VALIDATION GUIDE

PROCLEAR GP

Pharmaceutical Grade
Cartridge & Capsule filters

Contents

1. Introduction

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 sterilising 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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Registered No. ……

Date Issued: ……

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[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 Quality Management Systems
- BS EN ISO14001 Environmental Management Standard
- BS EN ISO13485 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

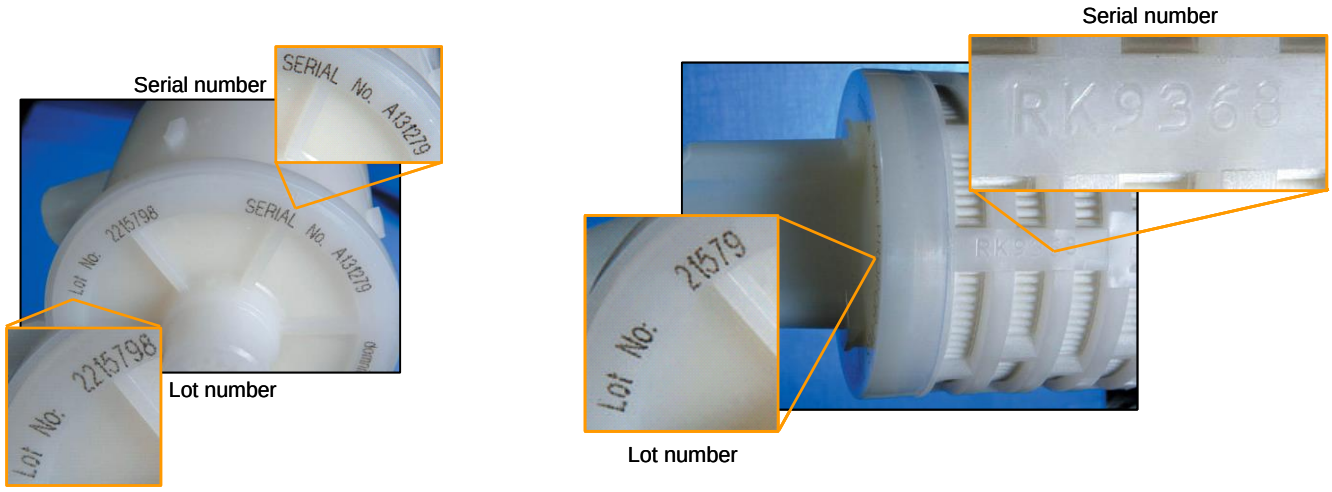
Parker domnick hunter works closely with suppliers to ensure materials supplied are of a consistently high quality and also to develop new materials as part of our ongoing product development activity. In addition to supplier certificates of conformity and analysis, incoming raw materials, including 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 sterilising grade filter capsules and cartridges.

2.4. Product and Lot Release Criteria

Prior to dispatch all Parker domnick hunter cartridges and capsules undergo final product quality control which includes a final 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.

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 PROCLEAR GP cartridges and capsules is 5 years (2 years for irradiated product).

3. Product Description

All products within the PROCLEAR GP 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.

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 Media	Glass microfibre / polypropylene
Upstream Support	Polypropylene
Downstream Support	Polypropylene
Inner Core	Polypropylene
Sleeve	Polypropylene
Endcaps (cartridge)	Polypropylene
Endcaps Insert	316L Stainless Steel
Capsule body (DEMICAP)	Polypropylene
Capsule body (MURUS)	Polypropylene
Capsule vent seals	Silicone
Cartridge o-rings (standard)	Silicone

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 PCGP2-95C-PS — 500 mm (20”) 0.5 micron PROCLEAR GP filter cartridge, pharmaceutical grade with ‘C’ style endcap and silicone o-rings.

PCGP [ ] - [ ] [ ] - [ ] [ ]

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

Code	Micron Rating
95	0.50
96	0.60

Ratings based on efficiencies of > or = 99.98% using internal test procedure SOP081 based on ASTM F795-88 1993

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]
V	Viton™[3]
S	Silicone

Small Scale DEMICAP Capsules

Example PEGPB-95TT-PN3 — B size 0.5 micron PROCLEAR GP DEMICAP capsule, pharmaceutical grade with tri-clamp connections supplied non-sterile in packs of 3.

PEGP [ ] - [ ] [ ] [ ] - [ ] [ ] [ ]

Code	Accessory
FB	Filling Bell*

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

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

Code	Micron Rating
95	0.50
96	0.60

Ratings based on efficiencies of > or = 99.98% using internal test procedure SOP081 based on ASTM F795-88 1993

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
S	Showerhead
Q	Walther QRC Male
R	Grommel QRC Male

Code	Variant Ref
P	Pharmaceutical

Code	Sterilisation Grade
N	Supplied non sterile
S	Supplied Gamma Pre-Sterilised

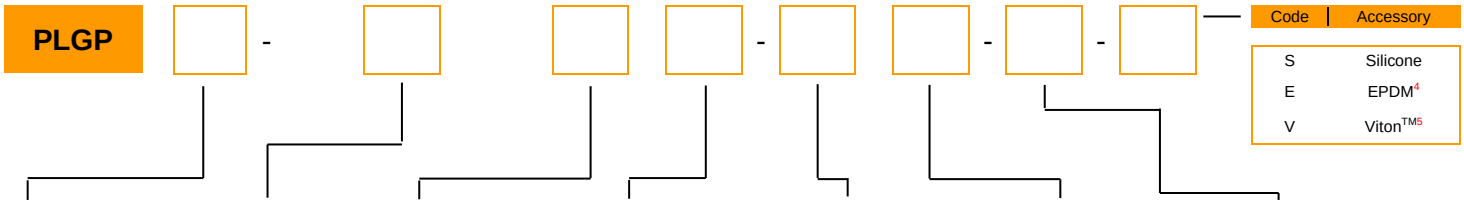
Code	Additional Specification
3	Pack of 3

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

Large Scale MURUS capsules

Example PLGP1-95TT-PN-L-S

10 “ 0.5 micron PROCLEAR GP MURUS capsule with tri-clamp connections, pharmaceutical grade, supplied non-sterile with inline design and silicone o-rings.



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
95	0.5
96	0.6

Ratings based on efficiencies of > or = 99.98% using internal test procedure SOP081 based on ASTM F795-88 1993

Code	Inlet Connection Type
T	1” Tri-clamp
A	¾” Tri-clamp
B	1½” Tri-clamp
D	1” Hosebarb

Code	Outlet Connection Type
T	1” Tri-clamp
A	¾” Tri-clamp
B	1½” Tri-clamp
D	1” Hosebarb

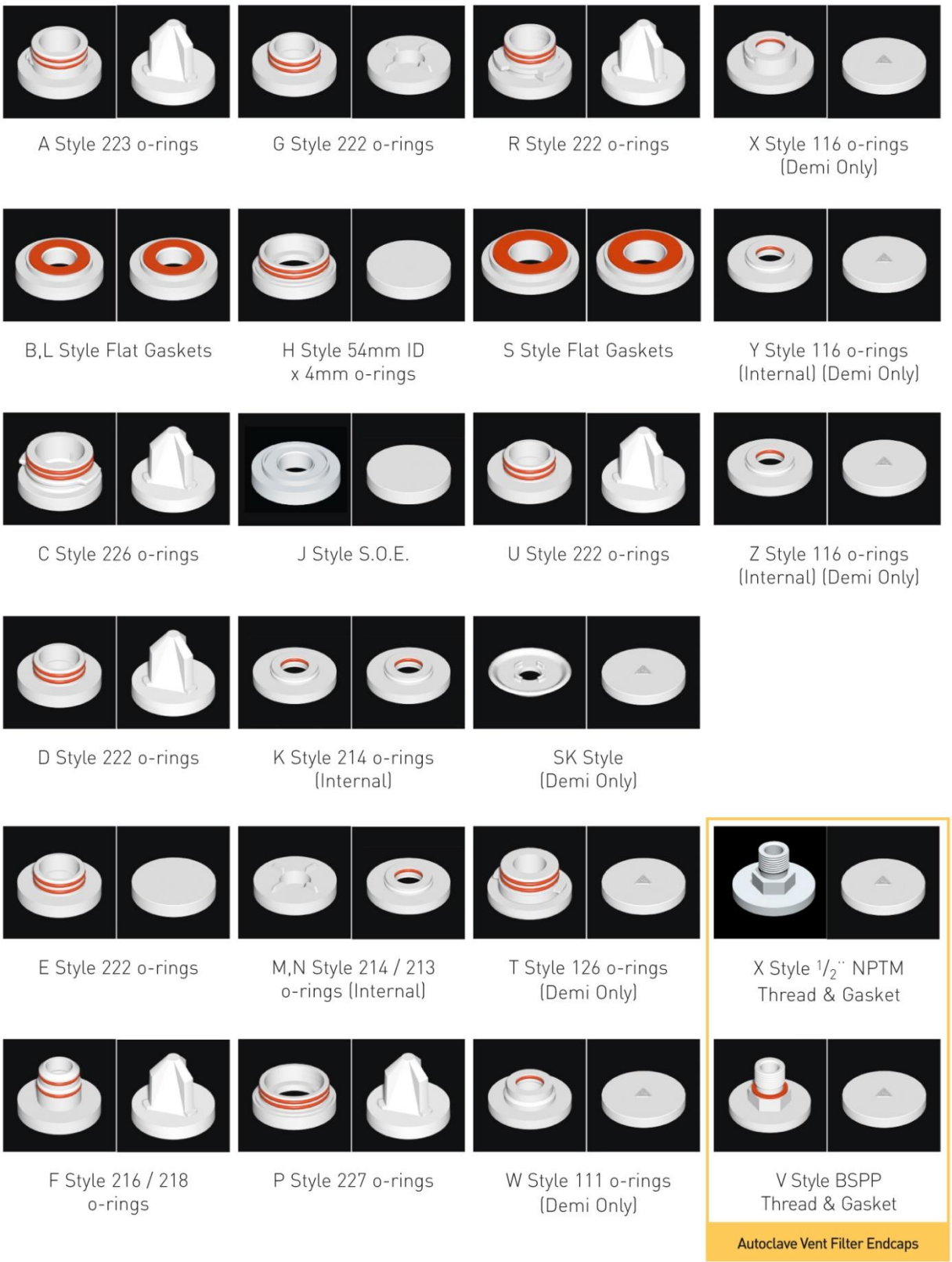
Code	Variant Ref
P	Pharmaceutical

Code	Sterilisation Grade
N	Supplied non sterile
S	Supplied Gamma Pre-Sterilised

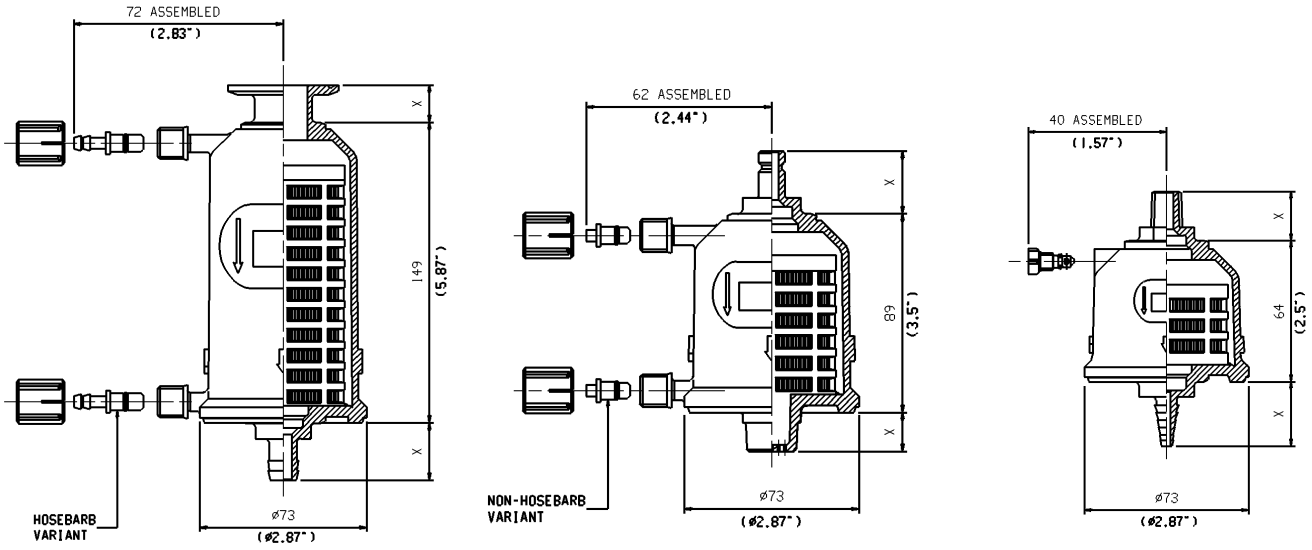
Code	Design
L	In-line
T	T-port

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

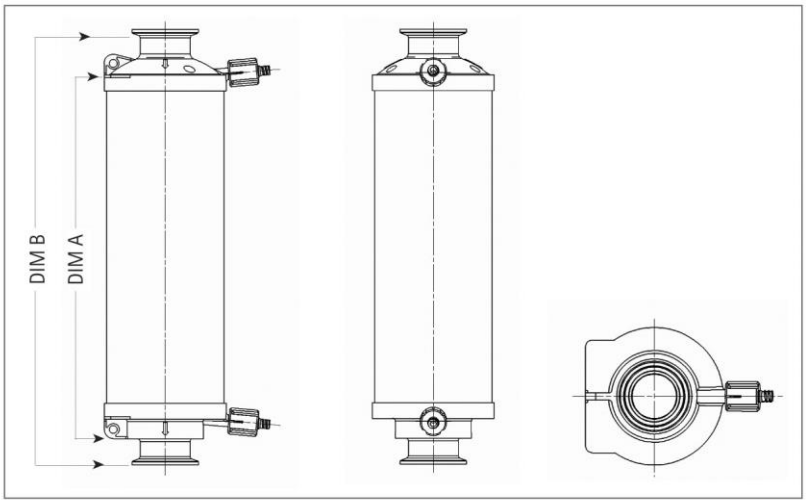
3.3. Cartridge Endcap Configurations



3.4. Capsule Dimensions



Dimensions



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

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

DEMICAP Inlet / Outlet Connection Styles

1″ Tri-Clamp | Stepped Hosebarb | 1/4″ NPTM Thread | 1/2″ Hosebarb | 1/2″ NPTM Thread

MURUS Inlet/Outlet Connection Styles

1 1/2" Tri-Clamp | 1" Hosebarb | 1" Tri-Clamp | 1" Tri-Clamp T-Port | 3/4" Tri-Clamp

4. Product Specifications

4.1. Capsule Operating Pressures and Temperatures

Testing to verify the maximum operating temperatures and pressures was conducted post autoclaving and post irradiation to simulate worst-case conditions.

DEMICAP

Post Autoclave (11 Porous load cycles @ 130ºC)

Serial Number	Batch Number	Capsule Surface Temperature (ºC)	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 (ºC)	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 PROCLEAR GP DEMICAP range of capsules has been set at 5.0 barg @ 40ºC.

MURUS Large Scale Capsule

The maximum operating temperatures and pressures for the MURUS range were evaluated using the PROPOR SG cartridge variant. This is applicable for the complete pharmaceutical range as it is the capsule housing integrity and the seals which are being tested and these are common across the PROPOR and PROCLEAR ranges. The results below are a sample from those manufactured during validation.

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

Serial Number	Burst Pressure barg @ 25ºC
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 @ 25ºC
9233MU006	18.67
9233MU008	18.24
9233MU010	17.20
9233MU012	19.11
9233MU014	20.52
9233MU016	20.58

Elevated Temperature

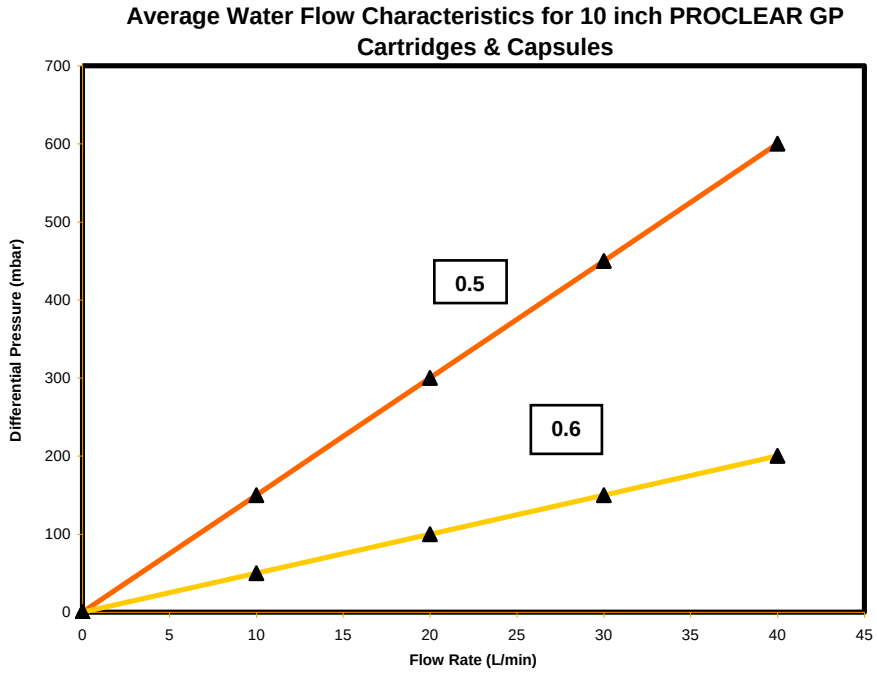
Serial Number	Capsule Surface Temperature (ºC)	Burst Pressure barg
9171MU001	52.9	13.37
9171MU003	54.3	16.71
9171MU005	52.6	14.30
9171MU007	53.0	14.59
9171MU009	52.3	13.12
9171MU012	54.2	14.25

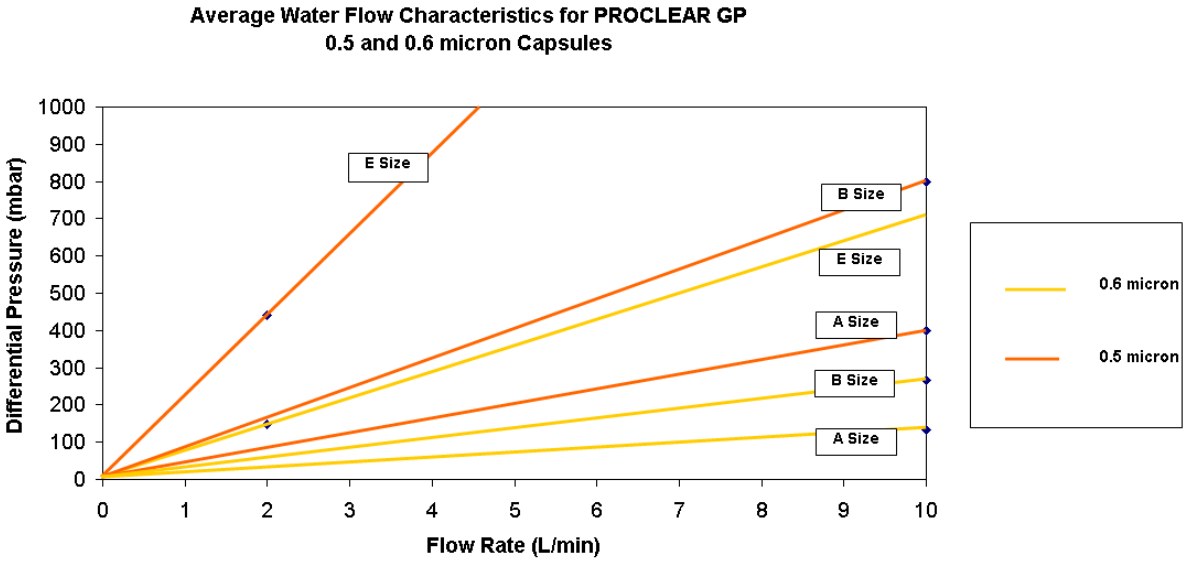
Conclusion

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

4.2. Flow Rates

Cartridge flow rates were determined for filters from three separate lots. The flowrates for the MURUS capsule range are the same as those for the equivalent size cartridge.





4.3. Effective Filtration Area (EFA)

Product Size	Surface Area (m^2)	Surface Area (ft^2)
3	0.96	10.3
2	0.64	6.9
1	0.32	3.4
K	0.16	1.7
A	0.12	1.3
B	0.06	0.6
E	0.03	0.3

4.4. Hold Up Volume

Pharmaceutical Capsule Product Hold Up Volumes						
Product	1 barg Air purge			2 barg air purge		
	A size Capsule Hold up Volume (ml)	B size Capsule Hold up Volume (ml)	E size Capsule Hold up Volume (ml)	A size Capsule Hold up Volume (ml)	B size Capsule Hold up Volume (ml)	E size Capsule Hold up Volume (ml)
PROCLEAR GP	54.4	27.9	17.3	51.2	23.7	15.5

4.5. 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 capsules pre and post autoclaving.

Batch Number	Serial Number	Pre-Autoclave @ 121 ºC 0 cycles Mass Bubble Point (mbar)	Post-Autoclave @ 121 ºC 11 cycles Mass Bubble Point (mbar)
3528821	DC308156	276	270
3528821	DC308155	272	278
3528821	DC308157	255	255
3528831	DC308158	269	258
3528831	DC308159	263	270
3528831	DC308160	248	260
3512123	DC308164	264	270
3512123	DC308165	259	266
3512123	DC308166	264	269

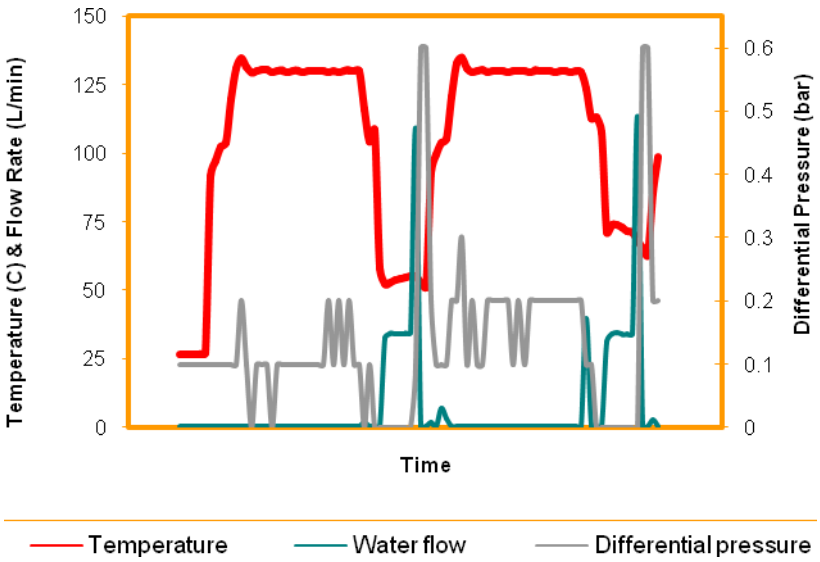
NOTE: Failure is indicated by a significant reduction (>20%) in bubble point

Conclusion

The PROCLEAR GP range of filter capsules can be autoclaved up to 10 cycles at 121ºC (250ºF), which includes a 10% safety factor.

4.6. 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 sterilisation was determined by evaluating three 10 inch cartridges from three separate batches.

Batch Number	Serial Number	Pre-SIP Mass Bubble Point (mbar)	Post-SIP Mass Bubble Point (mbar)
3508108	88522 BH	241	219
3504797	88472 BH	237	228
3504798	88293 BH	246	228

NOTE: Minimum failure is indicated by a significant reduction (>20%) in bubble point

Conclusion

The PROCLEAR GP range of filter cartridges can be steam sterilised up to 10 cycles at 121°C (250°F).

4.7. Chemical Compatibility

The following data is indicative of PROCLEAR GP 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[6] 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.

[6] International Union of Pure and Applied Chemistry

4.8. Gamma Sterilisation (Capsules)

4.8.1. Validation of gamma sterilisation process

The required sterilisation 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 sterilising 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 sterilisation dose and guaranteeing an SAL of 10^{-6} in accordance with ISO/EN WD, 11137-2.

Conclusion

The current sterilisation 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.

4.8.2. Capsule integrity after irradiation

27 PROCLEAR GP DEMICAP capsules were irradiated at a sterilisation dose of 45.6 kGy. Following irradiation the capsules were tested using reverse bubble point to confirm product integrity. The data is shown in the table below.

Serial Number	Mass Bubble Point (mbar)	Result
DC308143	208	**Pass**
DC308144	191	**Pass**
DC308145	211	**Pass**
DC308146	193	**Pass**
DC308147	193	**Pass**
DC308148	214	**Pass**
DC308150	212	**Pass**
DC308152	225	**Pass**
DC308154	190	**Pass**
DC308132	240	**Pass**
DC308134	213	**Pass**
DC308135	219	**Pass**
DC308136	200	**Pass**
DC308137	230	**Pass**
DC308138	190	**Pass**
DC308139	195	**Pass**
DC308141	194	**Pass**
DC308142	190	**Pass**
DC308119	230	**Pass**
DC308121	199	**Pass**
DC308122	220	**Pass**
DC308123	240	**Pass**
DC308124	207	**Pass**
DC308125	230	**Pass**
DC308126	214	**Pass**
DC308127	218	**Pass**
DC308128	243	**Pass**

NOTE: Minimum bubble point is set at 150mber

Conclusion

PROCLEAR GP capsules can be subjected to a sterilisation dose of up to 40 kGy without loss of integrity.

5. Cartridge and Capsule Cleanliness

PROCLEAR GP 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 PROCLEAR GP 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

Serial Number	Control	Sample Aliquots No. (mg / 50 ml)					Results
		1	2	3	4	5	
	NVE	NVE	NVE	NVE	NVE	NVE	
DC308120	<1	4	1	1	<1	<1	<8
DC308133	3	4	3	3	2	3	<15
DC308149	<1	<1	<1	1	<1	<1	<5

Conclusion

Total NVEs extracted in the first 5 litre flush of purified water for an A size PROCLEAR capsule is <15 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	
T892185	1	1	<1	<1	<1	<1	<5
T892194	<1	3	1	1	1	1	<7
T892191	1	5	2	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 PROCLEAR GP 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

Serial Number	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	
DC308120	6	0.1	7	0	7	0	6	0.1	7	0	7	0	**Pass**
DC308133	6	0.1	7	1	7	1	7	1	7	1	6	0.1	**Pass**
DC308149	6	0.1	7	0	7	0	7	0	6	0.1	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	
T892185	6	1	6	1	6	1	6	1	6	1	6	1	**Pass**
T892194	6	1	7	0	6	1	6	1	6	1	6	1	**Pass**
T892191	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 PROCLEAR GP 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	1	2	3	4	5	
DC308120	-	+	-	-	-	-	-	**Pass**
DC308133	-	+	-	-	-	-	-	**Pass**
DC308149	-	+	-	-	-	-	-	**Pass**

Conclusion

Aqueous extracts from the A size PROCLEAR GP capsule were shown to contain < 0.25 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	1	2	3	4	5	
T892185	-	+	-	-	-	-	-	**Pass**
T892194	-	+	-	-	-	-	-	**Pass**
T892191	-	+	-	-	-	-	-	**Pass**

Conclusion

Aqueous extracts from the 10 inch PROCLEAR GP were shown to contain < 0.25 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 PROCLEAR GP 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

Serial Number	Size Bands µm	Average Counts per ml in 1 Litre Samples Taken Post 1 Litre Flush						Result
		Clean Water Control	2nd Litre	4th Litre	6th Litre	8th Litre	10th Litre	
DC308120	>2	0.01	5.23	1.54	0.83	0.58		**Pass**
	>5	0.01	1.65	0.36	0.11	0.13		
	>10	0.01	0.87	0.08	0.06	0.05		
	>25	0.00	0.08	0.00	0.00	0.01		
DC308133	>2	0.46	9.48	3.54	2.03	1.18		**Pass**
	>5	0.24	2.87	0.96	0.28	0.03		
	>10	0.15	1.16	0.28	0.15	0.09		
	>25	0.01	0.10	0.03	0.02	0.02		
DC308149	>2	0.61	2.34	0.93	1086	1.40		**Pass**
	>5	0.24	0.35	0.14	0.39	0.22		
	>10	0.06	0.03	0.02	0.10	0.05		
	>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						Result
		Clean Water Control	2nd litre	4th litre	6th litre	8th litre	10th litre	
T892185	>2	0.00	20.81	20.95	9.47	4.91		**Pass**
	>5	0.00	1.73	1.73	0.75	0.38		
	>10	0.00	0.23	0.15	0.08	0.04		
	>25	0.00	0.03	0.03	0.02	0.01		
T892194	>2	0.06	42.67	37.48	16.91	7.28		**Pass**
	>5	0.04	3.34	3.39	1.49	0.62		
	>10	0.01	0.39	0.27	0.10	0.04		
	>25	0.00	0.07	0.06	0.02	0.01		
T892191	>2	0.06	18.65	9.73	6.26	4.50		**Pass**
	>5	0.03	1.89	0.94	0.50	0.36		
	>10	0.01	0.29	0.10	0.06	0.05		
	>25	0.00	0.05	0.02	0.01	0.01		

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 a PROCLEAR GP cartridge 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

Serial Number	Control		Sample Aliquots No. (Purple / Pink Colour Remains)					Result
	+ve	-ve	1	2	3	4	5	
DC308120	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
DC308133	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
DC308149	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**

Conclusion

PROCLEAR GP 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	
T892185	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
T892194	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**
T892191	No	Yes	Yes	Yes	Yes	Yes	Yes	**Pass**

Conclusion

PROCLEAR GP 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 PROCLEAR GP 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

Serial Number	Filtrate Sample		Results	
	TOC (ppb)	Conductivity (µS/cm)	TOC (ppb)	Conductivity (uS/cm)
DC308120	125	0.524	**Pass**	**Pass**
DC308133	180	0.901	**Pass**	**Pass**
DC308149	180	0.704	**Pass**	**Pass**

Conclusion

The filtrate quality from an A size PROCLEAR GP 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 (uS/cm)
T892185	0.45	0.366	**Pass**	**Pass**
T892194	1.37	0.862	**Pass**	**Pass**
T892191	0.71	1.099	**Pass**	**Pass**

Conclusion

The filtrate quality from a 10 inch PROCLEAR GP 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.

6. Tests for Biocompatibility

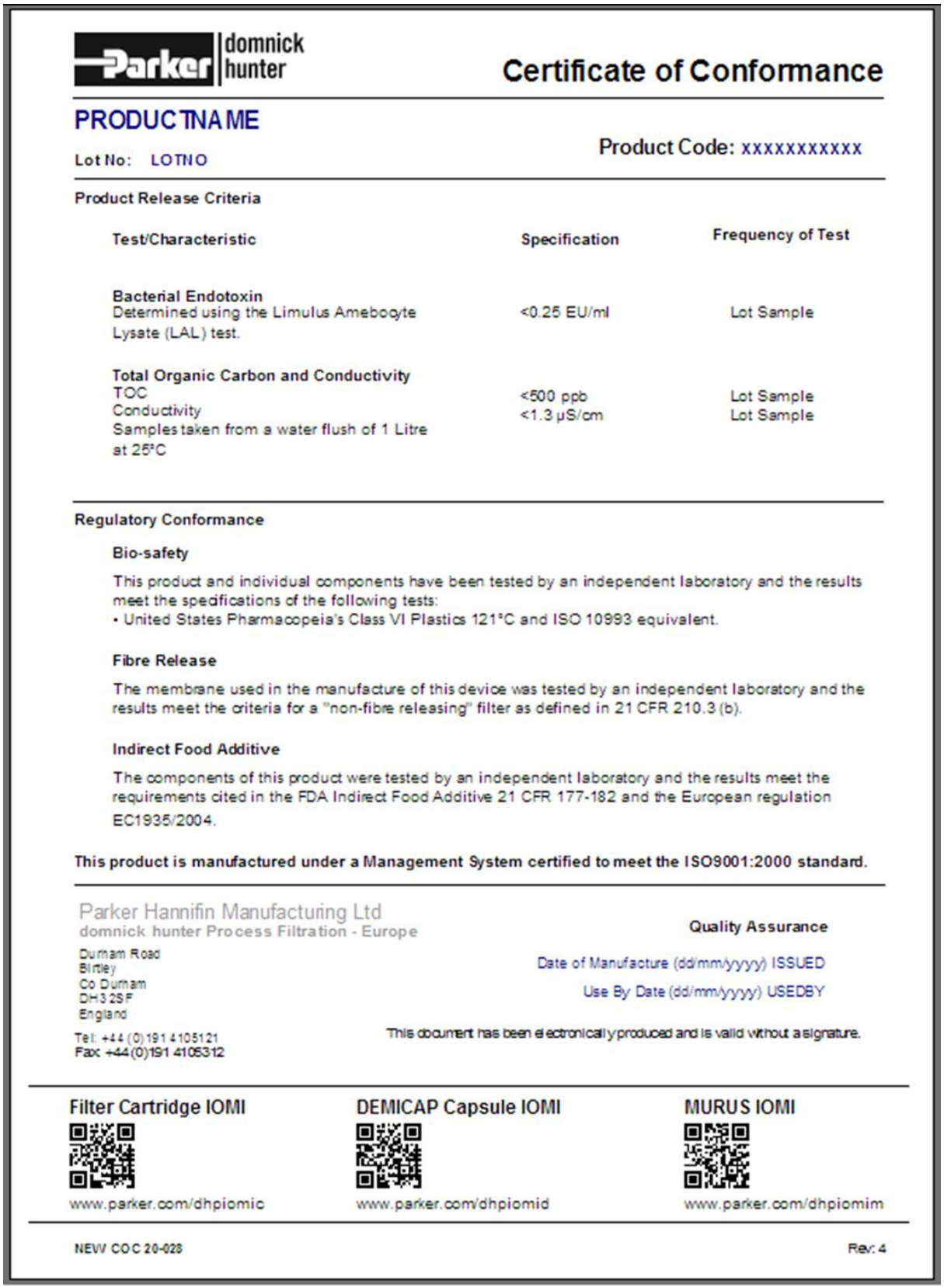
An independent research establishment has assessed the biological safety associated with the use of PROCLEAR GP filters designed for processing pharmaceutical products.

The materials used in the construction of PROCLEAR GP 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
Core / Sleeve / Endcaps	Injection Moulded Polypropylene	99G-0104 1999	Toxikon Corp
Filtration Media	Glass Microfibre	03-B0754-G1 03-3290-G1-3 03-B0752-N1	Toxikon Corp
Filtration Media Supports	Polypropylene Non-Woven	99G-0105 1999	Toxicon Corp
Filtration Media Supports	Polypropylene Expanded Net	99G-0523 1999 99G-0519 1999	Toxicon Corp

7. Certificate of Conformance

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



Parker domnick hunter

Certificate of Conformance

PRODUCTNAME

Product Code: xxxxxxxxxxx

Lot No: LOTNO

Product Release Criteria

Test/Characteristic	Specification	Frequency of Test
Bacterial Endotoxin Determined using the Limulus Amebocyte Lysate (LAL) test.	<0.25 EU/ml	Lot Sample
Total Organic Carbon and Conductivity		
TOC	<500 ppb	Lot Sample
Conductivity	<1.3 µS/cm	Lot Sample
Samples taken from a water flush of 1 Litre at 25°C		

Regulatory Conformance

Bio-safety

This product and individual components have been tested by an independent laboratory and the results meet the specifications of the following tests:
• United States Pharmacopeia's Class VI Plastics 121°C and ISO 10993 equivalent.

Fibre Release

The membrane used in the manufacture of this device was tested by an independent laboratory and the results meet the criteria for a "non-fibre releasing" filter as defined in 21 CFR 210.3 (b).

Indirect Food Additive

The components of this product were tested by an independent laboratory and the results meet the requirements cited in the FDA Indirect Food Additive 21 CFR 177-182 and the European regulation EC1935/2004.

This product is manufactured under a Management System certified to meet the ISO9001:2000 standard.

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Quality Assurance

Date of Manufacture (dd/mm/yyyy) ISSUED

Use By Date (dd/mm/yyyy) USEDBY

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NEW COC 20-028 Rev: 4

Documentation Approval Section

Q.A. Approval

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Date: April 2017

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