60 °C exceeded 7.3 bar (105.9 psi), thus supporting the maximum operating pressures detailed in Table 10: Maximum Operating Pressures of Stax Depth Filter Capsules.

Table 10

Maximum Operating Pressures of Stax Depth Filter Capsules

Pall Filter Part Number	Maximum Operating Pressure
SXL***, SXM***, SXS***	3.5 bar (50.8 psi) at up to 25 °C 1.0 bar (14.5 psi) at up to 60 °C

6. Creep-Rupture Testing

6.1 Introduction

The purpose of these tests was to demonstrate that Stax depth filter capsules are robust and maintain structural integrity and operating safety while under pressure for extended periods of time. Tests were performed at 25 °C and at 60 °C with large, medium, and small Stax depth filter capsules (part numbers SXL***, SXM***, SXS***, respectively) after exposure to two (2) autoclave cycles at 125 °C.

6.2 Summary of Methods

Standard capsules of the three available capsule sizes (large capsule: SXL; medium capsule: SXM; small capsule: SXS) from four (4) different media batches were used for the tests. The capsules were equipped with various sheet filter types. The sheet filter types were chosen to represent Seitz filter sheets in P-grade in single and double-layer configuration. Prior to the creep-rupture testing samples of the capsules were pre-treated with two (2) autoclave cycles at 125 °C.

Each capsule was creep-rupture tested in a fixture to simulate how it is fixed in the stainless steel chassis. The capsules were filled with water at the respective test temperature (25 °C or 60 °C) and connected to a creep-rupture test rig designed to maintain set pressures within the capsule. The capsule and test fixture were then fully immersed into a water tank maintained at the test temperature and the internal test pressures maintained until failure of the capsule occurred. At this end point, the failure time and mode were noted.

6.3 Results

The test results of the creep-rupture tests are shown in Figure 8: Creep-Rupture Pressure Test Results for Stax Capsules at 25 °C and Figure 9: Creep-Rupture Pressure Test Results for Stax Capsules at 60-63 °C. The two trend lines in each graph represent the data points for the small and medium capsules, and for the large capsules. An extrapolation of the trend lines predict a creep-rupture of samples maintained at constant maximum operating pressure (3.5 bar/50.8 psi at 25 °C, 1 bar/14.5 psi at 60 °C) in excess of 10,000 hours (416 days).

Figure 8

Creep-Rupture Pressure Test Results for Stax Capsules at 25 °C

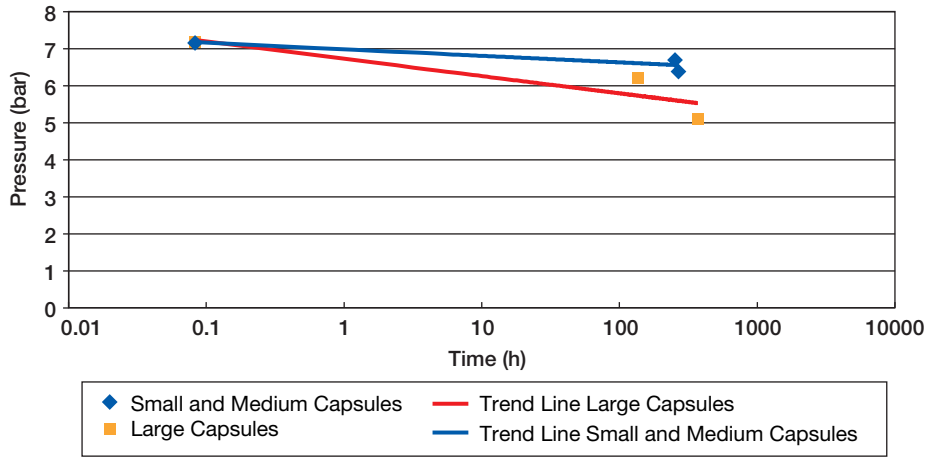
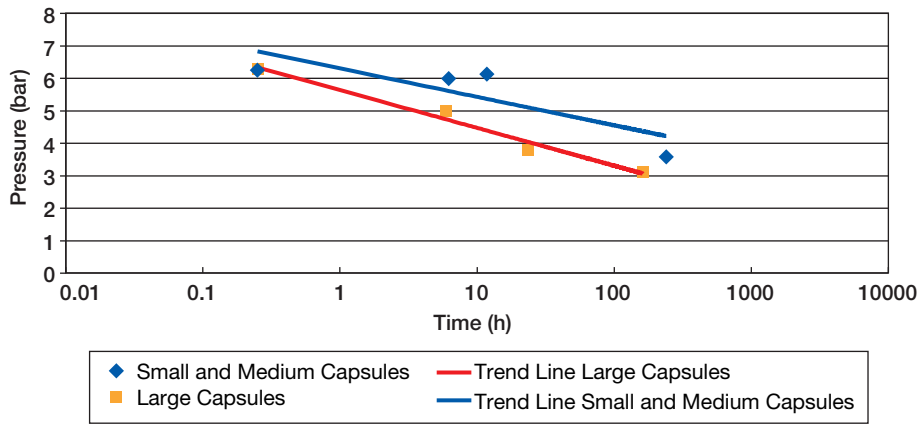


Figure 9

Creep-Rupture Pressure Test Results for Stax Capsules at 60 – 63 °C



6.4 Conclusions

Stax depth filter capsules have been designed for single cycle use when operated at up to 3.5 bar (50.8 psi) up to 25 °C and 1.0 bar (14.5 psi) at up to 60 °C for 8 hours in continuous use. An extrapolation of the trend lines of the creep-rupture data from large, medium, and small Stax depth filter capsules (part numbers SXL***, SXM***, SXS***) presented in this report predict a creep-rupture of capsules maintained at constant maximum operating pressure (3.5 bar (50.8 psi) at 25 °C; 1 bar (14.5 psi) at 60 °C) in excess of 10,000 hours (416 days), thus demonstrating the very large safety margins that have been incorporated into these pressure claims. Please contact Pall for further advice on longer operating times, if required.

7. Extractables Testing Using Water and Ethanol 96%

7.1 Introduction

The purpose of this series of tests was to quantify and characterize the material that can be extracted from the moldings of Stax capsule systems using water and ethanol 96%.

Information on the extractables and rinse-up behavior of the incorporated Seitz filter sheets can be obtained in the Pall documents USTR 2366 “Pall® P-series Depth Filter Media” and USTR 2404 “Pall® SUPRAdisc HP Depth Filter media”.

Water is considered a suitable “worst case” model solvent for a majority of aqueous solutions while ethanol 96% is considered a suitable worst case model solvent for general organic fluids.

7.2 Summary of Methods

Typical Stax capsule system moldings were used for the tests. Selected moldings were cut to allow for the required handling (subsequently called “mold samples”) and submitted to the extraction tests: Total Non-volatile Residue (NVR), Inductively Coupled Plasma (ICP) Spectroscopy, Total Organic Carbon (TOC), and Fourier Transform Infrared Spectroscopy (FTIR).

7.2.1 Preparation of the Stax Capsule System Mold Samples

Prior to the extraction test, the mold samples were autoclaved to maximize the quantity of any extractable material present. The cut mold samples were loosely wrapped in aluminum foil and autoclaved for two 1-hour cycles at 125 °C ± 2 °C, using a slow exhaust cycle. Visible droplets of water remaining on the mold samples were allowed to evaporate at room temperature before the extraction was performed.

7.2.2 Extraction Procedure of the Stax System Capsule Mold Samples

Extraction tests were performed in a known volume of deionized water or ethanol 96% at ambient temperature. The mold samples were fully immersed in the extraction fluid in a clean glass container and agitated during the extraction period by means of an orbital shaker. Some mold samples 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.

7.2.3 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 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 aqueous extraction liquid was taken and analyzed by ICP for various inorganic ions.

Analysis by TOC

Following the extraction period, a sample volume of the aqueous extraction liquid was taken and analyzed for TOC.

Analysis by FTIR

Only the extraction with ethanol 96% provided sufficient NVR for FTIR analysis, while the NVRs of the aqueous extracts were too minute to be analyzed. FTIR analysis of the NVR was performed to provide information on the nature of its organic compounds.

7.3 Results

7.3.1 Results of NVR and TOC Determination

The Table 11: Non-volatile Aqueous (DI water) Extractables and Total Organic Carbon Obtained using Stax Capsule System Mold Samples after Autoclaving at 125 °C ± 2 °C shows the levels of aqueous NVR and TOC obtained from the first extraction of three Stax capsule system mold samples. The NVR values were extremely low and ranged from 0.4 mg to 1.0 mg per extracted sample.

The Table 11: Non-volatile Aqueous (DI water) Extractables and Total Organic Carbon Obtained using Stax Capsule System Mold Samples after Autoclaving at 125 °C ± 2 °C also shows the results of the second (consecutive) extraction of one of the Stax capsule system mold samples.

Table 11

Non-volatile Aqueous (DI water) Extractables and Total Organic Carbon Obtained using Stax Capsule System Mold Samples[1] after Autoclaving at 125 °C ± 2 °C[2]

Sample Identification Extraction[3]	NVR (mg) First Extraction	NVR (mg) Second Extraction	TOC (ppb)	TOC (ppb) First Extraction[3]
Mold Sample A Surface area 0.02989 m^2	0.5	nd[4]	340	nd
Mold Sample B Surface Area 0.029755 m^2	1.0	0.3	394	294
Mold Sample C Surface Area 0.0302 m^2	0.4	nd	392	nd

[1] Cut from Typical Stax Moldings to Allow for the Required Handling
[2] 24-Hours Extraction Time at Ambient Temperature
[3] TOC Level of Ultrapure Water Blank: 133 ppb
[4] Not determined

The Table 12: Non-volatile Ethanol 96% Extractables Obtained using Stax Capsule System Mold Samples after Autoclaving at 125 °C ± 2 °C shows the levels of ethanol 96% NVR obtained from the first extraction of four Stax capsule system mold samples. The NVR values were extremely low and ranged from 2.1 mg to 1.0 mg per extracted sample.

The Table 12: Non-volatile Ethanol 96% Extractables Obtained using Stax Capsule System Mold Samples after Autoclaving at 125 °C ± 2 °C also shows the results of the second (consecutive) extraction of one of the Stax capsule system mold samples.

Table 12

Non-volatile Ethanol 96% Extractables Obtained using Stax Capsule System Mold Samples[1] after Autoclaving at 125 °C ± 2 °C[2]

Sample Identification	NVR (mg) First Extraction	NVR (mg) Second Extraction
Mold Sample D Surface area 0.029361 m^2	1.0	nd[3]
Mold Sample E Surface Area 0.029329 m^2	1.6	0.9
Mold Sample F Surface Area 0.030191 m^2	2.1	nd
Mold Sample G Surface Area 0.02908 m^2	2.0	nd

[1] Cut from Typical Stax Moldings to Allow for the Required Handling
[2] 24-Hours Extraction Time at Ambient Temperature
[3] Not determined

7.3.2 Results of FTIR Analysis

Typical infrared spectra of the ethanol 96% non-volatile extractables obtained using Stax capsule system mold samples after autoclaving at 125 °C ± 2 °C are shown in Figure 10 and 11. Figure 10 shows the infrared spectrum of mold sample D, Figure 11 shows the infrared spectrum of mold sample G.

Figure 10

Infrared Spectrum of the Ethanol 96% NVR from Stax Capsule System Mold Sample D of the First Extract

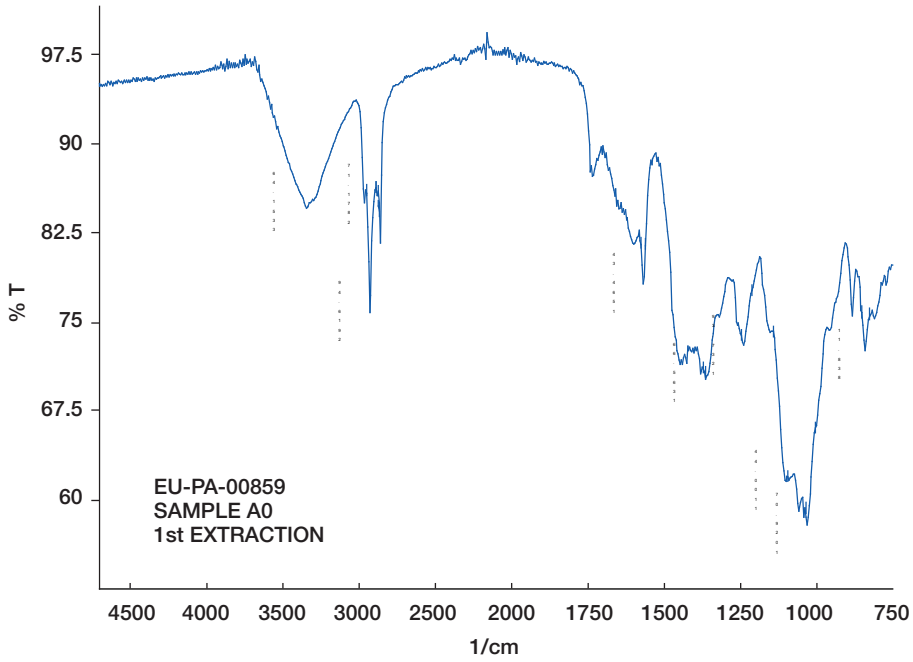
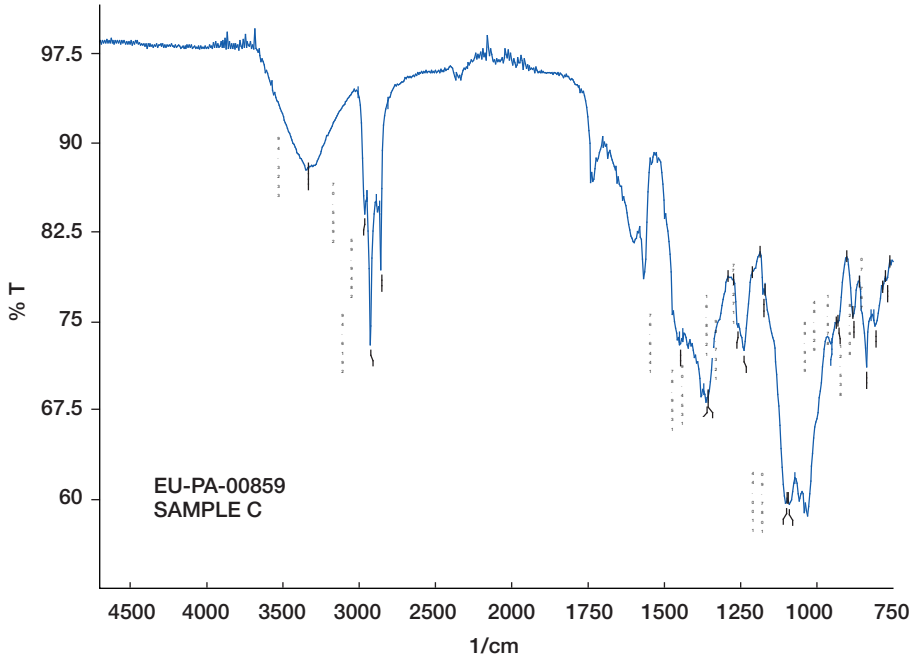


Figure 11

Infrared Spectrum of the Ethanol 96% NVR from Stax Capsule System Mold Sample G of the First Extract



7.3.3 Results of ICP Analysis

The Table 13: ICP Analysis Results of the Aqueous Extracts Obtained using Stax Capsule Systems Mold Samples after Autoclaving at 125 °C ± 2 °C shows the ICP results obtained from the first extraction and second (consecutive) extraction of three Stax capsule system mold samples, that were tested, and of an ultrapure water blank sample.

Table 13

ICP Analysis Results of the Aqueous Extracts Obtained using Stax Capsule Systems Mold Samples[1] after Autoclaving at 125 °C ± 2 °C

Sample Identity	Al (µg/L)	Fe (µg/L)	Mn (µg/L)	Ni (µg/L)	Cr (µg/L)	Cu (µg/L)	Zn (µg/L)	Cd (µg/L)	Pb (µg/L)
Ultrapure Water Blank	< 4	< 4	< 0.2	< 0.1	0.14	< 10	< 1.05	< 0.01	< 0.2
Mold Sample A Surface Area 0.02989 m²									
1st Extract	< 4	< 4	< 0.2	0.161	< 0.1	< 10	5.79	< 0.01	< 0.2
Mold Sample B Surface Area 0.029755 m²									
1st Extract	< 4	< 4	< 0.2	0.242	< 0.1	< 10	3.67	< 0.01	< 0.2
2nd Extract	< 4	< 4	< 0.2	< 0.1	0.11	< 10	1.17	< 0.01	< 0.2
Mold Sample C Surface Area 0.0302 m²									
1st Extract	< 4	< 4	< 0.2	0.255	0.11	< 10	5.52	< 0.01	< 0.2

[1] *Cut from Typical Stax Moldings to Allow for the Required Handling*

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

7.3.4 Calculation of NVR for Stax Capsule System Moldings based on Area Ratios

The mold samples from Stax capsule systems moldings had to be cut for extraction due to handling requirements of the extraction procedure and did not reflect the actual fluid contact area of the various Stax capsule system moldings. The amount of NVR extracted from two moldings, which only differ in fluid contact area, will increase directly proportionally based on the ratios of the fluid contact areas, thus allowing the assessment of the total NVR, which can be extracted from the actual Stax capsule systems moldings, based on area ratios.

The areas of the Stax capsule system mold samples, which have been extracted, and the area of the actual Stax system capsule moldings were compared and the ratio of areas calculated. The resulting factors of area ratios were used to calculate the NVR, which will typically be extracted from that molding. The resulting NVRs from Stax capsule system moldings are shown in Table 14: NVRs Calculated for the Stax Capsule Systems Moldings based on Area Ratios after Autoclaving at 125 °C ± 2 °C and Table 15: Ethanol 96% NVRs Calculated for the Stax Capsule Systems Moldings based on Area Ratios after Autoclaving at 125 °C +/- 2 °C.

Table 14

Aqueous NVR Calculated for the Stax Capsule Systems Moldings based on Area Ratios after Autoclaving at 125 °C ± 2 °C

Sample Identity	Aqueous NVR Capsule Small (mg)	Aqueous NVR Capsule Medium (mg)	Aqueous NVR Capsule Large (mg)	Aqueous NVR Vent Manifold (mg)	Aqueous NVR Distribution Manifold (mg)
NVR calculated based on Mold Sample A Surface Area 0.02989 m²					
1st Extract	6.1	6.7	7.9	0.4	1.7
NVR calculated based on Mold Sample B Surface Area 0.029755 m²					
1st Extract	12.3	13.4	15.8	0.7	3.5
2nd Extract	3.1	3.4	4.0	0.2	0.9
NVR calculated based on Mold Sample C Surface Area 0.0302 m²					
1st Extract	4.5	5.0	5.9	0.3	1.3

Table 15

Ethanol 96% NVRs Calculated for the Stax Capsule Systems Moldings based on Area Ratios after Autoclaving at 125 °C ± 2 °C

Sample Identity	Ethanol 96% NVR Capsule Small (mg)	Ethanol 96% NVR Capsule Medium (mg)	Ethanol 96% NVR Capsule Large (mg)	Ethanol 96% NVR Vent Manifold (mg)	Ethanol 96% NVR Distribution Manifold (mg)
NVR calculated based on Mold Sample D Surface area 0.029361 m²					
1st Extract	12.4	13.6	16.0	0.7	3.5
NVR calculated based on Mold Sample E Surface Area 0.029329 m²					
1st Extract	19.8	21.8	25.6	1.1	5.6
2nd Extract	11.2	15.3	14.4	0.6	3.2
NVR calculated based on Mold Sample F Surface Area 0.030191 m²					
1st Extract	25.4	27.7	32.8	1.5	7.1
NVR calculated based on Mold Sample G Surface Area 0.02908 m²					
1st Extract	25.0	27.4	32.3	1.4	7.0

7.4 Conclusions

Information on the extractables and rinse-up behavior of the Seitz filter sheets incorporated into Stax capsules can be obtained in the Pall documents USTR 2366 “Pall® P-series Depth Filter Media” and USTR 2404 “Pall® SUPRAdisc HP Depth Filter media”. Recommended rinse-up volume is 50 L/m² filter area for single-layer configurations, while 100 L/m² filter area is recommended for the HP depth filter sheets (double-layer configuration).

The average amount of NVR extracted from Stax capsule system mold samples (without filter medium) in water at ambient temperature was extremely low and ranged from 0.4 mg to 1.0 mg per extracted mold sample. The NVR value of the second (consecutive) water extraction was significantly lower than that obtained in the first extraction and amounted to 0.3 mg per mold sample.The average amount of NVR extracted from Stax capsule system mold samples (without filter medium) in ethanol 96% at ambient temperature ranged from 1.0 mg to 2.1 mg per extracted mold sample. The NVR value of the second (consecutive) ethanol 96% extraction was also significantly lower than that obtained in the first extraction of that sample and amounted to 0.9 mg. The area-ratio based calculations for the Stax capsule system moldings highlight the typical amount of NVR which can be extracted from the actual molded parts.

The FTIR spectrum of the 96% ethanol non-volatile residues of all mold samples tested indicates the presence of polypropylene. The FTIR spectrum of the second (consecutive) extract of a mold sample tested 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.

The presence of the various inorganic ions analyzed by ICP Spectroscopy was extremely low. The results of almost all extract samples analyzed were under the limit of detection or in the range of the level in the ultrapure water blank. Slightly increased values were found for Ni in the first extracts of the three samples (0.161 – 0.255 µg/L); in the second (consecutive) extract, the content of Ni was below detection limit (< 0.1 µg/L). Increased values were also found for Zn in the first extracts of the three samples (3.67 – 5.79 µg/L); in the second (consecutive) extract, the content of Zn (1.17 µg/L) was near the value of the ultrapure water blank (1.05 µg/L).

The TOC content of all extracts (340 – 394 ppb) was greater than the water blank (133 ppb). The second (consecutive) extract showed a lower TOC value (294 ppb) than the first extract of that mold sample (394 ppb).

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

The extraction tests for the Stax capsule system moldings have demonstrated depletion of the total soluble material in a second extraction. This indicates that suitable flushing regimes, such as the required flushing for the incorporated filter sheets (50 L/m^2 filter area for single-layer configurations, 100 L/m^2 filter area for double-layer configuration), will remove the extractables from the Stax capsule system moldings below detection level. Process-specific evaluation for specific Stax capsule systems is recommended.

8. Biological Reactivity Tests on the Materials of Construction

8.1 Introduction

The purpose of this study was to evaluate the biological suitability of the molding and gasket materials of construction of Stax depth filter capsules. Information on the Biological Reactivity Tests of the incorporated Seitz filter sheets can be obtained in the Pall documents USTR 2366 “Pall® P-series Depth Filter Media” and USTR 2404 “Pall® SUPRAdisc HP Depth Filter media”. Pall Corporation certifies in Works Certificates that no material of animal origin is used in the production of the Seitz depth filter sheets.

The materials of construction are detailed in Table 16: Materials of Construction of Stax Capsule System Moldings.

Table 16

Materials of Construction of Stax Capsule System Moldings

Stax capsule system moldings	Glass filled polypropylene
Gasket	Silicone elastomer

Stax capsule system moldings 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.

8.2 Summary of Methods

The following tests were performed:

- Biological Reactivity Tests *in vivo* for Class VI Plastics (121 °C) as described in the current United States Pharmacopoeia (USP) Chapter <88>.
- Hemolysis Tests (Saline Extraction Method) according to the following references:

  FDA Guidelines for Intraocular Lenses, June 1980 Revision

  - "Guidelines for Blood-Material Interactions", Report of the National Heart, Lung and Blood Institute Working Group, NIH Publication No. 80-2185, U.S. Department of Health and Human Services, 1985
  - STS Procedure, BCT-001.1: Hemolysis Test for Biomaterials
  - ANSI/AAMI/ISO 10993-12:2007, Biological Evaluation of Medical Devices - Part 12: Sample Preparation and Reference Materials (Identical to ISO 10993-12:2007)
  - United States Pharmacopoeia and National Formulary, Current Edition
  - ANSI/AAMI/ISO 10993-4:2002/A1:2006, Biological Evaluation of Medical Devices - Part 4: Selection of Tests for Interactions with Blood
- Minimum Essential Medium (MEM) Elution Cytotoxicity Tests according to the following references:
  - Association for the Advancement of Medical Instrumentation (AAMI) Standards and Recommended Practices, 2000 Edition: Biological Evaluation of Medical Devices, Volume 4S2, Supplement 2 – Part 5: Tests for Cytotoxicity: *in vitro* methods (identical to ISO 10993-5:1999)
  - ANSI/AAMI/ISO 10993-12:2007, Biological Evaluation of Medical Devices - Part 12: Sample Preparation and Reference Materials (Identical to ISO 10993-12:2007)
  - United States Pharmacopoeia and National Formulary, Current Edition, Chapter <87> Biological Reactivity Tests *in vitro;* Elution Tests
  - STS Procedure, CYT-001: MEM Elution Test – USP and ISO Methods

8.2.1 Biological Reactivity Test *in vivo* for Class VI Plastics (121 °C)

The Biological Reactivity Tests *in vivo* for Class VI Plastics (121 °C) as described in the current United States Pharmacopoeia (USP) Chapter <88> testing procedures described in the USP include:

- Injection of extracts of plastic materials (Systemic Injection Test; Intracutaneous Test)
- Implantation of the solid material into animal tissue (Implantation Test)

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 one (1) hour. The most

stringent condition not resulting in physical changes in the plastic is recommended. Therefore the filter materials were extracted at 121 °C for one (1) hour.

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

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

Implantation Tests
Implantation tests were also performed, in order to subject the materials of construction to the most stringent conditions included in the USP. Each of the materials of construction for the Stax capsule system moldings was implanted separately.

8.2.2 Hemolysis Tests (Saline Extraction Method)
The purpose of this study was to determine the percent hemolysis of whole blood produced by exposure to a saline (0.9% Sodium Chloride) extract of the test material. Fresh, whole rabbit blood was the test system chosen for this study because it provides a sensitive test for materials that are incompatible with blood cells. The justification for use of this test system is from the FDA Intraocular Lense Guidelines (June 1980) and the National Heart, Lung and Blood Institute Working Group (1985).

8.2.3 Minimum Essential Medium (MEM) Elution Cytotoxicity Tests
The MEM Elution Tissue Culture Test is an *in vitro* procedure designed to determine the biological reactivity of mammalian cell cultures following incubation with extracts of the test article, and it is appropriate for high-density materials. The L929 mammalian fibroblast was chosen as the test system. The extraction medium used to prepare the extracts from the test articles was Serum Supplement MEM.

8.3 Results
No biological response or hemolysis was observed in any of the tests performed and therefore the materials used in the Stax capsule systems passed all of the tests specified.

8.4 Conclusions
The materials of construction used in the Stax capsule system moldings 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. They also met Hemolysis Tests (Saline Extraction Method) and the MEM Elution Cytotoxicity Tests.

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