VALIDATION GUIDE

PROPOR SG

Pharmaceutical Grade (0.1. 0.2 and 0.45 micron)

Cartridge & Capsule filters

Contents

1. Introduction

Sterilization grade filters that come into contact with pharmaceutical products, such as injectable or infusion liquids, must conform to strictly defined quality standards.

By using filter technology that conforms to the standards laid down by the various certifying bodies, the quality of the final product can be assured. Contamination can also be prevented from entering the final product by its comprehensive removal at each stage of the primary and secondary process.

When sterilizing grade filters are used in the manufacture of products, the interactions between product, filter and process must be fully investigated and validated.

Guidelines for validation can be sourced from publications issued by the FDA, EMEA, USP, EP, BP, PDA[1], etc. This validation document has been produced with these guidelines in mind to enable the end user to incorporate this information within their own validation documentation or standard operating instructions for the process.

NOTE

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Department: ……

Address: ……

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……

Registered No. ……

Date Issued: ……

Signed ……

[1] FDA, EMEA, USP, EP, BP, PDA – Food and Drug Administration, European Medicines Evaluation Agency, United States, European and British Pharmacopoeia, Parenteral Drug Association.

2. Quality Assurance

Quality is built into all Parker domnick hunter filtration products through a rigorous product design process, careful selection of suppliers and materials, and manufacture within a highly controlled environment using validated production technologies in adherence to cGMP.

2.1. Quality and Environmental Management Systems

Parker domnick hunter is certified to current versions of the following quality standards by Lloyds Register Quality Assurance.

- BS EN ISO9001 (Current Revision) Quality Management Systems
- BS EN ISO14001 (Current Revision) Environmental Management Standard
- BS EN ISO13485 (Current Revision) Medical Devices

Copies of the original certificates are available upon request.

2.2. Manufacturing Facilities

Parker domnick hunter continues to invest substantially in installation of the latest clean room and manufacturing technology. All manufacturing systems are validated using statistical methodologies (process, product and software) and constantly monitored using statistical process control charts. All personnel within the manufacturing operations are fully trained in cGMP and against competency frameworks to ensure their suitability to operate within specific manufacturing areas.

2.3. Material Conformity

Parker domnick hunter works closely with suppliers to ensure materials supplied are of a consistently high quality and also to develop new materials as part of our ongoing product development activity. In addition to supplier certificates of conformity and analysis, incoming raw materials, including moulded parts, membranes and supports, and elastomeric seals, are subject to an appropriate level of incoming inspection. This includes bacterial challenge on each lot of membrane used in the manufacture of sterilizing grade filter capsules and cartridges.

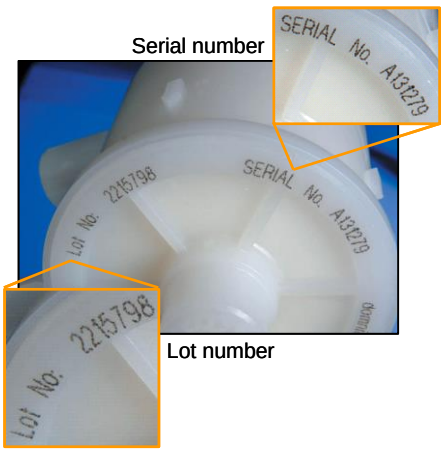
2.4. Product and Lot Release Criteria

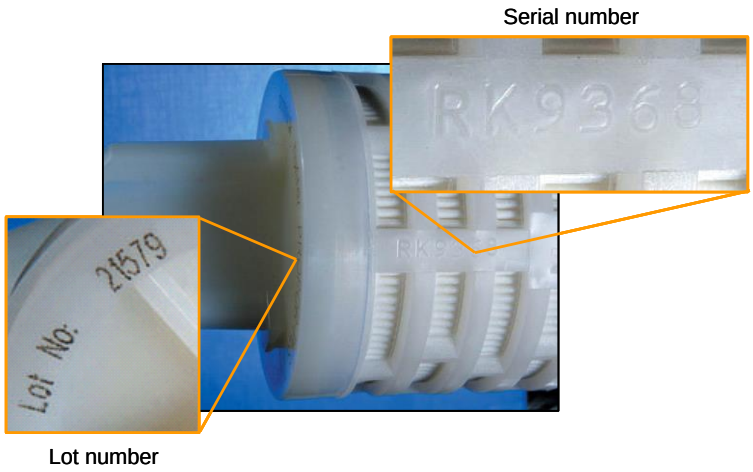
Prior to shipment all Parker domnick hunter capsules and cartridges undergo final product quality control. 100% of testable products undergo a non-destructive integrity test (diffusional flow). This includes a high volume flush with water that meets or exceeds the current EP and USP standards for purified water. Products are dried using HEPA filtered air and sealed in a protective polyethylene bag within the controlled manufacturing environment prior to final pack and despatch.

In addition a sample is taken from each production lot and tested to demonstrate conformity to validated claims.

2.5. Product Traceability

The product code and type, lot number and unique capsule serial number are printed on all products. Additionally, the lot number is identified on the protective bag label and the box label within which the cartridge / capsule is packed. The serial number provides complete traceability back to pleated materials used in the manufacture of each capsule and the manufacturing processes through the module routing sheet.





2.6. Product Shelf-Life

The shelf-life for PROPOR SG cartridges and capsules is 3 years (2 year for irradiated product).

3. Product Description

All products within the PROPOR SG range have been designed for use in bioprocessing and pharmaceutical applications. All jointed surfaces are assembled by the use of heat sealing technology. No resins or binders are used in the manufacture of the filter and no surfactants are added to aid wetting. This guide includes support information for the range of 0.1, 0.2 and 0.45 micron filters.

3.1. Materials of construction

All materials meet the FDA requirements as defined in Title 21 Code of Federal Regulations and the BioSafety Tests as defined in the current USP including the Class VI Plastics Testing.

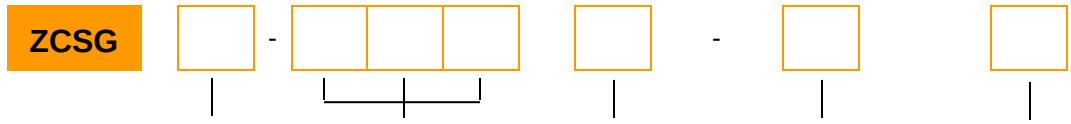
Filtration Membrane	Polyethersulphone
Upstream Support	Polyester
Downstream Support	Polyester
Inner Core	Polypropylene
Sleeve	Polypropylene
Endcaps (cartridge)	Nylon
Capsule body (DEMICAP)	Nylon
Capsule body (MURUS)	Polypropylene
Capsule vent seals	Silicone
Cartridge o-rings (standard)	Silicone
Filling bell	Polycarbonate

3.2. Product Coding

Product code structures indicate the cartridge / capsule sizes, micron ratings, endcap configurations and o-rings that are available within the product range.

Cartridges

Example ZCSG2-020C-PS — 500 mm (20") 0.2 micron PROPOR SG filter cartridge, pharmaceutical grade with 'C' style endcap and silicone o-rings.



Code	Length (mm)	Length (inch)	Diameter (mm)
B	65	2.5	56
A	125	5	56
K	125	5	72
1	250	10	72
2	500	20	72
3	750	30	72
4	1000	40	72

Code	Micron Rating
010	0.10
020	0.20
045	0.45

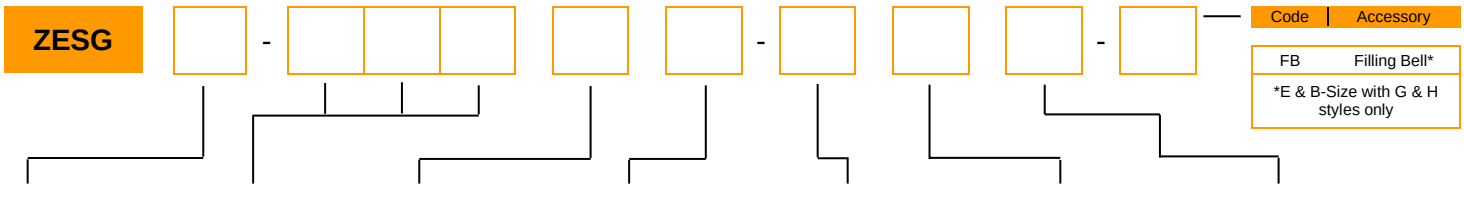
Code	10" Endcap Style
B	Dh DOE
C	P-7
G	M-0
R	S-28

Code	Variant Ref
P	Pharmaceutical

Code	o-rings
E	EPDM[2]
P	FEP Encapsulated Silicone
V	Viton™[3]
S	Silicone

Small-Scale DEMICAP Capsules

Example ZESGB-020TT-PN3 — B size 0.2 micron PROPOR SG DEMICAP capsule, pharmaceutical grade with tri-clamp connections supplied non-sterile in packs of 3.



Code	Accessory
FB	Filling Bell*

*E & B-Size with G & H styles only

Code	Length (mm)	Length (inch)
E	113	4.4
B	140	5.5
A	200	7.9

Code	Micron Rating
010	0.10
020	0.20
045	0.45

Code	Inlet Connection Type
T	1" Tri-clamp
N	½" NPT Male
H	½" Hosebarb
G	Stepped 6 mm – 12 mm Hosebarb
M	¼" NPT Male
Q	Walther QRC Male
R	Grommel QRC Male

Code	Outlet Connection Type
T	1" Tri-clamp
N	½" NPT Male
H	½" Hosebarb
G	Stepped 6 mm – 12 mm Hosebarb
M	¼" NPT Male
Q	Walther QRC Male
R	Grommel QRC Male

Code	Variant Ref
P	Pharmaceutical

Code	Sterilization Grade
N	Supplied non sterile
S	Supplied Gamma Pre-Sterilized

Code	Additional Specification
3	Pack of 3

[2] **EPDM** – Ethylene Propylene Diene Monomer Rubber
[3] **Viton™** is a registered trademark of DuPont Dow Corporation

Large-Scale MURUS capsules

Example ZLSG1-020TT-PN-L-S 10" 0.2 micron PROPOR SG MURUS capsule with tri-clamp connections, pharmaceutical grade, supplied non-sterile with inline design and silicone o-rings.

ZLSG [ ] - [ ][ ][ ] [ ] [ ] - [ ] [ ] - [ ] - [ ]

Code	Accessory
S	Silicone
E	EPDM[4]
V	Viton™[5]

Code	Length (mm)	Length (inch)
K	125	5
1	250	10
2	500	20
3	750	30

Code	Micron Rating
010	0.10
020	0.20
045	0.45

Code	Inlet Connection Type
T	1" Tri-clamp
A	¾" Tri-clamp
B	1½" Tri-clamp
D	1" Hosebarb
H	½" Hosebarb

Code	Outlet Connection Type
T	1" Tri-clamp
A	¾" Tri-clamp
B	1½" Tri-clamp
D	1" Hosebarb
H	½" Hosebarb

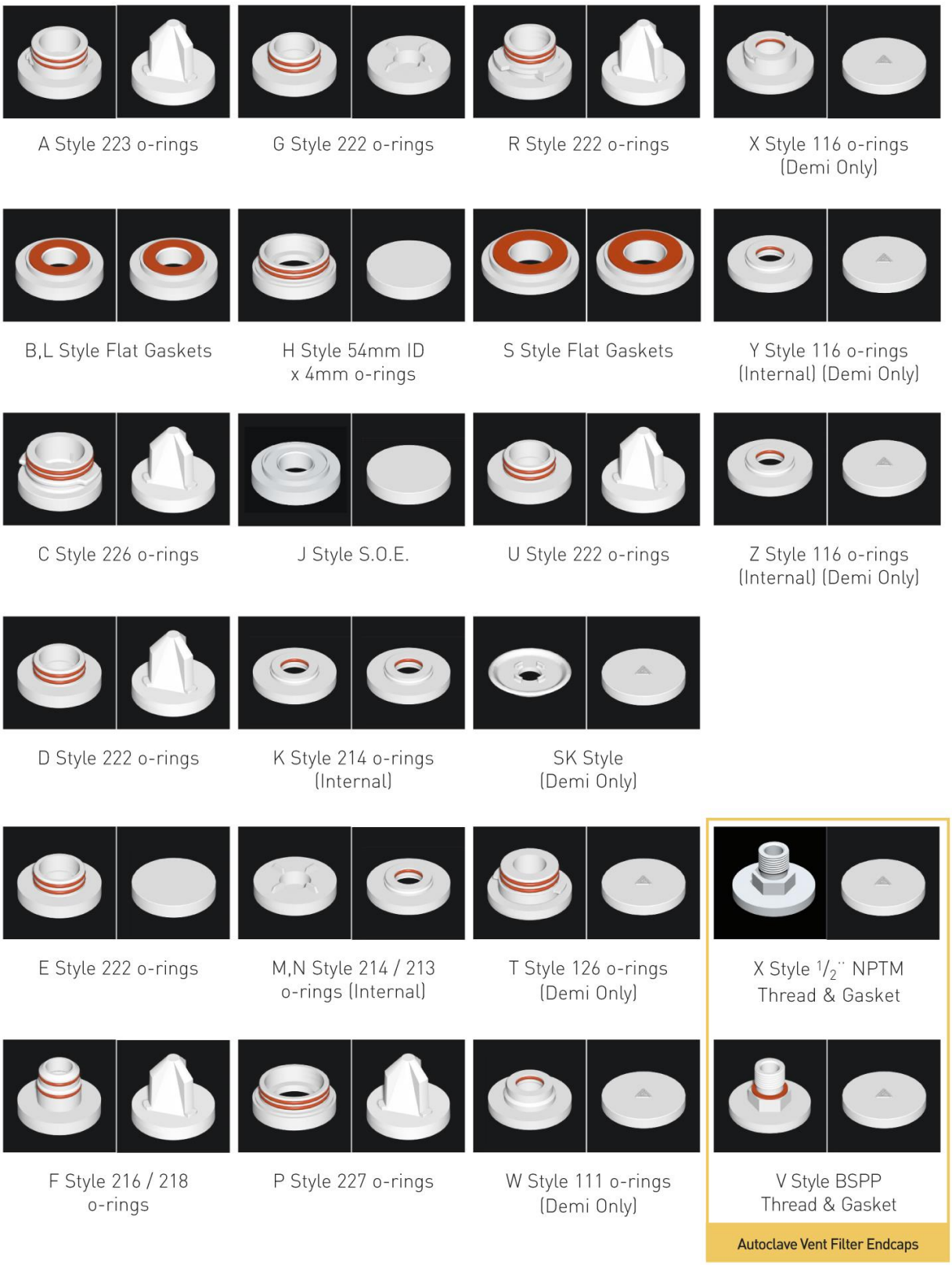
Code	Variant Ref
P	Pharmaceutical

Code	Sterilization Grade
N	Supplied non sterile
S	Supplied Gamma Pre-Sterilized

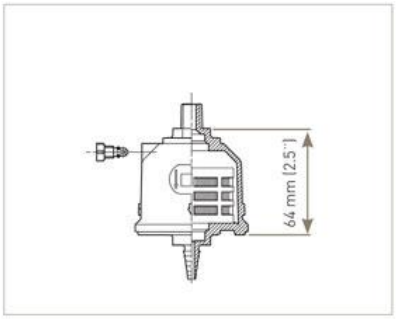
Code	Design
L	In-line
T	T-port
M	Streamline Valves

[4] **EPDM** – Ethylene Propylene Diene Momomer Rubber.
[5] Viton is a registered trademark of DuPont Dow Corporation.

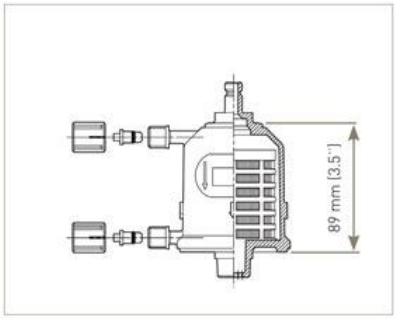
3.3. Cartridge Endcap Configurations



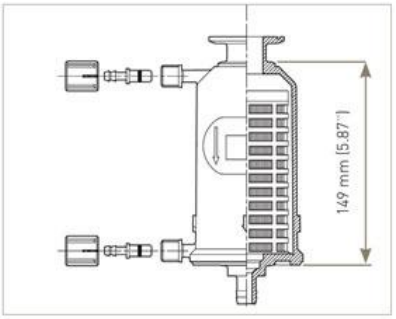
3.4. Capsule Dimensions



'E' Size

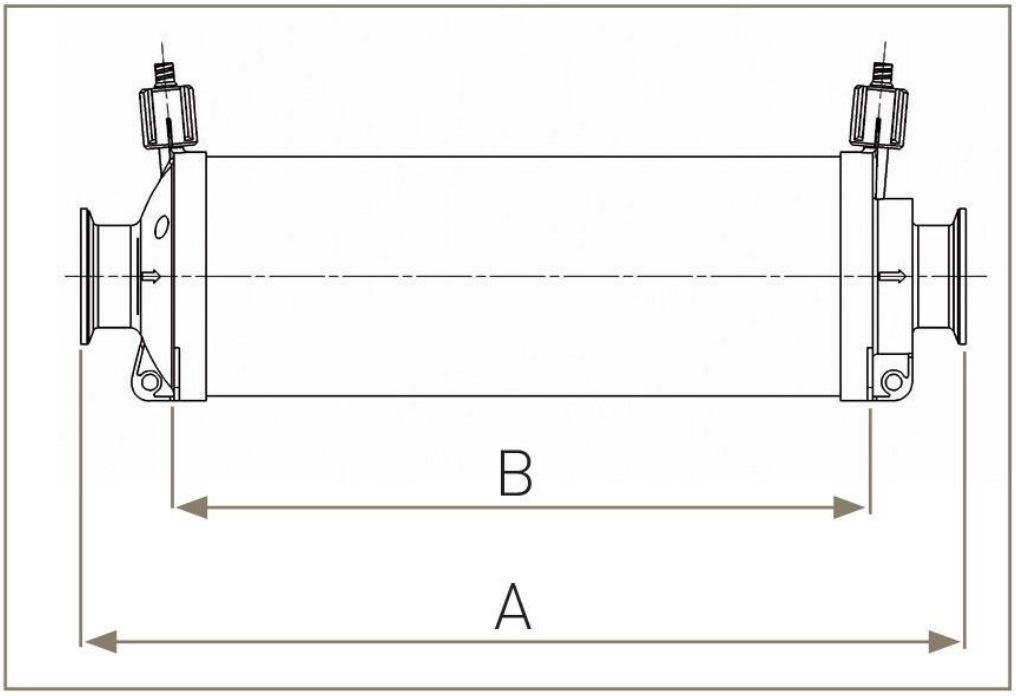


'B' Size



'A' Size

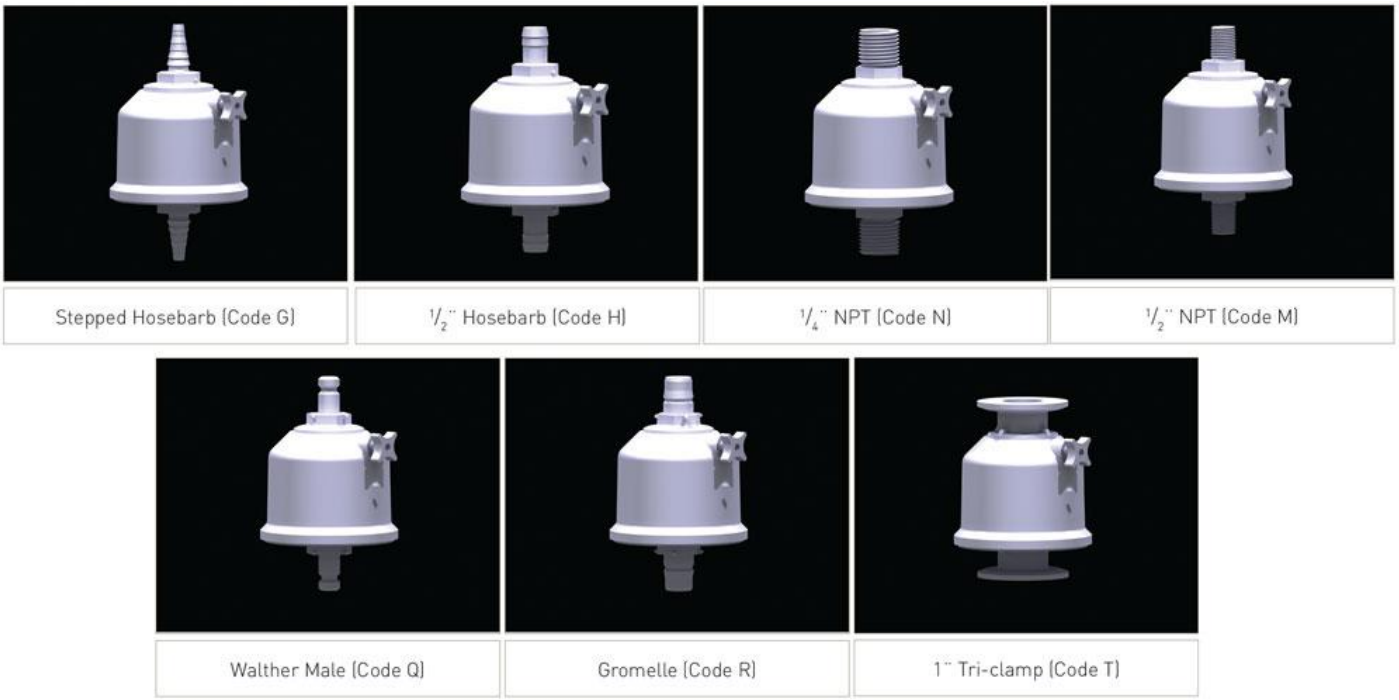
Dimensions



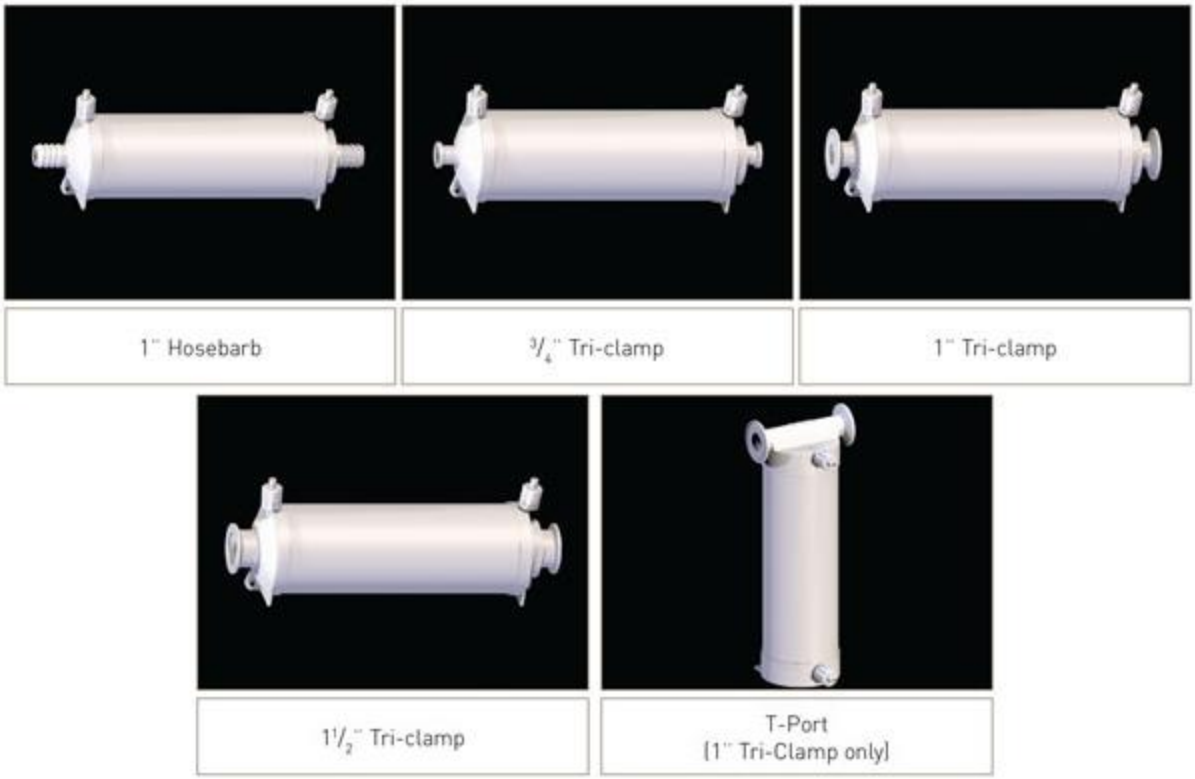
Cartridge Type	'A'	'B'
10" 250 mm	13.07" 332 mm	10.30" 262 mm
20" 500 mm	22.79" 579 mm	20.04" 509 mm
30" 750 mm	32.56" 827 mm	29.80" 757 mm

Dimensions shown are typical lengths for $1^{1}/_{2}$" Tri-Clamp.
Further dimensions available from Parker domnick hunter.

DEMICAP Inlet / Outlet Connection Styles



MURUS Inlet/Outlet Connection Styles



4. Product Specifications

4.1. Cartridge Operating Differential Pressures and Temperatures

The maximum operating temperatures and differential pressures were qualified by running water at temperature through a 10 inch PROPOR SG 0.2 cartridge for 30 minutes.

Serial Number	Batch Number	Differential Pressure (barg)	Temperature (ºC)	Differential Flow (mL / min)
20703CA	2F8076	4.1	40	5.7
20718CA	2F8075	4.1	40	4.7
20685CA	2F8074	4.0	40	5.1
20701CA	2F8076	3.0	60	4.1
20713CA	2F8075	3.0	60	6.3
20690CA	2F8074	3.0	60	4.0
20703CA	2F8076	2.0	82	7.3
20718CA	2F8075	2.0	80	5.2
20685CA	2F8074	2.0	80	4.2

Note: The maximum allowable diffusional flow for a 10 inch PROPOR SG 0.2 micron is 16 mL / min.

Conclusion

The recommended maximum differential operating pressures at various temperatures are shown below:

Temperature		Differential Pressure	
°C	°F	bar	psi
20	68	5.00	72.5
40	104	4.00	58.0
60	140	3.00	43.5
80	176	2.00	29.0

4.2. Capsule Operating Pressures and Temperatures

Testing to verify the maximum operating temperatures and pressures was conducted on a PROPOR 0.2 micron grade product post autoclaving and post irradiation to simulate worst-case conditions.

DEMICAP

Post Autoclave (11 Porous load cycles @ 130°C)

Serial Number	Batch Number	Capsule Surface Temperature (°C)	Burst Pressure (barg)
DC272048	3485129	44.3	9.65
DC272053	3485129	45.0	8.56
DC273519	3485129	44.4	8.34
DC289414	3506050	44.4	9.97
DC289415	3506050	45.3	9.14
DC289416	3506050	44.7	9.66
DC289417	3506050	45.0	10.08
DC289418	3506050	44.8	8.51
DC289419	3506050	45.7	8.90

Post Irradiation (minimum dose of 45.6 kGys)

Serial Number	Batch Number	Capsule Surface Temperature (°C)	Burst Pressure (barg)
DC294108	3500959	45.0	10.08
DC294110	3500959	45.0	10.67
DC294113	3500959	44.9	9.38
DC294142	3504739	45.0	9.29
DC294143	3504739	44.6	8.34
DC294146	3504739	42.4	8.57
DC289422	3506051	44.2	7.97
DC289423	3506051	44.3	9.28
DC289424	3506051	44.2	8.49

Conclusion

The recommended maximum operating temperature and pressure for the PROPOR SG DEMICAP range of capsules has been set at 5.0 barg @ 40°C.

MURUS Large-Scale Capsule

The maximum operating temperatures and pressures for the MURUS range were evaluated using a variety of tests to cover all possible applications.

Post Autoclave for 10" Capsules (5 Porous load cycles @ 130ºC)

Serial Number	Burst Pressure barg @ 21ºC
9134MU001	22.41
9134MU002	23.36
9134MU003	17.80
9134MU004	20.90
9134MU005	20.92
9134MU006	23.63

Post Irradiation for 10" Capsules (minimum dose of 45.6 kGys)

Serial Number	Burst Pressure barg @ 21ºC
9233MU006	18.67
9233MU008	18.24
9233MU010	17.20
9233MU012	19.11
9233MU014	20.52
9233MU016	20.58

Elevated Temperature

Serial Number	Capsule Surface Temperature (ºC)	Burst Pressure barg @ 21ºC
9171MU001	52.9	13.37
9171MU003	54.3	16.71
9171MU005	52.6	14.30
9171MU007	53.0	14.59
9171MU009	52.3	13.12
9171MU012	54.2	14.25

Conclusion

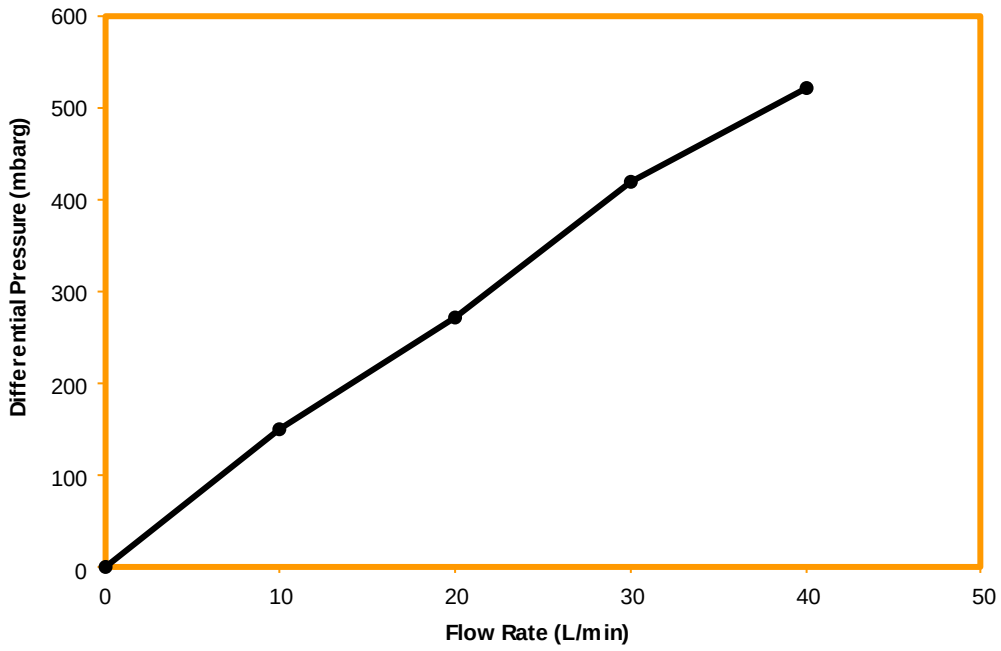
From the data above the recommended maximum operating temperatures and pressures for the PROPOR SG MURUS range of capsules has been set at 5.5 barg @ 25ºC and 2.8 barg @ 60ºC.

4.3. Flow Rates

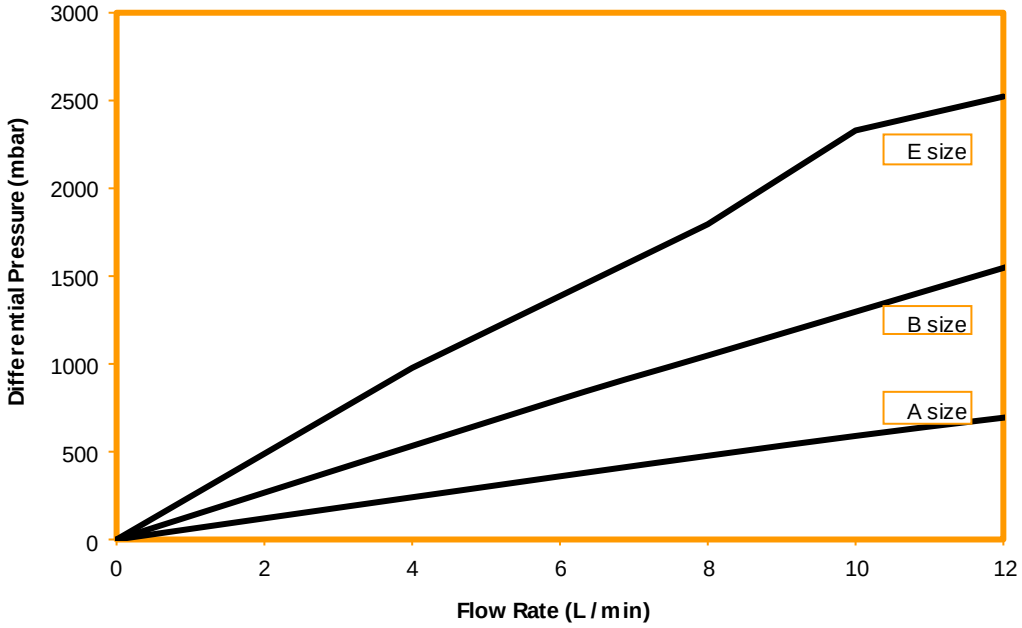
Cartridge flow rates were determined for filters from three separate lots.

PROPOR SG 0.1

Water Flow Characteristics for 10 inch Cartridges & Capsules

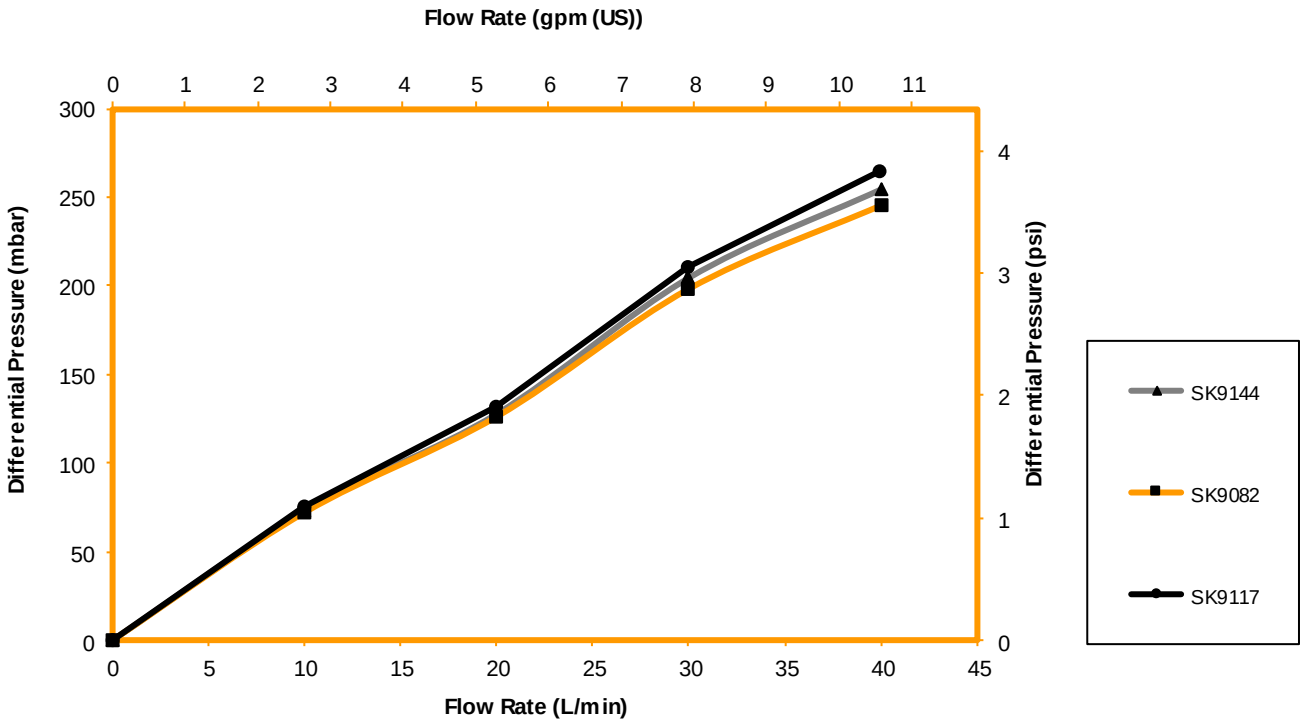


Average Water Flow Rates for Small-Scale Cartridges & Capsules

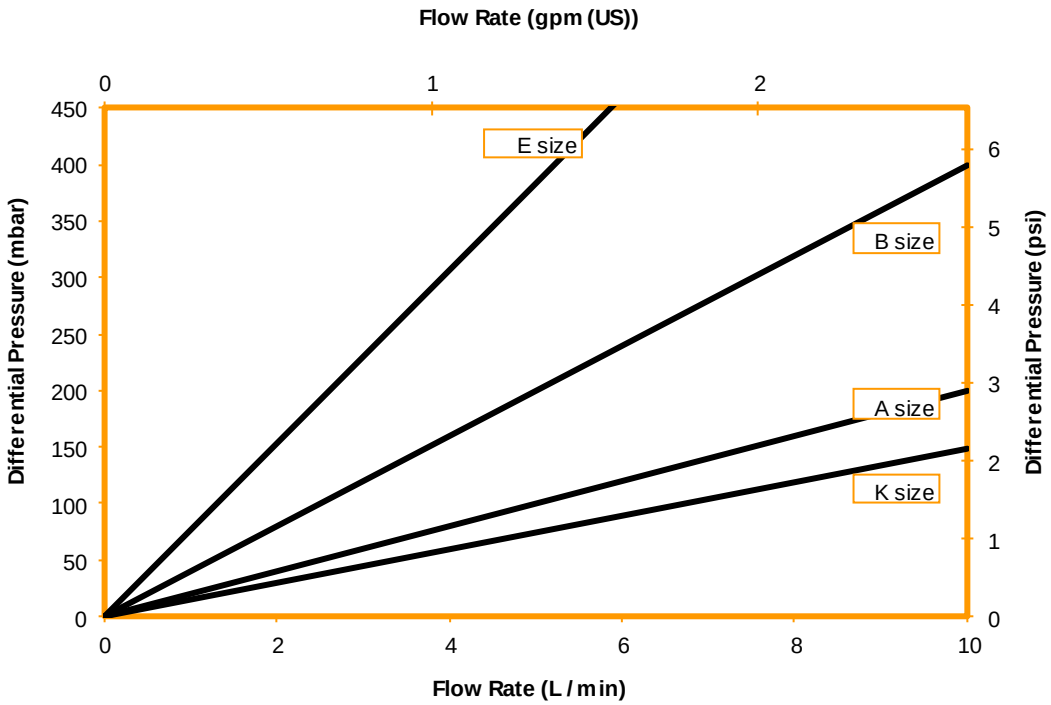


PROPOR SG 0.2

Water Flow Characteristics for 10 inch Cartridges & Capsules

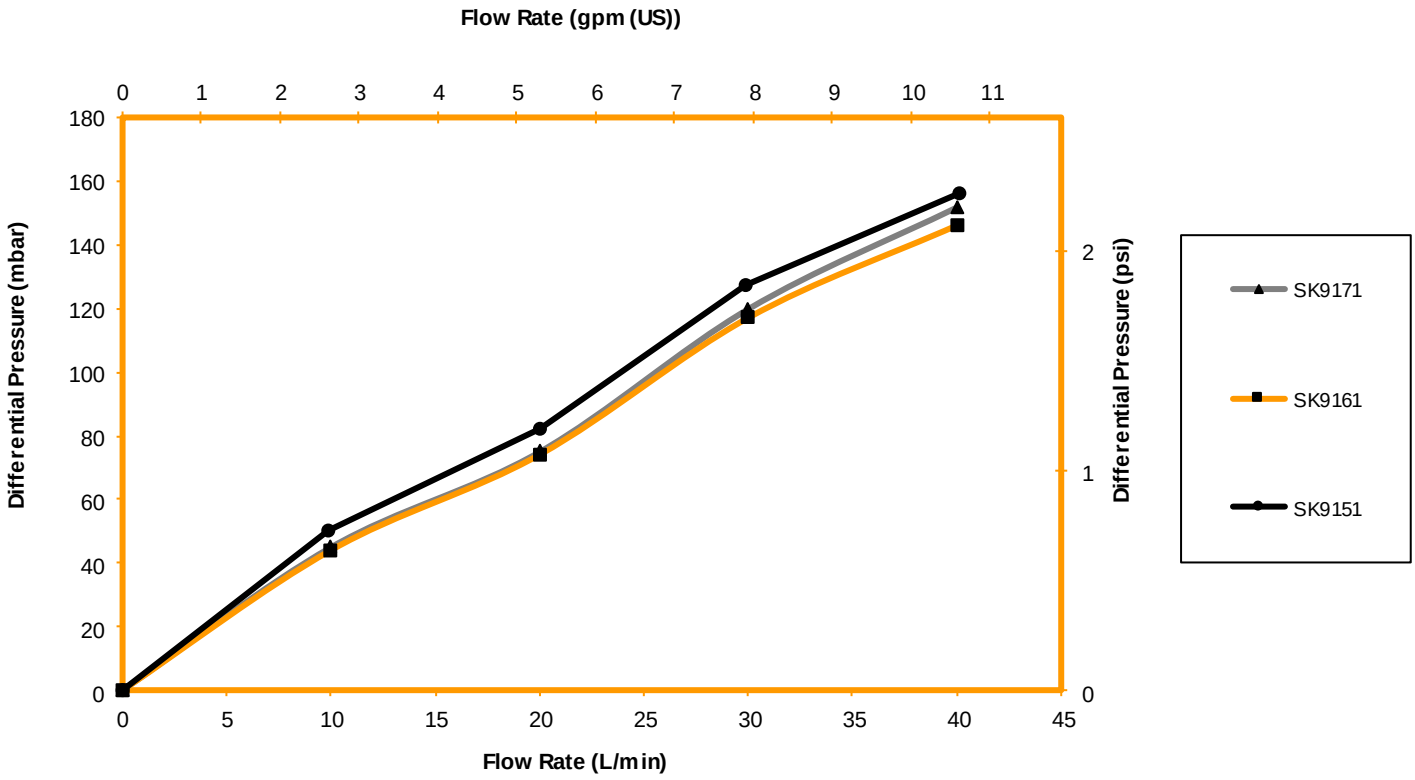


Average Water Flow Rates for Small-Scale Cartridges & Capsules



PROPOR SG 0.45

Water Flow Characteristics for 10 inch PROPOR SG 0.45 Cartridges & Capsules



4.4. Effective Filtration Area (EFA)

Product Size	Surface Area (m^2)	Surface Area (ft^2)
3	1.65	17.77
2	1.10	11.84
1	0.55	5.92
K	0.26	2.80
A	0.20	2.25
B	0.10	1.10
E	0.05	0.50

4.5. Hold Up Volume

Pharmaceutical Capsule Product Hold Up Volumes (mL)								
Product	1 barg air purge				2 barg air purge			
	10" MURUS	A size	B size	E size	10" MURUS	A size	B size	E size
PROPOR SG	184.4	61.4	31.4	19.4	119.6	40.5	21.6	15.2

4.6. Autoclave Life

DEMICAP

The autoclave life of capsules was determined using a porous load cycle.

The resistance to autoclaving was determined by evaluating the integrity of nine 'A' size PROPOR SG 0.2 capsules pre and post autoclaving.

Serial Number	Integrity Test Values Post Autoclave @ 130°C		
	0 Cycles	11 Cycles	
	Diffusional Flow (mL / min)	Diffusional Flow (mL / min)	Bubble Point (mbar)
DC272054	4.8	5.1	4048
DC272061	5.9	5.5	4001
DC273525	5.8	5.6	4280
DC294103	4.4	5.0	4593
DC294106	5.5	5.7	4466
DC294109	4.5	5.1	4449
DC294144	4.6	4.0	4698
DC294151	3.6	5.5	4506
DC454153	4.4	5.2	4444

NOTE: Maximum allowable diffusional flow for an A size PROPOR SG is 5.8 mL / min
Minimum bubble point for an A size PROPOR SG is 3.38 bar.

Conclusion

The PROPOR SG range of filter capsules can be autoclaved up to 10 cycles at 130°C (266°F), which includes a 10% safety factor.

MURUS Large-Scale Capsules

The autoclave life of capsules was determined using a porous load cycle.

The resistance to autoclaving was determined by integrity testing nine 10" size MURUS PROPOR SG capsules pre and post autoclaving. The results below are a sample from those manufactured during validation.

Serial Number	Integrity Test Values Post Autoclave @ 134ºC	
	0 Cycles	5 Cycles
	Diffusional Flow (mL / min)	Diffusional Flow (mL / min)
1934MU001	5.1	8.5
1934MU002	6.6	9.7
1934MU003	6.7	13.1
1934MU004	3.6	9.2
1934MU005	4.6	8.8
1934MU006	8.3	13.0
1934MU007	7.2	14.5
1934MU008	9.2	11.2
1934MU009	4.1	9.9

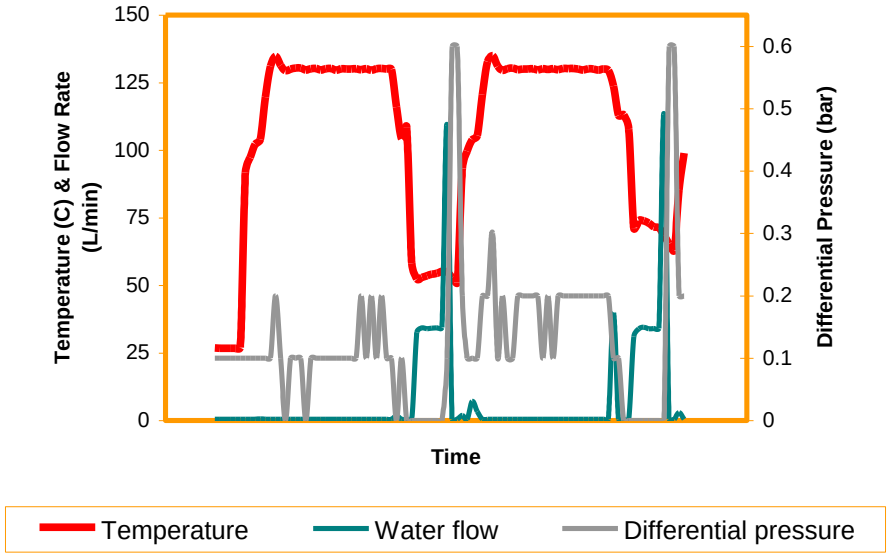
NOTE: Maximum allowable diffusional flow for a 10" MURUS PROPOR SG is 16.0 mL / min

Conclusion

The PROPOR SG range of filter capsules can be autoclaved up to 5 cycles at 134ºC (266ºF).

4.7. Cartridge Steam Life

The steam life of cartridges was determined using the Steam in Place (SIP) cycle shown below, which replicates extreme conditions. This includes a combination of steaming for 30 minutes at temperature followed by ambient water flow during the cooling phase of each cycle.



The resistance to steam sterilization was determined by evaluating three production batches of 10 inch cartridges. A representative sample is shown below.

Batch	Serial No	Integrity Test Values post SIP @ 130°C			
		0 cycles		33 cycles	
		Diff flow (mL/min)	B.pt (mbar)	Diff flow (mL/min)	B.pt (mbar)
1	SK9085	12.3	4338	12.6	4487
	SK9112	9.6	4638	10.9	4788
	SK9132	9.3	4838	11.1	4938
2	20681CA	10.4	4646	12.5	4546
	20719CA	10.6	4696	10.6	4345
	20700CA	10.6	4595	13.1	4616
3	S353460	11.2	4356	11.8	4320
	S352461	12.6	4564	12.8	4523
	S352468	10.4	4657	10.6	4609

NOTE: Maximum allowable diffusional flow for a 10 inch PROPOR SG is 16 mL / min
Minimum bubble point for a 10 inch PROPOR SG is 3.38 bar.

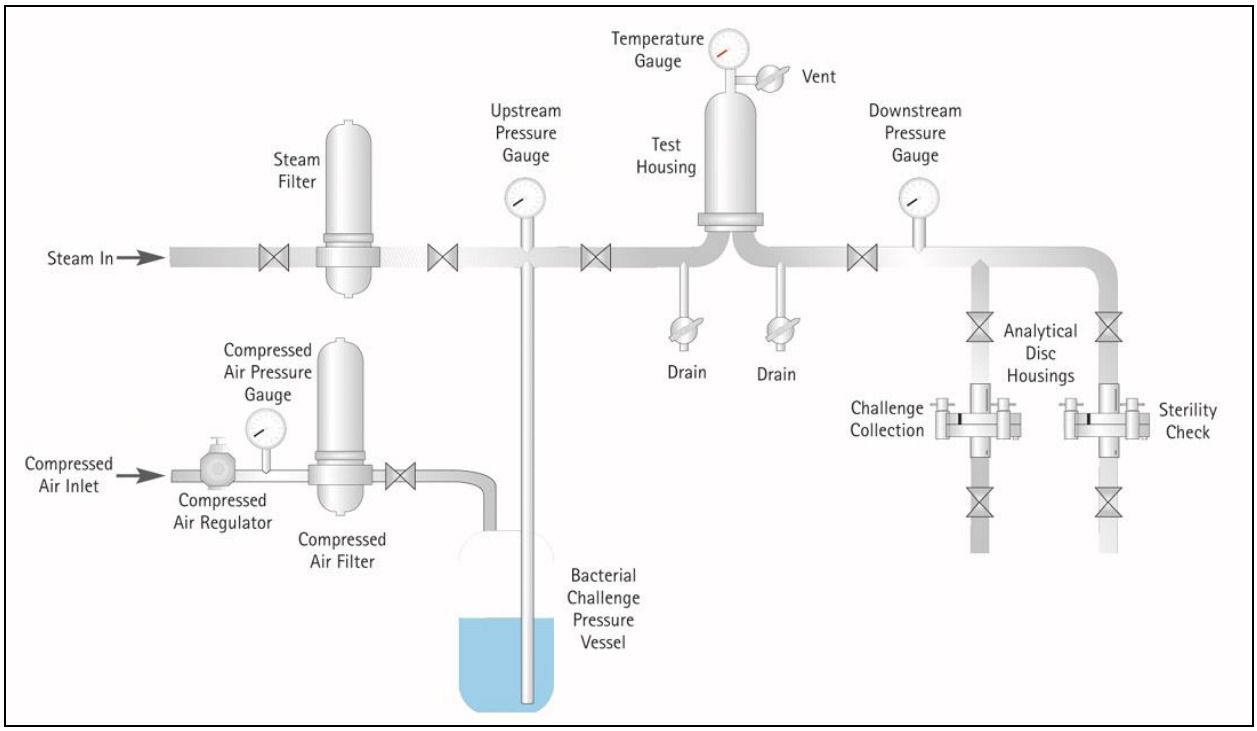
Conclusion

The PROPOR SG range of filter cartridges can be steam sterilized up to 30 cycles at 130°C (266°F), which includes a 10% safety factor.

4.8. Retention

The correlation between bacterial challenge and a non-destructive integrity test has been demonstrated using the procedure documented in the current revision of ASTM F838 'Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration'[6]. This methodology has been used for the 0.1 and 0.2 micron (sterilizing-grade) products; 0.45 micron filters are challenged using the same basic methodology but utilizing *Serratia marcescens* as the appropriate test organism.

Liquid Bacterial Challenge Schematic



Under these test conditions, the test filter is challenged with a minimum of 10^7 viable *Brevundimonas diminuta* (ATCC 19146) per square centimetre of effective filtration area. Any organisms that pass through the test filter are collected and cultured on the surface of analytical discs. In this way colonies may be counted and bacterial species identified. The filter retention is quantified by expressing the filter's efficiency to remove the challenge organism from the challenge suspension as a Log Reduction Value (LRV).

$$LRV = Log_{10} \left({}^{\text{Number of organisms in the challenge}} / {}_{\text{Number of organisms in the filtrate}} \right)$$

[6] Previous reference to the guidance document *Microbial Evaluation of Filters for Sterilising Liquids*, HIMA Document No. 3 Vol. 4, April 1982, referred to in USP<1211> *Sterilisation by Filtration* has been superseded by the equivalent ASTM F838.

4.9. Diffusional Flow Correlation Data

PROPOR SG 0.2 Sterilizing Grade

The correlation between diffusional flow and bacterial challenge for PROPOR SG 0.2 micron cartridges is shown in the table below. This data shows that a 250mm (10") PROPOR SG 0.20 μm filter exhibiting a diffusional flow of <20.0 mL/min when completely wetted with water, at a test pressure of 2.80 barg (40.6 psig) at 20°C (68°F) will produce a sterile filtrate.

Filter type: ZCSG1 -020C-P PROPOR SG 0.2 μm 10" cartridge

Challenge organism: *Brevundimonas diminuta* (ATCC 19146)

Serial No.	Diffusional Flow (Air in Water) @ 2.80 barg (40.6 psig) mL/min	Total Challenge Level Cfu ($x10^{11}$)	Organisms Passed cfu	LRV[7]
G26417	5.0	91.10	0	12.96
G26330	7.0	1.49	0	11.20
G26322	9.0	1.70	0	11.20
G26517	9.0	2.11	0	11.30
G26414	10.0	7.42	0	11.90
G53781	10.0	1.10	0	11.00
G20674	12.0	2.45	0	11.39
G51334	12.0	0.75	0	10.90
20681CA	12.5	1.01	0	11.00
20719CA	14.0	0.62	0	10.79
20700CA	15.0	0.97	0	10.99
G26327	17.0	1.16	0	11.10
G26317	19.0	3.65	0	11.60
G26423	20.0	10.30	0	12.00
G08180	26.0	1.10	194	8.75
G18241	26.0	1.16	45	9.40
G08185	26.0	1.12	202	8.74
G18242	29.0	0.95	39	9.40
G08240	39.0	1.17	TNTC[8]	<7.00
G53776	43.0	0.90	880	8.00
F97934	49.0	0.74	1840	7.60

Conclusion

A maximum diffusional flow of 16mL/min for a water wetted 10" PROPOR SG filter cartridge provides complete assurance of a sterile effluent incorporating as it does a safety margin in relation to the correlation data above.

[7] Where organisms passed = 0, LRV is stated as *greater than*.
[8] TNTC - Too Numerous To Count.

PROPOR SG 0.1 Sterilizing Grade

In some applications where the contaminating organism is potentially smaller than *Brevundimonas diminuta* (ATCC 19146) a 0.1 micron filter is often installed in place of a 0.2 micron. There is currently no recognised standard for challenging a 0.1 micron filter so the product retention performance was tested in the same way as a 0.2 micron.

Filter type: ZCSG1 -010C-P PROPOR SG 0.1 µm 10" cartridge

Challenge organism: *Brevundimonas diminuta* (ATCC 19146)

Serial No.	Diffusional Flow (Air in Water) @ 4.80 barg (69.6 psig) mL/min	Total Challenge Level Cfu ($x10^{11}$)	Organisms Passed cfu	LRV[9]
75621	15.8	1.8	0	11.3
75620	17.8	0.59	0	10.8
70673	20.8	0.73	0	10.8
81332	21.0	0.83	0	10.9
75613	21.8	0.61	0	10.7
81329	22.0	1.2	0	11.1
81333	22.0	0.87	0	10.9
70682	24.8	0.63	0	9.7
76358	24.8	0.71	0	10.8

Conclusion

All filter cartridges challenged with a diffusional flow below the maximum of 27mL/min provided a sterile effluent

Retention to Mycoplasma (*Acholeplasma laidlawii*, ATCC 23206)

To provide further information on the retention characteristics of the PROPOR SG 0.1 a number of challenges were conducted with mycoplasma

Serial No.	Total Challenge Level Cfu ($x10^{10}$)	Challenge / sq cm (CFU/cm^2)	Organisms Passed cfu	LRV /cm^2[10]
76355CC	6.5	1.2×10^7	<1	>7.07
76356CC	6.5	1.2×10^7	<2	>6.77
DJ5286	1.6	2.9×10^7	<1	>7.46
76365CC	1.6	2.9×10^7	<1	>7.46
76381CC	1.6	2.9×10^7	<1	>7.46

Conclusion

All filter cartridges challenged with a diffusional flow below the maximum of 27mL/min provided a LRV /cm^2 on average >7.

[9] Where organisms passed = 0, LRV is stated as *greater than*.
[10] Where organisms passed = 0, LRV is stated as *greater than*.

PROPOR SG 0.45 Bioburden Reduction

Filter type: ZCSG1 -045C-P PROPOR SG 0.45 µm 10" cartridge

Challenge organism: *Serratia marcescens* (ATCC 14756)

Lot No.	Diffusional Flow (Air in Water) @ 1.70 barg (24.9 psig) mL/min	Total Challenge Level Cfu ($x10^{11}$)	Organisms Passed cfu	LRV[11]
BJJ	1.4	1.5	0	11.2
CGG	1.6	2.9	0	11.5
BJI	2.5	2.0	0	11.3
BJH	3.0	2.2	0	11.3
AJF	4.0	1.7	0	11.2
AJH	6.9	1.3	0	11.1
EDH	15.8	1.9	0	11.3

Conclusion

A maximum diffusional flow of 16mL/min for a water wetted 10" PROPOR SG 0.45 filter cartridge provides complete assurance of a sterile effluent when challenged with $>10^7$ / cm^2 organisms of *Serratia marcescens.*

4.10. Integrity Testing Data

The following integrity test limits have been determined from the 10 inch cartridge correlation data above. Limits for other sizes have been calculated directly from effective filtration area ratios for each variant. Unless specified otherwise, these limits are for water wet cartridges using air as the test gas.

Micron Rating	Minimum Bubble point[12]		Diffusional Flow Test Pressure		Maximum Diffusional Flow (mL / min)						
	bar	psi	bar	psi	30"	20"	10"	K	A	B	E
0.1	2.36	34.2	4.80	69.6	81.0	54.0	27.0	12.6	10.1	4.9	2.1
0.2	3.38	49.0	2.80	40.6	48.0	32.0	16.0	7.5	5.8	2.9	1.4
0.45	2.48	36.0	1.70	24.9	48.0	32.0	16.0	7.5	5.8	2.9	1.4

[11] Where organisms passed = 0, LRV is stated as *greater than*.
[12] Parker domnick hunter does not recommend the use of bubble point as an integrity test method for cartridges but values are given for use as an indicator of product integrity. Bubble Point for the 0.1µm product is in 60/40 v/v IPA/Water

4.11. Gamma Sterilization (Capsules)

4.11.1. Validation of gamma sterilization process

The required sterilization dose was determined from an analysis of the bioburden from three discrete production batches of DEMICAP products in accordance with VDMAX Method “Substantiation of 25 kGy as a sterilizing dose: A rational approach to establishing a verification dose” ref: ISO/EN WD,11137-3.

The average bioburden for the three batches of product tested when compared with reference to AAMI TIR27 indicated a sub process dose for a sterility assurance level of 10^{-2} to be 9.1 kGy. Ten capsules were subsequently irradiated at 9.1 kGy and individually tested for sterility. After the full incubation period zero tests gave a positive result therefore substantiating 25 kGy as a sterilization dose and guaranteeing an SAL of 10^{-6} in accordance with ISO/EN WD, 11137-2.

Conclusion

The current sterilization dose of 25 to 40 kGy is substantially in excess of the calculated sub process dose providing a high level of assurance of product sterility.

4.11.2. Capsule integrity after irradiation

Eight PROPOR SG DEMICAP capsules were irradiated at a sterilization dose of 45.6 kGy. Following irradiation the capsules were integrity tested using diffusional flow to confirm product integrity. The data is shown in the table below.

Serial Number	Diffusional Flow (mL / min)	Result
DC294149	3.6	**Pass**
DC294974	5.5	**Pass**
DC294152	3.7	**Pass**
DC294143	4.2	**Pass**
DC294118	5.5	**Pass**
DC294108	4.7	**Pass**
DC294123	5.6	**Pass**
DC294113	5.2	**Pass**

Maximum allowable diffusional flow for an A size PROPOR SG is 5.8 mL / min

Conclusion

PROPOR SG capsules can be subjected to a sterilization dose of up to 40 kGy without loss of integrity.

4.12. Chemical Compatibility

The following data is indicative of PROPOR SG cartridge & capsule compatibility with a range of chemicals at ambient temperature and 72 hour exposure. However it is recommended that specific process conditions are reviewed with your local Parker domnick hunter representative.

	BIO-X II	HIGH FLOW BIO-X	HIGH FLOW BIO-X VENT AUTOCLAVE	HIGH FLOW PREPOR GFA	HIGH FLOW TETPOR II	HIGH FLOW TETPOR H.T.	HIGH FLOW TETPOR VENTAUTOCLAVE	PROCLEAR PP	PROCLEAR GF	PROCLEAR GP	PROPOR MR	PROPOR SG	PROPOR HC	PROPOR BR	PROPOR LR	TETPOR AIR	TETPOR LIQUID	TETPOR PLUS	EPDM o-ring	VITON o-ring	SILICONE o-ring
Acetic acid 3.5N	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Acetic acid 8.75N	C	C	-	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	LC	LC	NC
Acetic acid conc.17.5N	C	C	-	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	LC	NC	NC
Acetone	C	C	-	C	C	C	C	C	C	C	NC	NC	NC	NC	NC	C	C	C	NC	NC	NC
Acetonitrile	C	C	-	LC	C	C	C	C	LC	LC	-	-	-	-	-	C	C	C	NC	NC	NC
Acidbrite 4 (Diversey) 3.0%$_{v/v}$	-	-	-	C	-	-	-	C	C	C	-	-	-	-	-	-	-	-	C	C	C
Ammonium Hydroxide 8N	C	C	C	C	C	C	C	C	C	C	LC	LC	LC	LC	LC	C	C	C	C	C	C
Ammonium Oxalate 0.07N	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Amyl Acetate	C	C	C	LC	C	C	C	C	LC	LC	LC	LC	LC	LC	LC	C	C	C	NC	NC	LC
Aqueous Ammonia 15.5N	C	C	C	LC	C	LC	C	C	LC	LC	LC	LC	LC	LC	LC	C	C	C	C	C	C
Benzyl Alcohol	C	C	C	NC	C	C	C	NC	NC	NC	-	-	-	-	-	C	C	C	C	C	C
Benzyalkonium Chloride 0.1%	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Boric acid,saturated	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Butan-1-ol	C	C	C	C	LC	LC	LC	C	C	C	C	C	C	C	C	NC	NC	NC	C	C	C
Butan-2-ol	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	LC	C	C
Carbon Tetrachloride	C	C	C	NC	C	C	C	NC	NC	NC	-	-	-	-	-	NC	NC	NC	NC	C	NC
Chloroform	C	C	C	NC	C	C	C	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	LC	NC
Cyclohexane	C	C	C	NC	-	-	-	NC	NC	NC	-	-	-	-	-	LC	LC	LC	NC	NC	NC
1,4 – Dioxane	C	C	C	LC	C	C	C	C	LC	LC	-	-	-	-	-	C	C	C	NC	NC	NC
Diverflow (Diversey) 3%v/v	-	-	-	NC	-	-	-	C	NC	NC	C	C	C	C	C	-	-	-	C	C	LC
Diversey 212G 0.6%v/v	-	-	-	C	-	-	-	C	C	C	-	-	-	-	-	-	-	-	C	C	C
Divosan Forte 0.5%v/v	-	-	-	C	-	-	-	C	C	C	C	C	C	C	C	-	-	-	C	C	C
Divosan XT 1%v/v	-	-	-	C	-	-	-	C	C	C	-	-	-	-	-	-	-	-	C	C	C
Ethanol	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C	LC
Ethanol 45%	-	-	-	C	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Ethyl Acetate	LC	LC	LC	LC	LC	LC	LC	LC	LC	LC	NC	NC	NC	NC	NC	LC	LC	LC	C	NC	LC
Formaldehyde 0.3%	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Formaldehyde 37%	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Formic acid conc.	C	C	C	NC	C	C	C	C	NC	NC	-	-	-	-	-	C	C	C	C	NC	NC
Glycerol	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Hexane	C	C	C	-	C	C	C	NC	-	-	-	-	-	-	-	-	-	-	NC	NC	NC

	BIO-X II	HIGH FLOW BIO-X	HIGH FLOW BIO-X VENT AUTOCLAVE	HIGH FLOW PREPOR GFA	HIGH FLOW TETPOR II	HIGH FLOW TETPOR H.T.	HIGH FLOW TETPOR VENTAUTOCLAVE	PROCLEAR PP	PROCLEAR GF	PROCLEAR GP	PROPOR MR	PROPOR SG	PROPOR HC	PROPOR BR	PROPOR LR	TETPOR AIR	TETPOR LIQUID	TETPOR PLUS	EPDM o-ring	VITON o-ring	SILICONE o-ring
Hydrochloric acid 1N	-	-	-	C	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Hydrochloric acid conc.	-	-	-	NC	-	-	-	C	NC	NC	-	-	-	-	-	C	C	C	NC	NC	NC
Hydrochloric acid conc.13%	C	C	C	-	C	C	C	-	-	-	-	-	-	-	-	-	-	-	NC	NC	NC
Hydrogen Peroxide	C	C	C	-	-	-	-	C	-	-	-	-	-	-	-	-	-	-	C	C	C
Hydrogen Peroxide 10% Volume	-	-	-	C	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Hydrogen Peroxide 100% Volume	-	-	-	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Methanol	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C
Methyl-Iso-Butylketone	C	C	C	C	C	C	C	C	C	C	NC	NC	NC	NC	NC	C	C	C	NC	NC	LC
Methylene Chloride @ 40°C	-	-	-	LC	-	-	-	LC	LC	LC	-	-	-	-	-	-	-	-	-	-	-
Nitric acid 2N 14.4%	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	LC	C	C
Nitric acid 15.8N	C	C	C	NC	C	NC	C	C	NC	NC	-	-	-	-	-	C	C	C	NC	NC	NC
Ozone	-	-	-	-	-	-	-	-	-	-	NC	NC	NC	NC	NC	-	-	-	-	-	-
Paraffin yellow	LC	LC	LC	LC	C	C	C	C	LC	LC	-	-	-	-	-	C	C	C	NC	C	NC
Pentane	C	C	C	LC	-	-	-	LC	LC	LC	-	-	-	-	-	LC	LC	LC	NC	C	NC
Peracetic acid 0.5% (10 wk test)	-	-	-	-	C	C	C	-	-	-	-	-	-	-	-	-	-	-	C	C	C
Peracetic acid 4%	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Perchloroethylene	-	-	-	-	-	-	-	-	-	-	NC	NC	NC	NC	NC	-	-	-	-	-	-
Petroleum spirits	-	-	-	NC	C	C	C	NC	NC	NC	-	-	-	-	-	LC	LC	LC	NC	C	NC
Phenol (aq) 0.5N	C	C	C	-	NC	-	NC	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Phenol 5%	-	-	-	C	-	-	-	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Phenol 0.25%	-	-	-	C	-	-	-	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Polyethylene Glycol 600	LC	LC	LC	NC	C	C	C	LC	NC	NC	NC	NC	NC	NC	NC	-	-	-	-	-	-
Polyglycol 2000-E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C
Potassium Dichromate 0.1N	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Potassium Iodine 0.6N	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Potassium Hydroxide 10N	C	C	C	NC	C	C	C	C	NC	NC	LC	LC	LC	LC	LC	C	C	C	C	C	C
Potassium Permanganate 0.1N	C	C	C	NC	C	LC	C	C	NC	NC	C	C	C	C	C	C	C	C	C	C	C
Propan-1-ol	C	C	C	NC	C	C	C	C	NC	NC	C	C	C	C	C	C	C	C	C	C	LC
Propan-2-ol	C	C	C	NC	C	C	C	C	NC	NC	C	C	C	C	C	C	C	C	C	C	LC
Propan-2-ol, 60:40 H_2O	C	C	C	NC	C	C	C	C	NC	NC	C	C	C	C	C	C	C	C	C	C	C
Pyridine	C	C	C	NC	C	C	C	C	NC	NC	NC	NC	NC	NC	NC	C	C	C	C	NC	C
Sodium Chloride 0.5N	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Saline Lactose Broth	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Sodium Hydroxide 1N 4%	NC	NC	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Sodium Hydroxide 7N 28%	NC	NC	NC	NC	C	C	C	C	NC	NC	NC	NC	NC	NC	NC	C	C	C	C	C	LC
Sodium Hypochlorite (14% Free Cl_2)	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C

	BIO-X II	HIGH FLOW BIO-X	HIGH FLOW BIO-X VENT AUTOCLAVE	HIGH FLOW PREPOR GFA	HIGH FLOW TETPOR II	HIGH FLOW TETPOR H.T.	HIGH FLOW TETPOR VENTAUTOCLAVE	PROCLEAR PP	PROCLEAR GF	PROCLEAR GP	PROPOR MR	PROPOR SG	PROPOR HC	PROPOR BR	PROPOR LR	TETPOR AIR	TETPOR LIQUID	TETPOR PLUS	EPDM o-ring	VITON o-ring	SILICONE o-ring
Sodium thiosulphate 0.1N	C	C	C	C	C	C	C	C	C	C	-	-	-	-	-	C	C	C	C	C	C
Sulphuric acid 1N	C	C	C	LC	C	C	C	C	LC	LC	C	C	C	C	C	-	-	-	C	C	C
Sulphuric acid conc.	NC	NC	NC	LC	LC	NC	LC	LC	LC	LC	NC	NC	NC	NC	NC	LC	LC	LC	-	-	-
Sulphurous acid	-	-	-	-	-	-	-	-	-	-	NC	NC	NC	NC	NC	-	-	-	-	-	-
Toluene	NC	NC	NC	-	NC	NC	NC	NC	-	-	NC	NC	NC	NC	NC	-	-	-	NC	LC	NC
1,1,1 Trichloroethane	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1,1,2 Trichloroethane	C	C	C	LC	C	LC	C	LC	LC	LC	NC	NC	NC	NC	NC	LC	LC	LC	NC	LC	LC
Trichloroacetic Acid 80%	-	-	-	LC	-	-	-	C	LC	LC	-	-	-	-	-	C	C	C	NC	LC	NC
Trichloroacetic Acid 5N	C	C	C	-	C	C	C	-	-	-	-	-	-	-	-	-	-	-	---		
Toluene	-	-	-	NC	-	-	-	-	NC	NC	-	-	-	-	-	-	-	-	NC	LC	NC
Xylene	LC	LC	LC	NC	LC	LC	LC	NC	NC	NC	LC	LC	LC	LC	LC	NC	NC	NC	C	LC	NC

Chemical Compatibility User Instructions and Notes

- The chemicals are arranged in alphabetical order using their most common or trade names. If the chemical in question does not appear to be listed, it may be found elsewhere in the table under a pseudonym, in particular its IUPAC[13] name.
- **Please note:**
  - Any product that has limited compatibility (LC) at ambient temperatures should not be used at a higher temperature.
  - The list of compatibilities does not take into account any synergistic effects of more than one chemical present in the solution to be filtered.

[13] International Union of Pure and Applied Chemistry

5. Cartridge and Capsule Cleanliness

PROPOR SG filters must meet stringent standards to be certified pharmaceutical (P) grade product by Parker domnick hunter. One aspect of this is to confirm levels of potential contaminants that may be added to a process stream by the addition of the filter capsule.

The following tests are designed to determine if contaminants can be released or extracted from the capsule filter and, where identified, a quantitative assessment is made.

5.1. Gravimetric Non Volatile Extractables in Water

The weight of non-volatile materials extracted from PROPOR SG cartridges and capsules was determined during a 10 litre room temperature purified water flush at constant flow to mimic normal operation (methodology defined in Internal Reference IPPF 118 developed from that defined in current USP <661>, Sub section Physicochemical Tests – Plastics.). Five 1 litre aliquots were taken at stepped intervals and assessed. 50 mL of each aliquot was evaporated in an acid washed crucible to constant weight. The NVE mass was identified and reported.

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No.	Control	Sample Aliquots No. (mg / 50 mL)					Results
		1	2	3	4	5	
	NVE	NVE	NVE	NVE	NVE	NVE	
DC289379	<1	1	<1	<1	<1	<1	<5
DC289376	<1	1	<1	<1	<1	<1	<5
DC289377	<1	1	<1	<1	<1	<1	<5

Conclusion

Total NVEs extracted in the first 5 litre flush of purified water for an A size PROPOR SG capsule is <5 mg.

10" Cartridge

Cartridge Serial No.	Control	Sample Aliquots No. (mg / 50 mL)					Results
		1	2	3	4	5	
	NVE	NVE	NVE	NVE	NVE	NVE	
P013113	1	<1	1	<1	<1	<1	<5
P013647	1	3	1	1	<1	1	<7
P013100	0	3	4	1	<1	<1	<10

Conclusion

Total NVEs extracted in the first 5 litre flush of purified water for a 10 inch cartridge is <10 mg.

5.2. Buffering Capacity

The impact on buffering capacity of materials extracted from PROPOR SG cartridges and capsules was determined during a 10 litre room temperature purified water flush at constant flow. Five 1 litre aliquots were taken at stepped intervals and assessed using a protocol developed from that defined in current USP <661>, Sub section Physicochemical Tests – Plastics.

The volume of 0.1 N hydrochloric acid or 0.01 N sodium hydroxide required to bring each of the 20 mL extracts and 20 mL control samples to pH 7 was compared and reported. If the difference in the volumes added is less than 10 mL, the potential impact of the extract as a buffer is considered acceptable.

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No.	Control		Sample Aliquots No. 1		2		3		4		5		Result
	Initial pH	ml added	Initial pH	ml added	Initial pH	ml added	Initial pH	ml added	Initial pH	ml added	Initial pH	ml added	
DC289379	6	1	6	1	6	1	6	1	6	1	6	1	**Pass**
DC289376	7	0	7	0	7	0	7	0	7	0	7	0	**Pass**
DC289377	7	0	7	0	7	0	7	0	7	0	7	0	**Pass**

Conclusion

The difference in the volumes added was less than 10 mL and therefore, the potential impact of the extract as a buffer is considered acceptable.

10" Cartridge

Cartridge Serial No.	Control		Sample Aliquots No. 1		2		3		4		5		Result
	Initial pH	mL added	Initial pH	mL added	Initial pH	mL added	Initial pH	mL added	Initial pH	mL added	Initial pH	mL added	
P013113	6	1	6	1	6	1	6	1	6	1	6	1	**Pass**
P013647	6	1	6	1	6	1	6	1	6	1	6	1	**Pass**
P013100	6	1	6	1	6	1	6	1	6	1	6	1	**Pass**

Conclusion

The difference in the volumes added was less than 10 mL and therefore, the potential impact of the extract as a buffer is considered acceptable.

5.3. Bacterial Endotoxins

Pyrogenicity, or the concentration of bacterial endotoxins, extracted from PROPOR SG cartridges and capsules was determined during a 10 litre room temperature purified water flush at constant flow. Five 1 litre aliquots were taken at stepped intervals and assessed using protocols defined in current USP <85>.

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No.	Controls				Sample Aliquots No. (-ve or +ve Gel in Duplicate)						Result
	-ve	0.25 EU / mL	0.125 EU / mL	0.0625 EU / mL	Control	1	2	3	4	5	
DC289379	-	+	+	+	-	-	-	-	-	-	**Pass**
DC289376	-	+	+	+	-	-	-	-	-	-	**Pass**
DC289377	-	+	+	+	-	-	-	-	-	-	**Pass**

Conclusion

Aqueous extracts from the A size PROPOR SG capsule were shown to contain < 0.125 EU / mL when tested in accordance with the Limulus Amoebocyte Lysate (LAL) test.

10" Cartridge

Cartridge Serial No.	Controls				Sample Aliquots No. (-ve or +ve Gel in Duplicate)						Result
	-ve	0.25 EU / mL	0.125 EU / mL	0.0625 EU / mL	Control	1	2	3	4	5	
P013113	-	+	+	+	-	-	-	-	-	-	**Pass**
P013647	-	+	+	+	-	-	-	-	-	-	**Pass**
P013100	-	+	+	+	-	-	-	-	-	-	**Pass**

Conclusion

Aqueous extracts from the 10 inch PROPOR SG were shown to contain < 0.125 EU / mL when tested in accordance with the Limulus Amoebocyte Lysate (LAL) test.

5.4. Particle and Fibre Shedding

The levels of particles and fibres released from PROPOR SG cartridges and capsules were determined. Three capsules from different production lots were flushed with one litre of purified water. Samples from subsequent aliquots up to a 10 litre flush were monitored using on-line particle counting and sizing in accordance with the requirements of:

a) Current USP <788> Particulate Matter in Injections, Sub Section Light Obscuration Particle Count Test – Large Volume Injections

b) EP2.9.19 – Particulate Contamination: Sub-Visible Particles – Method 1. Light Obscuration Particle Count Test.

c) Allowable limits:

- <25 particles per mL @ >= 10 µm
- <3 particles per mL @ >= 25 µm

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No	Size Bands µm	Average Counts per mL in 1 Litre Samples Taken Post 1 Litre Pulse						Result
		Clean Water Control	2nd Litre	4th Litre	6th Litre	8th Litre	10th Litre	
DC289379	>2	0.00	0.04	0.00	0.00	0.00		**Pass**
	>5	0.00	0.03	0.00	0.00	0.00		
	>10	0.00	0.03	0.00	0.00	0.00		
	>25	0.00	0.02	0.00	0.00	0.00		
DC289376	>2	0.00	0.71	0.00	0.00	0.00		**Pass**
	>5	0.00	0.51	0.00	0.00	0.00		
	>10	0.00	0.38	0.00	0.00	0.00		
	>25	0.00	0.17	0.00	0.00	0.00		
DC289377	>2	0.00	2.61	0.51	0.19	0.07		**Pass**
	>5	0.00	0.73	0.03	0.01	0.00		
	>10	0.00	0.03	0.00	0.00	0.00		
	>25	0.00	0.00	0.00	0.00	0.00		

Conclusion

All filters conform to the requirements of USP<788> and EP2.9.19 within the first 2 litres of a purified water flush.

10" Cartridge

Cartridge Serial No	Size Bands µm	Average Counts per ml in 1 Litre Samples Taken Post 1 Litre Pulse						Result
		Clean Water Control	2nd Litre	4th Litre	6th Litre	8th Litre	10th Litre	
P013113	>2	0.68	3.26	0.89	0.76	0.57		**Pass**
	>5	0.15	1.12	0.27	0.27	0.17		
	>10	0.06	0.36	0.08	0.10	0.05		
	>25	0.04	0.04	0.01	0.01	0.00		
P013647	>2	0.04	12.76	4.73	4.19	1.19		**Pass**
	>5	0.01	4.92	1.78	1.40	0.64		
	>10	0.00	2.42	0.84	0.57	0.29		
	>25	0.00	0.34	0.10	0.09	0.04		
P013100	>2	0.00	4.93	1.92	1.01	0.52		**Pass**
	>5	0.00	0.75	0.18	0.10	0.05		
	>10	0.00	0.23	0.05	0.02	0.01		
	>25	0.00	0.04	0.01	0.00	0.00		

Conclusion

All filters conform to the requirements of USP<788> and EP2.9.19 within the first 2 litres of a purified water flush.

5.5. Oxidisable Substances

The level of oxidisable substances extracted from an PROPOR SG cartridges and capsule was determined during a 10 litre room temperature purified water flush at constant flow. Five 1 litre aliquots were taken at stepped intervals and assessed using the method defined in the Monograph: Water, Purified, of the current European Pharmacopoeia (identified as an alternative to TOC (2.2.44)).

To 100 mL of extract, 10 mL of dilute sulphuric acid and 0.1 mL of 0.2 M potassium permanganate was added and boiled for 5 minutes. The extracts from the three test cartridges must remain pink to indicate an acceptable level of oxidisable substances.

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No.	Control		Sample Aliquots No. (Purple / Pink Colour Remains)					Result
	+ve	-ve	1	2	3	4	5	
DC289379	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
DC289376	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
DC289377	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**

Conclusion

PROPOR SG filter capsules meet current USP quality standards for oxidisable substances within the first 1 litre flush with purified water.

10" Cartridge

Cartridge Serial No.	Control		Sample Aliquots No. (Purple / Pink Colour Remains)					Result
	+ve	-ve	1	2	3	4	5	
P013113	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
P013647	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
P013100	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**

Conclusion

PROPOR SG filter cartridges meet the requirements of the current EP and USP quality standards for oxidisable substances within the first 1 litre flush with purified water.

5.6. Total Organic Carbon and Ionic Substances

TOC levels were determined for the PROPOR SG cartridges and capsules in accordance with standard production process and production specifications. Immediately after the flush, 200 mL is assessed for TOC and conductivity by an on line analyser. Measured TOC and conductivity levels are recorded.

The test method for TOC is in accordance with current USP <643> and EP 2.2.44. The test method for conductivity is in accordance with current USP <645> and EP 2.2.38.

Acceptable TOC limit: <500ppb

Acceptable conductivity limit: <1.3 µS / cm @ 25°C

Irradiated (45.6 kGy) 'A' size capsule

Cartridge Serial No.	Filtrate Sample		Results	
	TOC (ppb)	Conductivity (µS/cm)	TOC (ppb)	Conductivity (µS/cm)
DC289379	420	0.075	**Pass**	**Pass**
DC289376	145	0.061	**Pass**	**Pass**
DC289377	160	0.119	**Pass**	**Pass**

Conclusion

The filtrate quality from an A size PROPOR SG capsule conforms to the requirements of USP <643> (TOC) and USP 28<645> (conductivity) within the first 200 mL flush of purified water.

10" Cartridge

Cartridge Serial No.	Filtrate Sample		Results	
	TOC (ppb)	Conductivity (µS/cm)	TOC (ppb)	Conductivity (µS/cm)
P013655	258	0.070	**Pass**	**Pass**
P135339	205	0.070	**Pass**	**Pass**
P135344	180	0.071	**Pass**	**Pass**
P012430	170	0.076	**Pass**	**Pass**
P135342	215	0.072	**Pass**	**Pass**
P135341	195	0.071	**Pass**	**Pass**

Conclusion

The filtrate quality from a 10 inch PROPOR SG conforms to the requirements of USP <643> (TOC) and USP 28<645> and EP 2.2.38 (conductivity) within the first 200 mL flush of purified water.

5.7. Determination of extracted chemical compounds[14]

To assist in planning validation studies for a particular drug product, extraction tests in WFI (70°C for 24hrs) have been conducted to identify the compounds that could potentially leach into a drug product during aseptic filtration. This information can be used to assess potential toxicological effects of the leachable substances in-line with ISO 10993-17 “Methods for the establishment of allowable limits for leachable substances using health based risk”. The tests were conducted on products from the PROPOR range utilising the same materials of construction.

The analysis was performed on combined extracts from three 0.1m^2 filter cartridges pre and post autoclaving @ 130°C for 30 minutes. Extraction conditions for the cartridges were a static soak for 24 hours at 70°C. The results reported below are an average per cartridge for the three tested.

Metals Analysis via ICP-AES

Metals	Mass extract mg /cartridge	
	Pre autoclave	Post Autoclave
Ba	<0.04	<0.04
Ca	<0.06	<0.06
Cd	<0.04	<0.04
Co	<0.05	<0.05
Cr	<0.04	<0.04
Cu	<0.04	<0.04
Fe	<0.04	<0.04
K	<0.04	<0.04
Mg	<0.04	<0.04
Mn	<0.04	<0.04
Na	<0.04	<0.04
Ni	<0.08	<0.08
Pb	<0.08	<0.08
Zn	<0.04	<0.04

NOTE: All metal extracts were below the limit of detection of the instrumentation

Conclusion

All potential metal extracts were below the limit of detection of the instrumentation.

[14] Product formats, solutions and process conditions may influence type and concentration of leachables observed.

Headspace GC/MS

Volatile organic molecules that migrate into the contact solution during a prolonged contact step between a medical device or a test material and the extraction solution, may come from various sources such as monomer residues, solvent residues from various production steps, residues from polymer treatments or smaller polymer breakdown products.

The selected technique for this analytical method – Headspace coupled to a Gas Chromatography (GC) with Mass Spectrometry (MS) allows identification of the target analytes based on both retention time of the analytes in the chromatogram and the mass spectrum of the eluting compound at this specific retention time.

No compounds could be detected at a higher concentration than the method reporting limit of 79µg / cartridge.

Dichloromethane Extraction (DCM) + GC/MS

This analytical technique is used to identify potential migration of organic components. To improve the sensitivity of the total analytical method, the water samples were extracted with an organic solvent (DCM) with a low boiling point. Following extraction, the DCM phase was concentrated down to 2 mL to further enhance sensitivity.

The compounds identified were

- Butyrolactone
- 4-butoxy-1-butanol
- Caprolactam
- Azacyclotridecan-2-one

Dichloromethane Extraction (DCM) + LC/MS

This analytical technique is used to identify non-volatile or non-thermostable components such as anti-oxidants, plasticizers etc. To improve the sensitivity of the total analytical method, the water samples were extracted with an organic solvent (DCM) with a low boiling point. Following extraction the DCM phase was concentrated down to 2 mL to further enhance sensitivity.

The compounds identified were

- Erucamide

6. Tests for Biocompatibility

An independent research establishment has assessed the biological safety associated with the use of PROPOR SG filters designed for processing pharmaceutical products.

The materials used in the construction of PROPOR SG products meet the requirements of the current USP <88> Biological Reactivity tests at Plastics Class VI – 121°C. A matrix of test reports is given below:

Component	Material Description	Report References	Testing Agency
Endcaps	Injection Moulded Nylon	07-4844-G1	HRC Ltd. & Toxikon Corp.
Core	Injection Moulded Polypropylene	881320D/DHF 18/AC 881327D/DHF 19/AC 881344D/DHF 20/AC	HRC Ltd.
Filtration Membranes	Cast Polyethersulfone Membrane	99G-0108	Toxikon Corp.
Membrane Supports	Spunbond Polyester non-woven.	90676D/LML 1/AC 90678D/LML 3/AC 90677D/LML 2/AC	HRC Ltd.

7. Certificate of Conformance

To certify that Parker domnick hunter's PROPOR SG filter products meet the highest pharmaceutical quality and performance requirements, a Certificate of Conformance is issued.

Documentation Approval Section

Q.A. Approval

Approved By: Martin Newman

Title: Senior Quality Engineer

Date: April 2017

Technical Approval

Approved By: Andrew Kelly

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