Sartoguard PES

Validation Guide

SARTORIUS

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1. Introduction

Pharmaceutical products, such as injectable and infusion solutions or those which come in contact with open wounds, must conform to exactly defined quality standards. The desired quality of the final product can only be obtained when the entire production process is adequately safeguarded against contamination. Final product quality meeting the standards of the respective pharmacopeias can be achieved by using membrane filter technology at critical points where particles or microbes could contaminate a product or must be separated from it. Heat-stable final products can be sterilized practically and effectively by autoclaving. This process, however, does not remove particles or dead microorganisms which may release pyrogens.

Therefore, a prior membrane filtration run is required by cGMP regulations (Current Good Manufacturing Practice of the US Food and Drug Administration) to ensure that particles and microbes are removed. Solutions containing heat-labile products, such as antibiotics, can be cold sterilized by membrane filtration immediately before aseptic filling. Microbe retentive filtration (bacteria retentive according to the European Pharmacopeia 2 and DAB 10) or sterile filtration (sterilization by filtration in conformance with the current USP), respectively, is an important process step in the manufacture of sterile pharmaceutical products. When sterilizing filters are used in the manufacture of pharmaceuticals, the aseptic process must be validated, taking all aspects of the product and the production process into consideration.

Sartoguard PES, pleated membrane filter elements with a heterogeneous membrane, reliably fulfills the product-specific requirements which have to be imposed on a filter used in prefiltration applications. Validation is indispensable for guaranteeing the sterility of pharmaceuticals, and is a logical supplement and significant part of the cGMP regulations which have been in force for quite some time. Guidelines for validation are given in the US Code of Federal Regulations Title 21 and the current USP. In addition, guidelines have been established jointly by the Committee for Laboratories and Official Drug Product Inspection Services and the Department of Industrial Pharmacists of the Federation Internationale Pharmaceutique (F.I.P.), which is the European counterpart of the FDA. The term validation is defined by the F.I.P. guidelines as follows: "Validation, as used in these guidelines, comprises the systematic testing of essential production steps and equipment in the R & D and production departments, including testing and inspection of pharmaceutical products with the goal of ensuring that the finished products can be manufactured reliably and reproducibly and in the desired quality in keeping with the established production and quality control procedures".

We have compiled this validation guide so users of Sartoguard PES filter can plan, implement and document their own validation procedures.

1.1 Quality Assurance

Consistent high quality of Sartorius Sartoguard PES products is ensured by careful selection of the raw materials, well-planned and validated production technologies, and a Quality Management System in compliance with ISO 9001 standards. These standards apply to all manufacturing facilities (www.sartorius.com/qm-certificates) resulting in high batch-to-batch reproducibility.

ISO 9001 is recognized as the root Quality Management System throughout the Sartorius Stedim Biotech corporation. As such, the Quality Management Systems of our manufacturing sites are certified by an accredited notified body, following a risk-based approach implemented for the development and control of processes and quality measures. All of this ensures high quality and regulated product life cycles, including:

- Corrective and preventive actions
- Non-conformance management
- Training of employees
- Design and development controls and outputs, including changes
- Document control
- Control of production and service provision, including in-process control and batch release

Consequently, our products are qualified according to most stringent performance and industry standards as described in this Validation Guide. The quality and performance of our products are ensured by our supplier management policy, quality controls of in-coming raw materials, in-process monitoring and finished product batch release testing. Our engineering change request management and centralized documentation system ensure product and process consistency while enabling continuous improvement.

For further details regarding our manufacturing network and the established quality standards please refer to our Supply Chain Specification which is available upon request.

1.2 Prevention of Contamination

Sartoguard PES filter cartridges and T-Style Maxicaps® are sealed in protective plastics bags in a controlled production area. During production Sartoguard PES filter cartridges and T-Style Maxicaps® are dried to reliably prevent microbial growth, and thus rule out the possibility of pyrogen synthesis during shipping and storage.

Sartoguard PES Midicaps® and capsules sizes 4 are sealed in steam permeable protective plastic bags in a controlled production area. Following this step they are heat treated with steam to reliably prevent microbial growth, and thus rule out the possibility of pyrogen synthesis during shipping and storage.

1.3 Complete Traceability

The pore size, type and lot number are printed on the label of the protective plastic bag and on the label of the box in which the cartridge or capsule is packed. In addition, these specifications are imprinted on the outer cage of each filter cartridge or on the housing of each capsule. The traceable lot number allows convenient retrieval of all data complied on the materials used, production steps and QC tests.

1.4 Quality Management Systems

Sartorius implemented Quality Management Systems to assure consistent high quality of membrane filters and filter cartridges.

Exemplary Quality Systems Certificates:

- Quality Management System DIN EN ISO 9001:2000
- Quality Management System DIN EN 46001
- Quality Management System Intertek Certificate 9001:2000

The complete Quality Systems Certificates are continuously updated and can be downloaded on our website:
www.sartorius.com

1.5 Test Methods for the Quality Assurance

Lot Related Tests – 100 % Individual Testing

- Diffusion value of the element
- Flow rate and throughput of the membrane

Routine Testing of Randomly Sampled Filter Cartridges and Capsules

- Pyrogen testing
- Flow rate testing
- Steam sterilizability
- Extractable substances

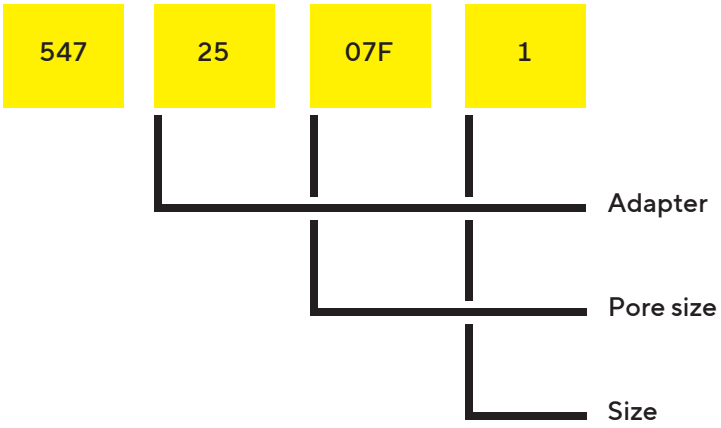
Testing Conducted for the Validation of the Filter Cartridges and Capsules

- Current USP Class VI Plastics Tests
  - Intracutaneous test
  - Systemic injection test
  - Implantation test
- Particle release
- pH change of the filtrate
- Conductivity changes of the filtrate
- Extractable substances
- Water flow rates
- Temperature and pressure resistance
- Sterilizability
  - In-line steam sterilization
- Autoclavability

2. Technical Specifications

2.1 Type and Part Number Overview

2.1.1 Sartoguard PES Standard Cartridge



Explanation

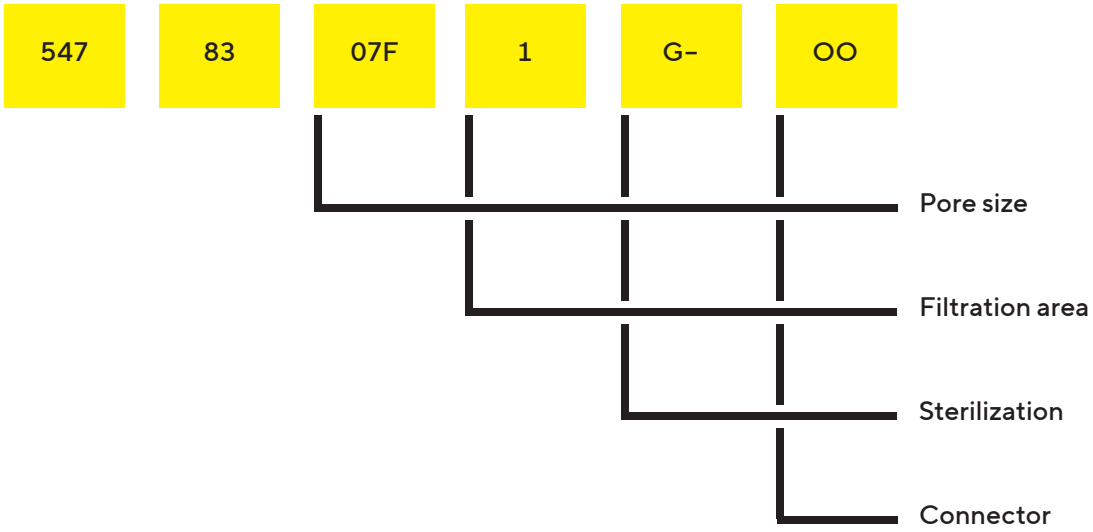
547
Sartoguard PES heterogeneous double layer polyethersulfone membrane filter

Adapter
25 S-adapter top, locking bayonet adapter with 226 double O-ring bottom

Pore size
07F 0.2 µm nominally
58G 0.1 µm nominally

Size		Filtration area
1	10"	0.8 m^2 | 8.6 ft^2
2	20"	1.6 m^2 | 17.2 ft^2
3	30"	2.4 m^2 | 25.8 ft^2

2.1.2 T-Style Maxicaps®



Explanation

547
Sartoguard PES heterogeneous double layer polyethersulfone membrane filter

Pore size
07F 0.2 µm nominally
58G 0.1 µm nominally

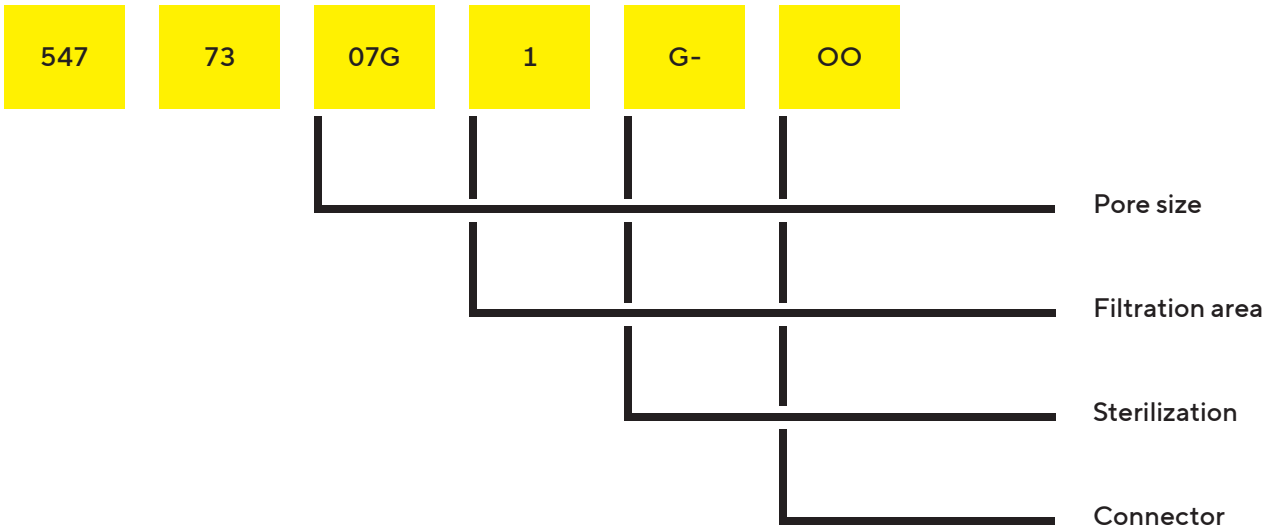
Effective filtration area
1 0.8 m² | 8.6 ft²
2 1.6 m² | 17.2 ft²
3 2.4 m² | 25.8 ft²

Sterilization
G– γ-irradiatable & autoclavable

Connectors
S Tri-clamp 50 mm (1½")
O ½" single stepped hose barb

Note
The first code letter of the connector code represents the inlet, the second code letter represents the outlet connector.

2.1.3 Maxicaps® | Gamma Maxicaps®



Explanation

547
Sartoguard PES heterogeneous double layer polyethersulfone membrane filter

Pore size
07F 0.2 µm nominally
58G 0.1 µm nominally

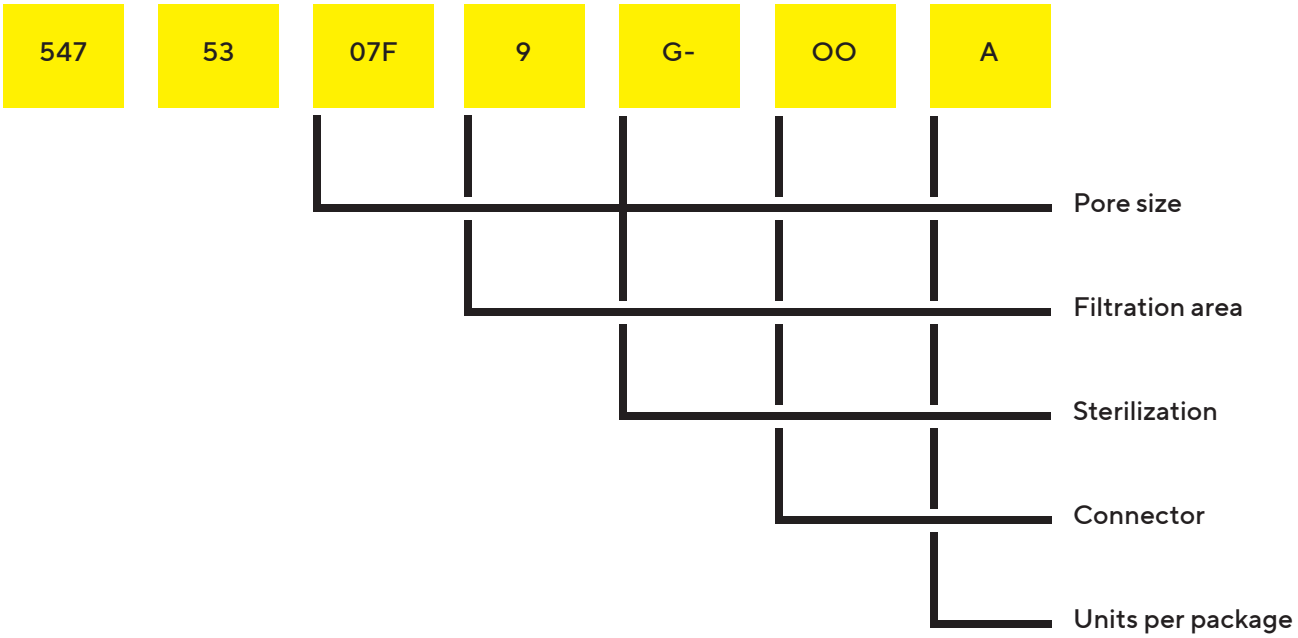
Effective filtration area
1 0.8 m^2 | 8.6 ft^2
2 1.6 m^2 | 17.2 ft^2
3 2.4 m^2 | 25.8 ft^2

Sterilization
G- γ-irradiatable
-- autoclavable

Connectors
S 1½" Tri-Clamp (sanitary)
O ½" single-stepped hose barb
F ¾" Tri-Clamp (sanitary)

Note
The first code letter of the connector code represents the inlet, the second code letter represents the outlet connector.

2.1.4 Midicaps®



Explanation

547
Sartoguard PES heterogeneous double layer polyethersulfone membrane filter

Pore size
07F 0.2 µm nominally
58G 0.1 µm nominally

Effective filtration area
7 0.065 m^2 | 0.7 ft^2
8 0.13 m^2 | 1.4 ft^2
9 0.26 m^2 | 2.8 ft^2
0 0.52 m^2 | 5.6 ft^2

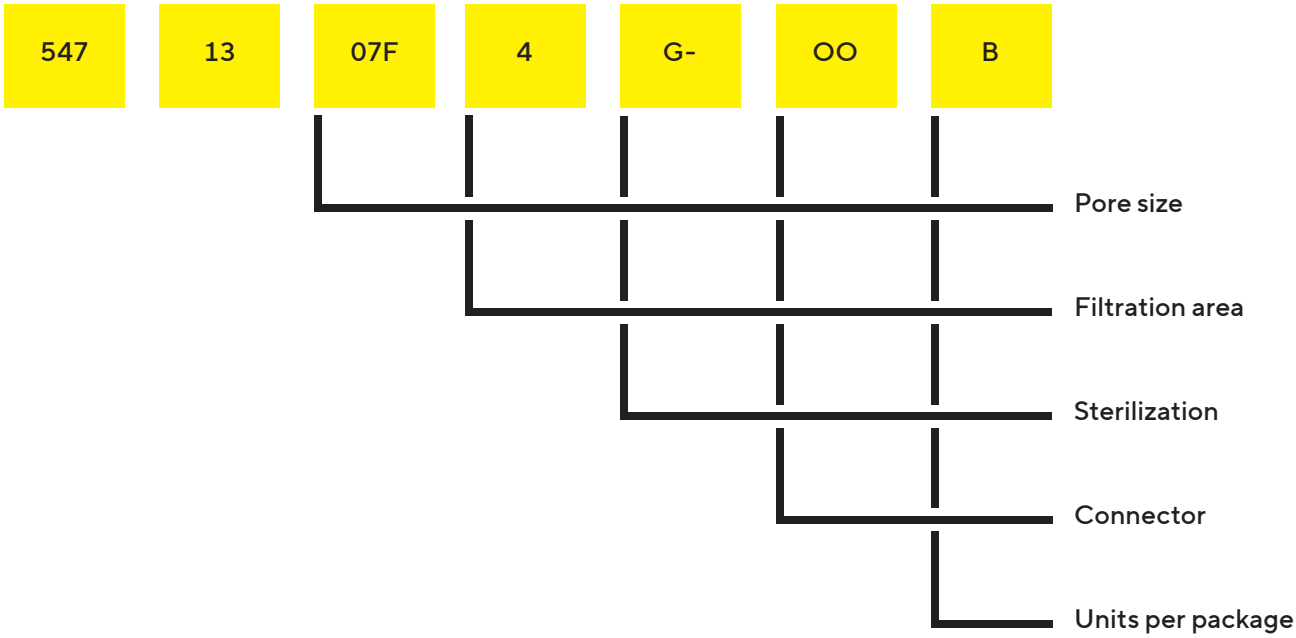
Connectors
S Tri-clamp 50 mm (1½")
O ½ single stepped hose barb

Sterilization
G- γ-irradiatable
-- autoclavable

Units per package
A Four pieces
V Two pieces

Note
The first code letter of the connector code represents the inlet, the second code letter represents the outlet connector.

2.1.5 Capsules Size 4



Explanation

547
Sartoguard PES heterogeneous double layer polyethersulfone membrane filter

Connectors
S Tri-clamp 25 mm (¾")
O 1¼" multiple stepped hose barb (with filling bell)

Pore size
07F 0.2 µm nominally
58G 0.1 µm nominally

Sterilization
G- γ-irradiatable
-- autoclavable

Effective filtration area
4 0.021 m^2 | 0.22 ft^2

Units per package
B Five pieces

Note
The first code letter of the connector code represents the inlet, the second code letter represents the outlet connector.

2.2 Filter Material

Hydrophilic highly asymetric; heterogeneous double layer polyethersulfone membrane filters, with the upstream filter membrane having a larger pore size than the final membrane.

2.3 Mechanism of Filtration

The retention of particles and microorganisms is achieved by a sieving mechanism through the polyethersulfone filter membrane. The throughput is enhanced through the use of fractionated filter membrane combinations where the two membranes have different retention ratings.

2.4 Pore Sizes Nominally

1.2 µm + 0.2 µm
0.8 µm + 0.1 µm

2.5 Materials of Construction

All materials meet the FDA requirements as defined in Title 21 Code of Federal Regulations. Biological reactivity testing, such as the Class VI Plastics Testing as described in the current USP, are also met and exceeded.

Upstream support layer:
Polypropylene
or
polyester (only γ-irradiatable products)

Filter membrane:
Polyethersulfone, double layer

Downstream support:
Polypropylene
or
polyester (only γ-irradiatable products)

Outer cage:
Polypropylene

Inner core:
Polypropylene

Endcaps | capsule housing:
Polypropylene

O-Rings | gaskets:
Silicone; optional:
EPDM or fluoroelastomer

2.6 Fiber Release

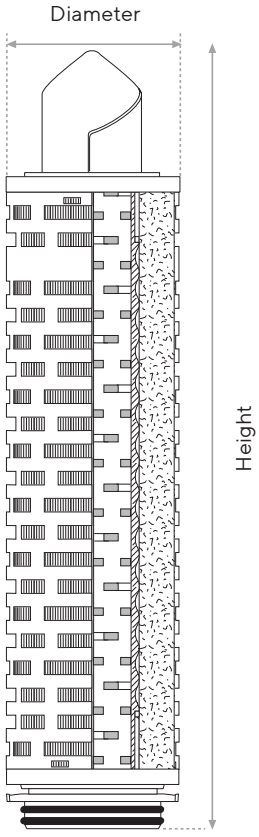
Sartoguard PES filter comply with Title 21 Code of Federal Regulations, Section 211.72 and 210.3 (b) (6) for non-fiber releasing filters.

2.7 Dimensions

2.7.1 Standard Cartridges

Adapter	Height 10" [mm]	Height 20" [mm]	Height 30" [mm]	Diameter [mm]
25	323	571	819	71

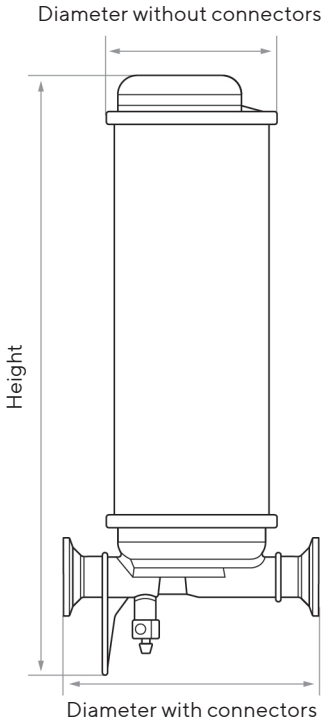
Height measurements include adapter and S-top as indicated in the drawing.



2.7.2 T-Style Maxicaps®

Total height

Size ["]	Connector Combinations [mm]				
	SS	SO	OO	SY	YY
10	390	382	382	390	390
20	639	631	631	639	639
30	889	881	881	889	889



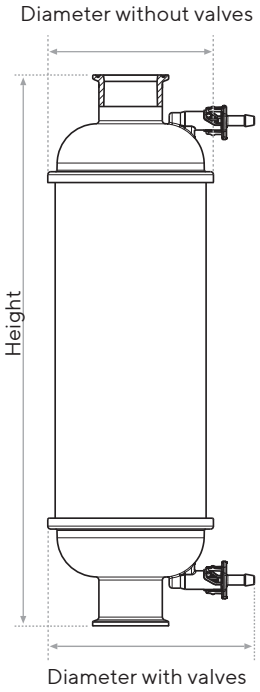
Total diameter (including connection)

Size ["]	Connector Combinations [mm]				
	SS	SO	OO	SY	YY
10	164	170	176	199	234
20	164	170	176	199	234
30	164	170	176	199	234

Total diameter (without connection)

Size ["]	All Connector Combination [mm]
10	110
20	110
30	110

2.7.3 Maxicaps® | Gamma Maxicaps®



Total height

Size ["]	Connector Combinations [mm]			
	SS	SO	OO	FF
10	363	369	375	363
20	617	623	629	617
30	867	873	879	867

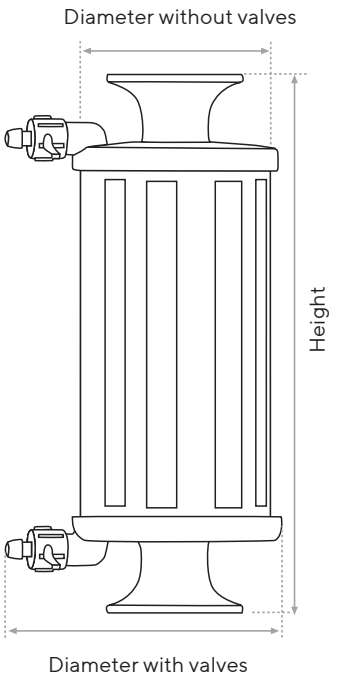
Total diameter

Size ["]	All Connector Combinations [mm]	
	including valves	without valves
10	137	137
20	137	137
30	137	137

2.7.4 Midicaps®

Total height

Size	Connector Combinations [mm]			
	SS	SO	OO	FF
0	332	339	345	331
9	199	206	212	198
8	149	156	162	148
7	115	121	128	114



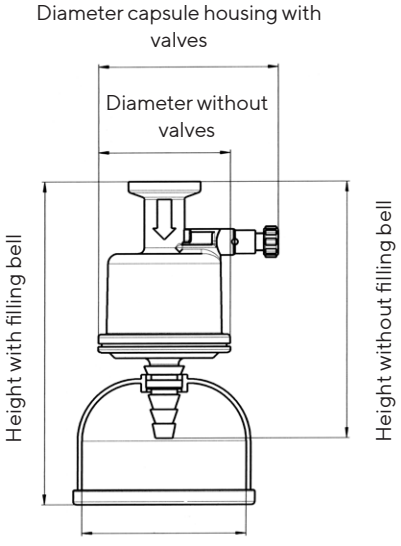
Total diameter

Size	All Connector Combinations [mm]	
	including valves	without valves
0	109	77
9	109	77
8	109	77
7	109	77

2.7.5 Capsules Size 4

Total height (without filling bell)

Size	Connector Combinations [mm]		
	SO	OO	SS
4	89	101	86



Total height (with filling bell)

Size	Connector Combinations [mm]	
	SO	OO
4	112	125

Total diameter

Size	All Connector Combinations [mm] (without Valves)
4	46

2.8 Maximal Allowable Differential Pressure

The maximum allowable differential pressure depends on the temperature at which the pressure is exerted. Maximum allowable differential pressures in the direction of filtration.

2.8.1 Cartridges

Temperature [°C]	20	80	121	134
Pressure [bar]	5	2	1.5	0.5
Pressure [psi]	72.5	29	22	7

2.8.2 T-Style Maxicaps®

Temperature [°C]	20	50
Pressure [bar]	5	3
Pressure [psi]	72.5	43.5

2.8.3 Midicaps®

Temperature [°C]	20	80
Pressure [bar]	5	2
Pressure [psi]	72.5	29

2.8.4 Capsules Size 4

Temperature [°C]	20	80
Pressure [bar]	4	2
Pressure [psi]	58	29

2.9 Maximum Back Pressure for Cartridges, T-Style Maxicaps®, Midicaps® and Capsules

The maximum allowable pressure in reverse of the direction of filtration:

Temperature [°C]	20	100	121	134
Pressure [bar]	2	1	0.5	0.3
Pressure [psi]	29	14.5	7	4

2.10 Wetting the Filters for Integrity Testing

For each filter element, rinse the filters in the direction of flow for 5 minutes with a differential pressure of 0.3 bar | 4 psi backpressure 0.5 bar | 7 psi in order to assure that the filters have been wetted completely. Generally, filters are wetted with water. In cases where a different wetting medium is used, if the surface tension of the fluid is different from water (> 70 dynes/cm), different integrity test values than indicated on the next page may be required.

2.11 Sterilization

Autoclaving of wet filter cartridges, T-Style Maxicaps®, Midicaps® and capsules up to a maximum temperature of 134 °C, for 30 minutes

or

In-line steam sterilization of wetted cartridges with a maximum of 2.3 bar | 34 psi inlet pressure and 2 bar | 29 psi outlet pressure (max. Δp= 0.3 bar | 5 psi).

T-Style Maxicaps® can be sterilized by gamma irradiation (max. 50 kGy) or alternatively by autoclaving.

Note

T-Style Maxicaps®, Midicaps® and capsules cannot be in-line steam sterilized.

2.12 Integrity Tests Limits

2.12.1 Cartridges | Maxicaps® | T-Style Maxicaps®

Pore Size [µm]	Height ["]	Test Pressure [bar	psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar	psi]
0.2	10	1.2	17.5	18	1.8	26
	20	1.2	17.5	36	1.8	26
	30	1.2	17.5	54	1.8	26
0.1	10	1.5	22	25	2.8	40.5
	20	1.5	22	50	2.8	40.5
	30	1.5	22	75	2.8	40.5

2.12.2 Midicaps®, Capsules Size 4

Pore Size [µm]	Size	Test Pressure [bar	psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar	psi]
0.2	4	1.2	17.5	1.1	1.8	26
	7	1.2	17.5	3	1.8	26
	8	1.2	17.5	4	1.8	26
	9	1.2	17.5	6	1.8	26
	0	1.2	17.5	12	1.8	26
0.1	4	1.5	22	1.1	2.8	40.5
	7	1.5	22	3	2.8	40.5
	8	1.5	22	6	2.8	40.5
	9	1.5	22	9	2.8	40.5
	0	1.5	22	18	2.8	40.5

3. Flow Rates

Background
Test filter elements are placed into individual Sartorius filter housings (Sartorius housings, Type 340011P25TT112A or 331019P15TT112A). Capsules are directly installed into the piping system, using sanitary flanges. The piping system to and from the filters has an inner diameter of 25 mm | 1 inch resp. 15 mm | 0.6 inch. The water inlet is opened and the filter housings are completely vented.

The filters are rinsed for approximately 5 minutes at 0.3 bar | 4 psi differential pressure to assure complete wetting. The filter elements are then integrity tested to assure that only integral filters are tested. The inlet pressure (Pi) is held constant at 2.5 bar | 36 psi.

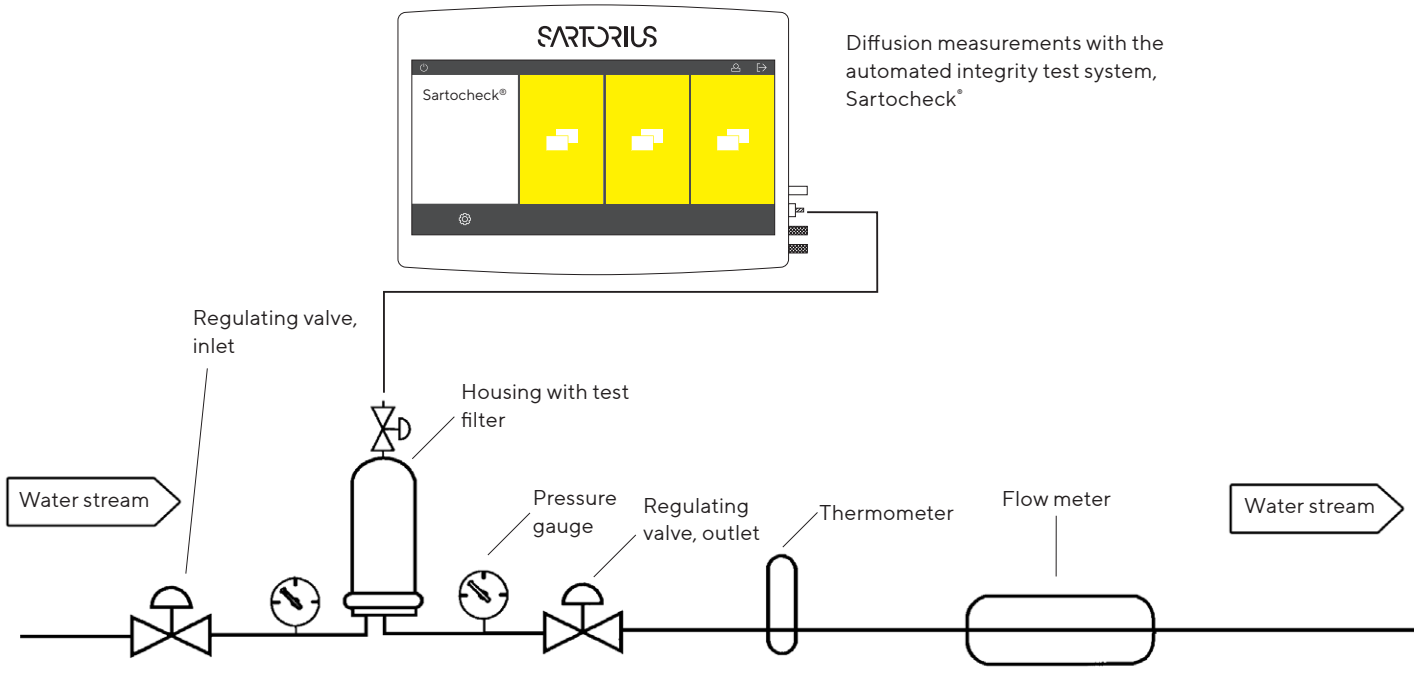
Through the adjustment of valves on the downstream side of the filter housing, the required differential pressure for the test measurements is established. After achieving a constant differential pressure, the flow rate is recorded from the flow meter and the temperature is noted. The flow meter used in this testing was a Fisher & Porter COPA XM Magnetic Inductive Flow Meter Model D10D1465.

Results
The flow rate curves for water through Sartoguard PES filter elements of the various filtration areas versus differential pressure are on the following pages.

Note
The flow rate is strongly influenced by the viscosity of the medium being filtered. For this reason, all flow rate measurements are taken at 20 °C so that the influence of temperature on viscosity is not a factor.

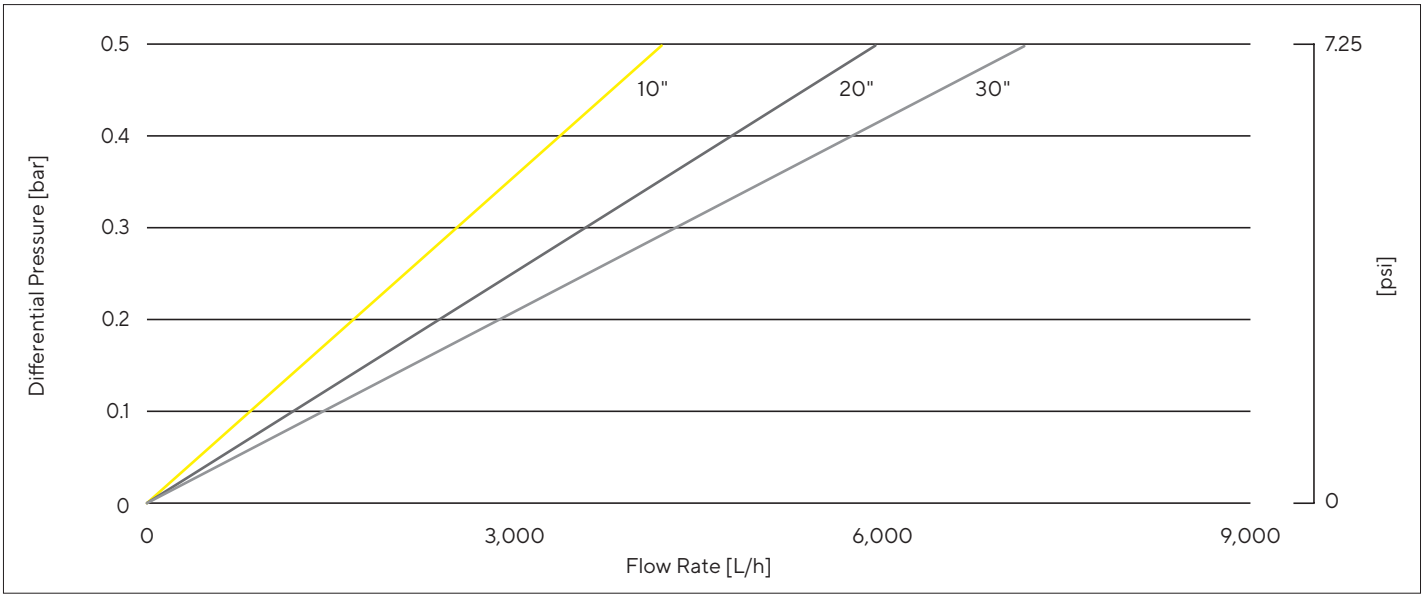
For flow rate measurements of 20" and 30" filter elements, the flow rates reach a point where the geometry of the piping and the filter housing begin to contribute to the overall differential pressure (resistance to flow). At a flow rate of approximately 7,000 L/h (120 L/min), the filter membrane surface area is no longer the flow limiting factor, but the housing and piping system begin to have increasing effects on differential pressure. For this reason the flow rates are only recorded at limited differential pressures.,

Test set-up

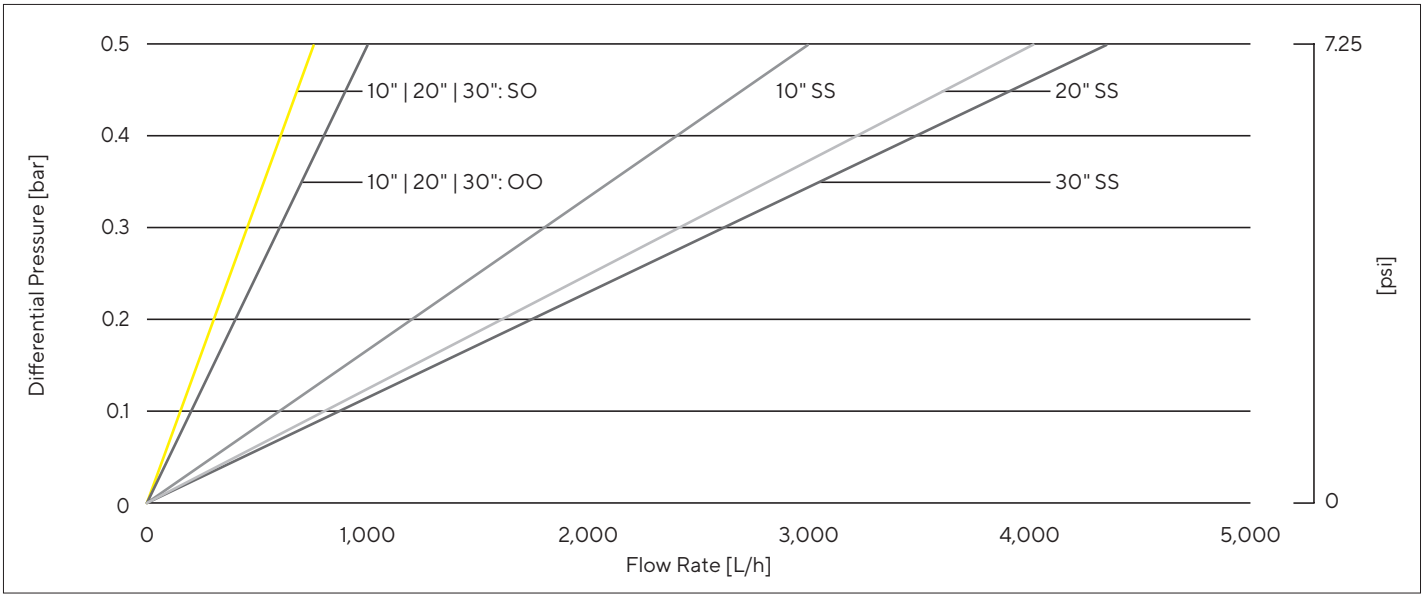


3.1 Sartoguard PES 0.2 µm Nominally

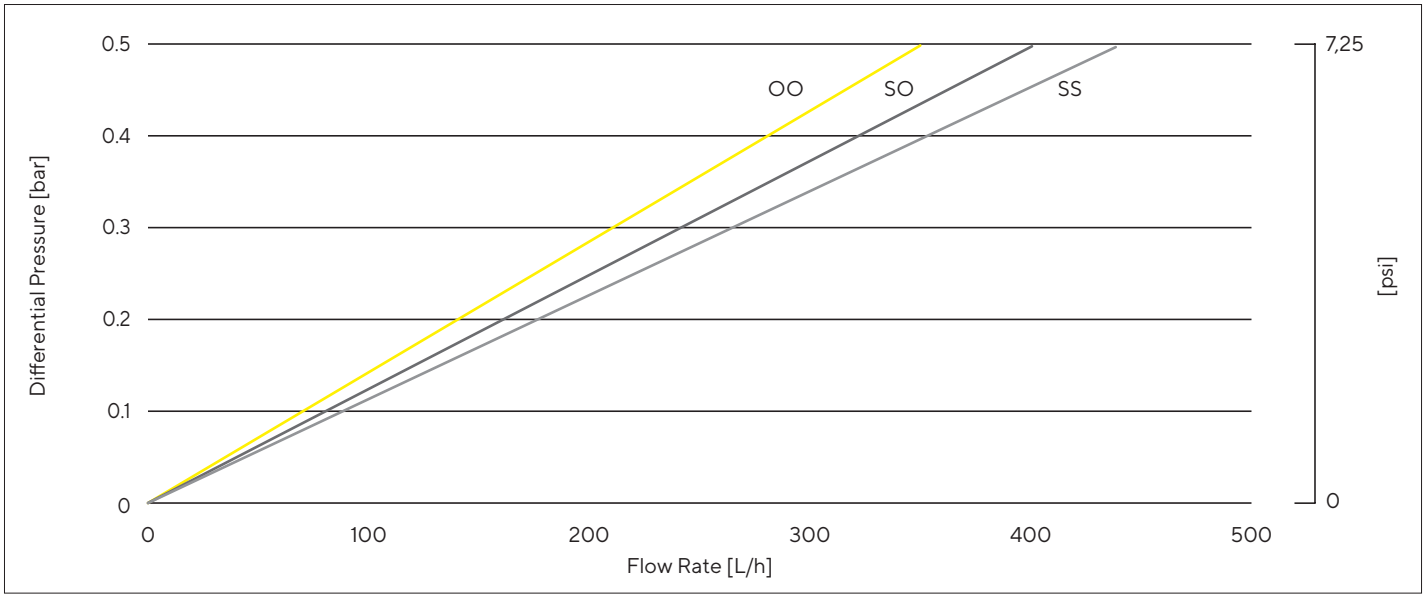
3.1.1 Water Flow Rates for Standard Cartridges



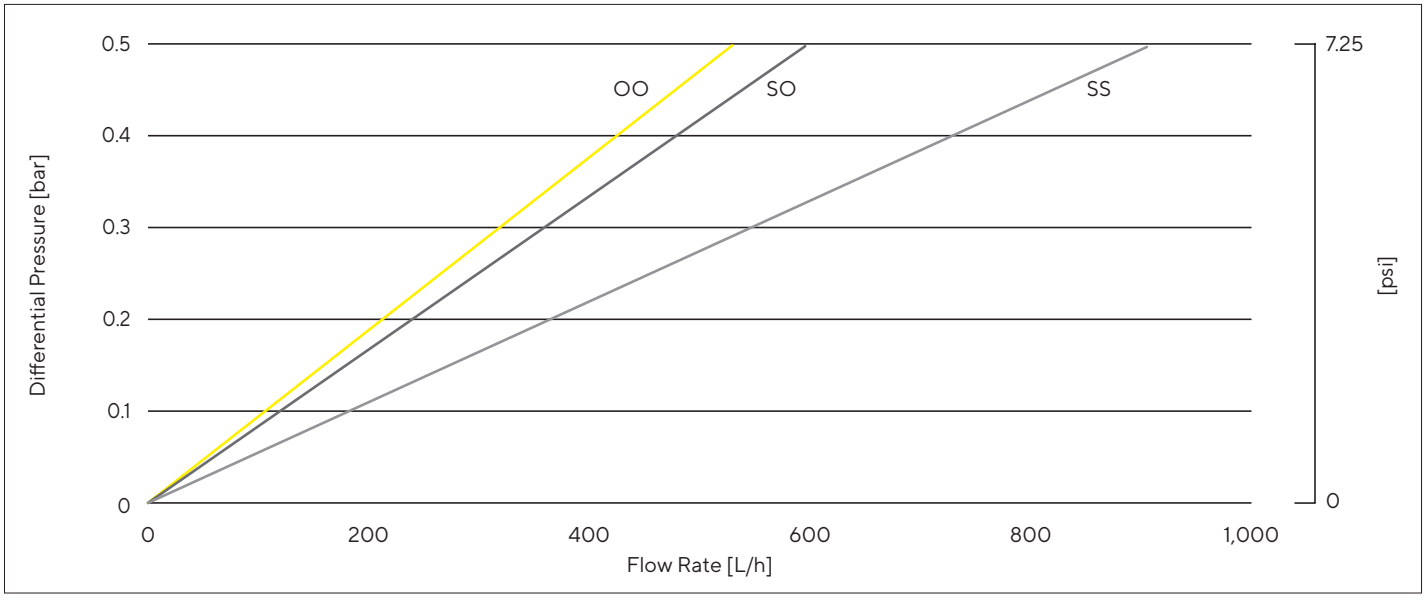
3.1.2 Water Flow Rates for T-Style Maxicaps®



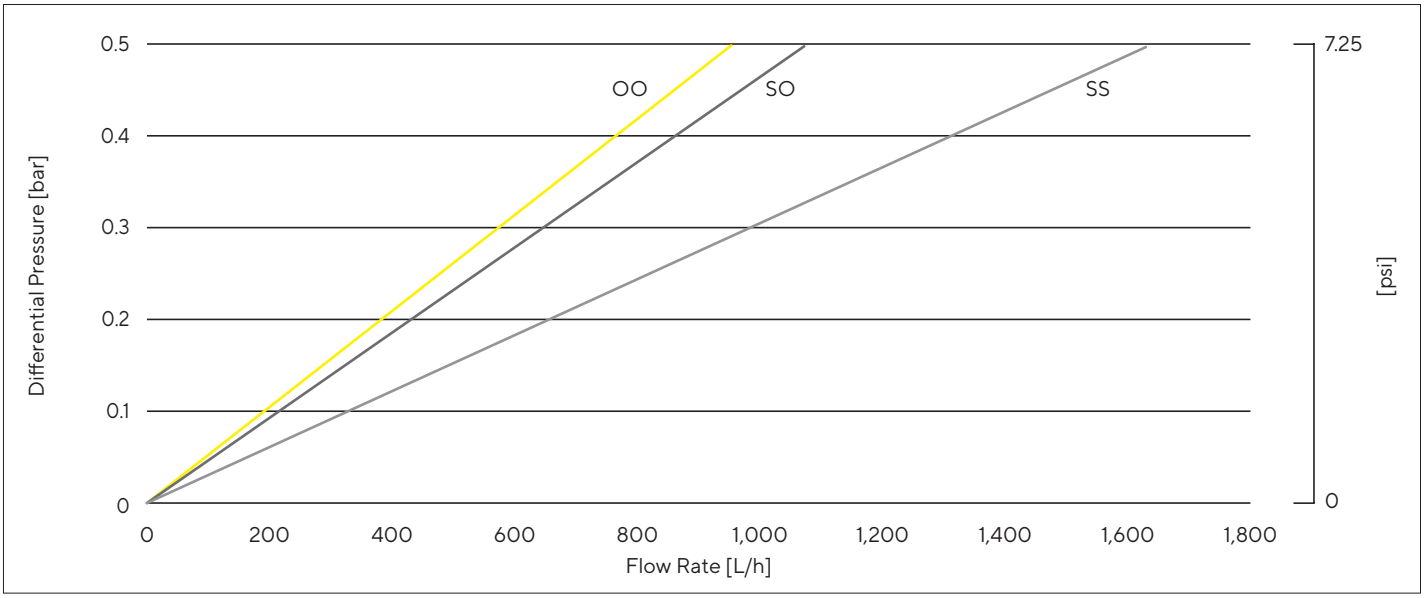
3.1.3 Water Flow Rates for Midicaps® Size 7



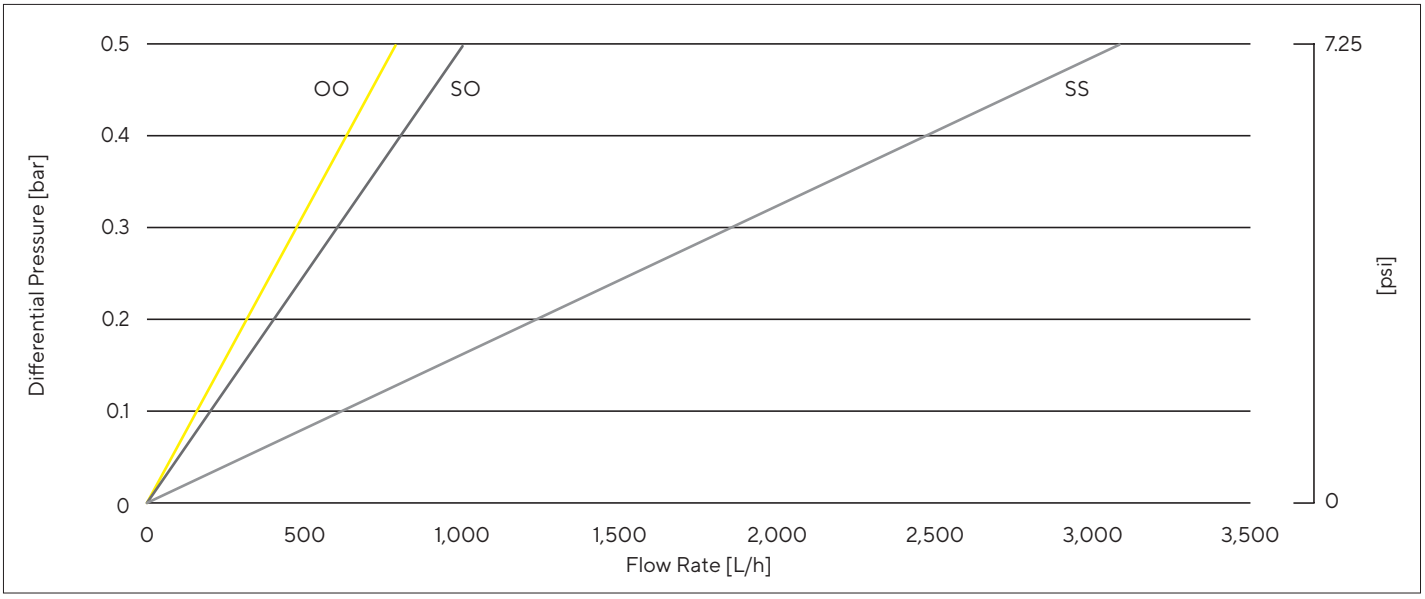
3.1.4 Water Flow Rates for Midicaps® Size 8



3.1.5 Water Flow Rates for Midicaps® Size 9

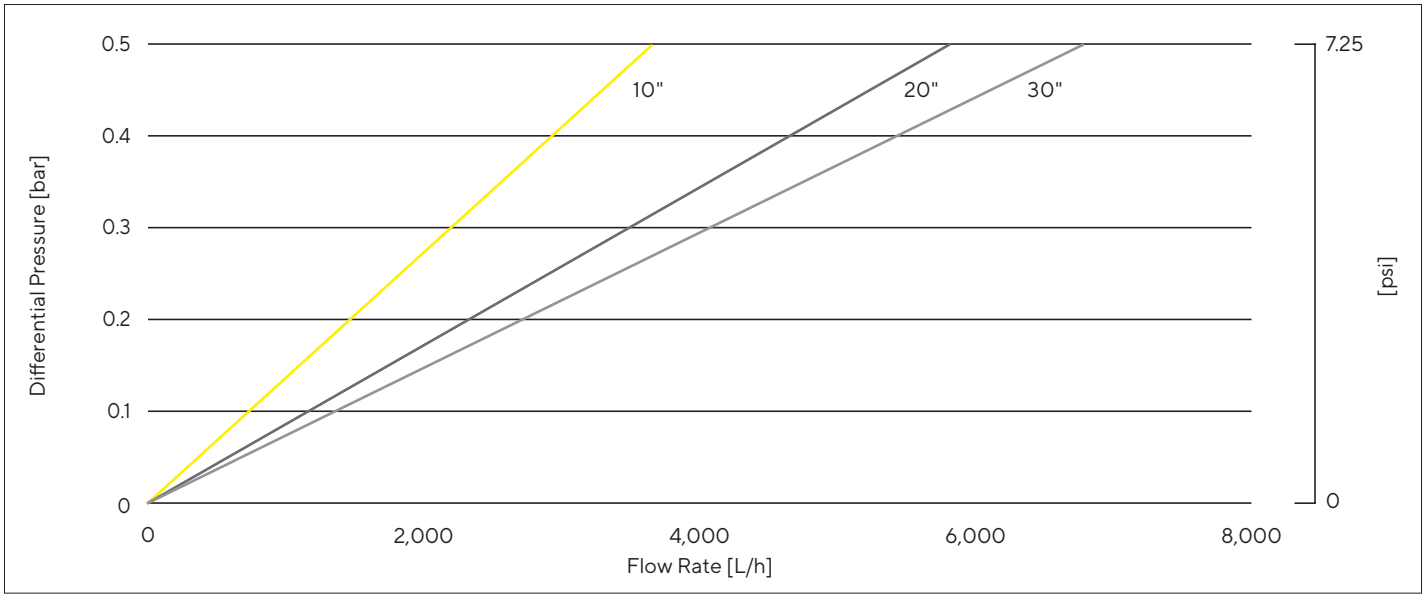


3.1.6 Water Flow Rates for Midicaps® Size 0

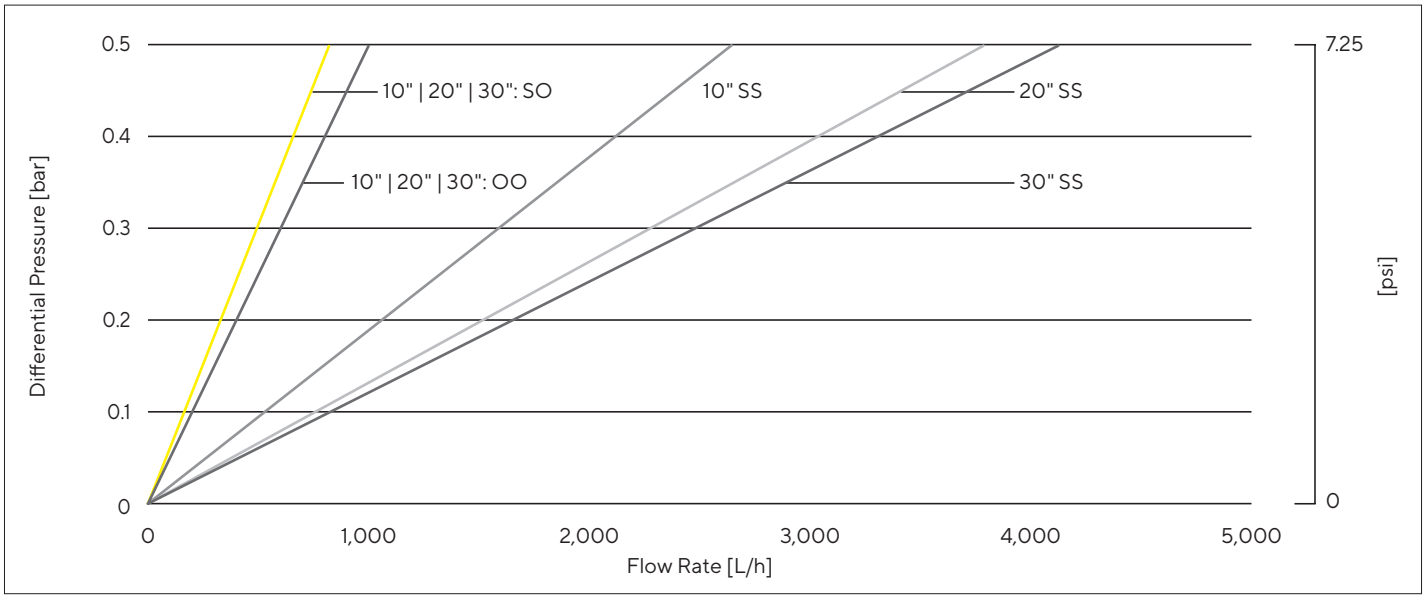


3.2 Sartoguard PES 0.1 µm Nominally

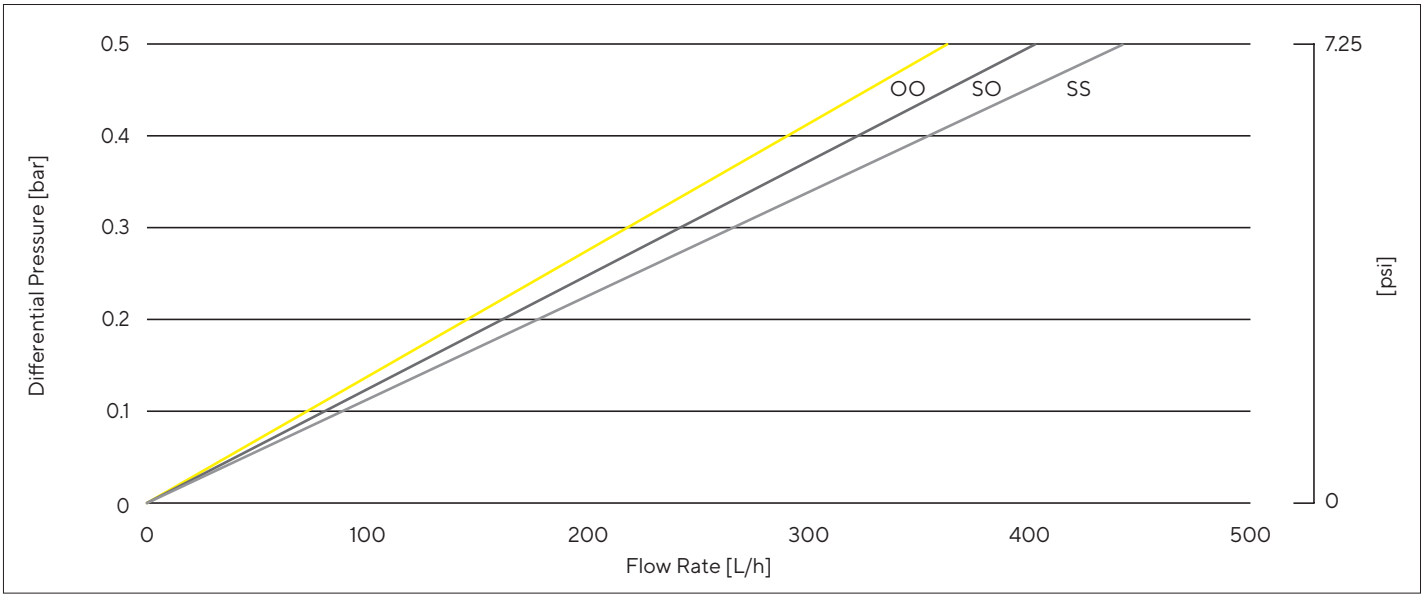
3.2.1 Water Flow Rates for Standard Cartridges



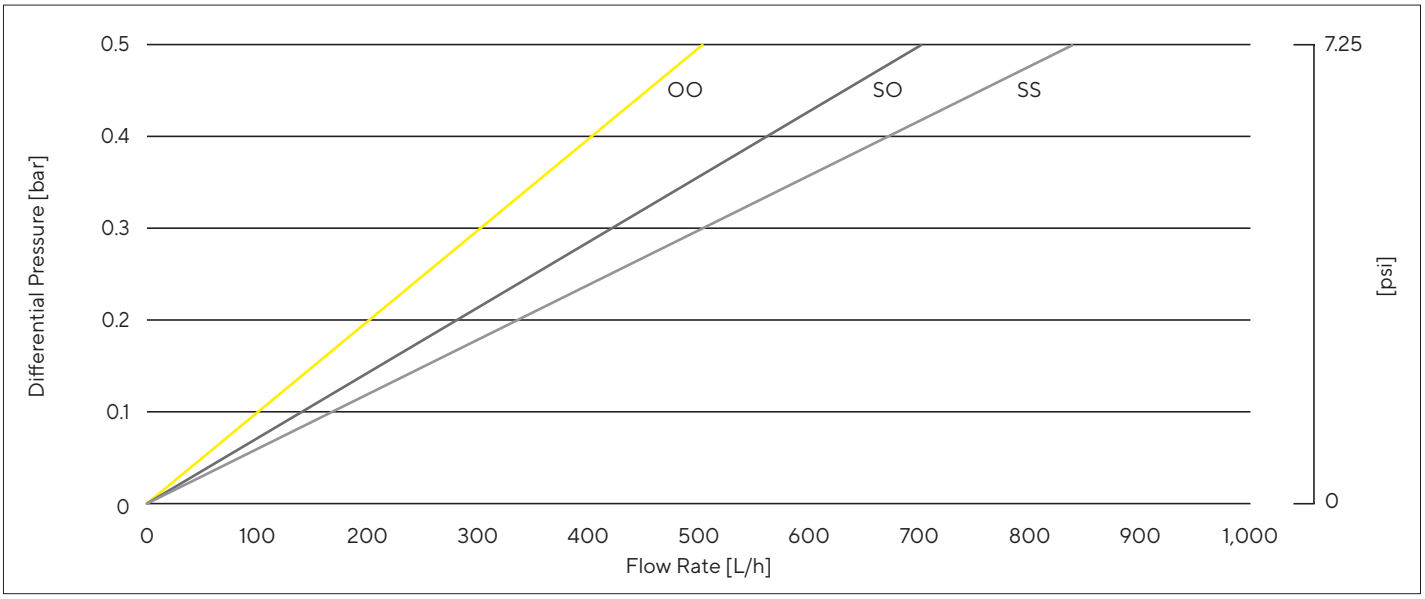
3.2.2 Water Flow Rates for T-Style Maxicaps®



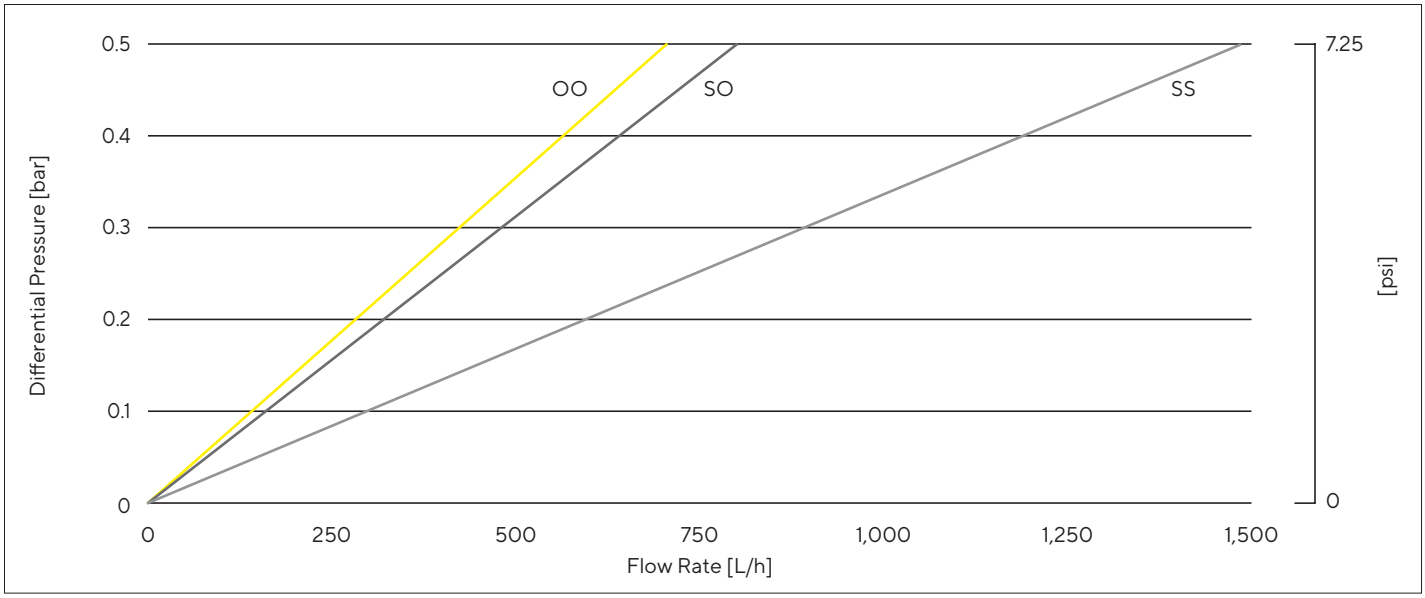
3.2.3 Water Flow Rates for Midicaps® Size 7



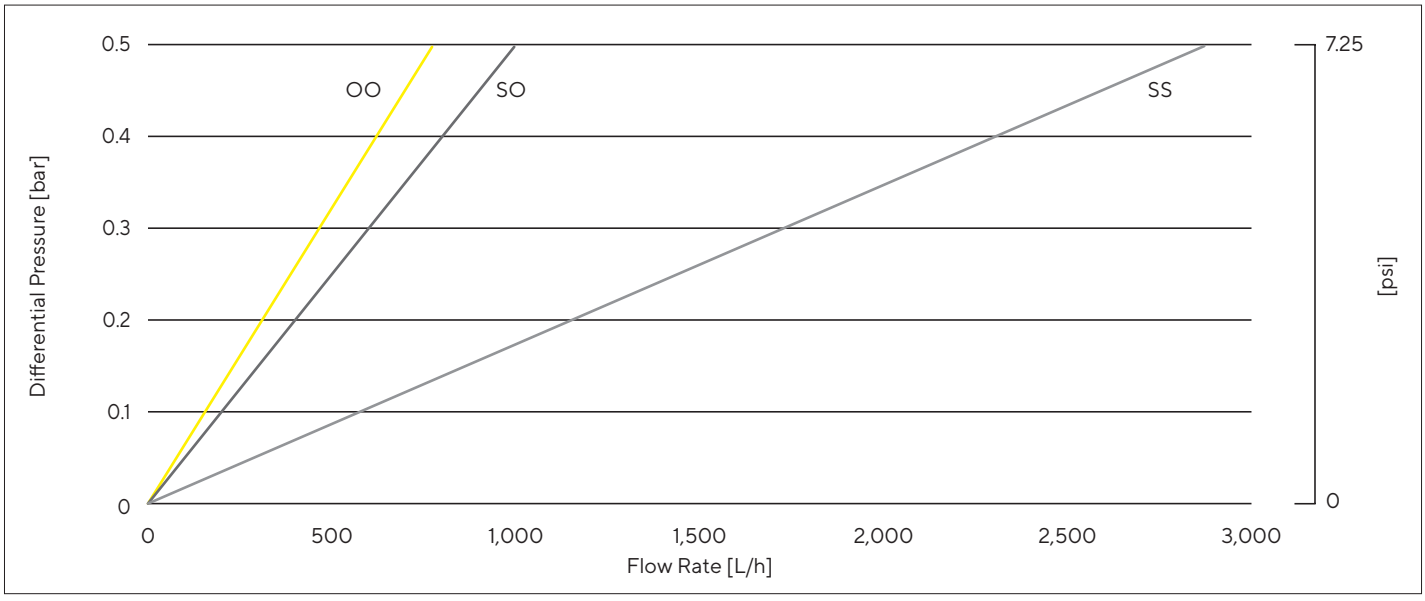
3.2.4 Water Flow Rates for Midicaps® Size 8



3.2.5 Water Flow Rates for Midicaps® Size 9



3.2.6 Water Flow Rates for Midicaps® Size 0



4. Chemical Compatibility – Sartoguard PES

Compatibility measurement with complete filter element, but different O-ring materials:

	Silicone	EPDM	Fluoroelastomer
Acids			
HCL, 30 %	■	■	■
HCL, 25 %	■	■	■
HNO_3, 10 %	■	■	■
HNO_3, 65 %	□	□	■
H_2SO_4, conz.	--	--	--
H_SO_4, 25 %	□	■	■
H_3PO_4, 25 %	□	■	■
Formic acid, conz.	--	□	--
Formic acid, 25 %	□	■	□
Acetic acid, conz.	□	■	□
Acetic acid, 25 %	--	■	□
Trichloracetic acid, 25 %	□	■	--
Trichloracetic acid, 10 %	□	■	--
Citric acid	■	■	■
Tartaric acid	■	■	■
Lactic acid	■	■	■
Bases			
Ammonia, 10 %	□	■	--
Ammonia, 30 %	--	■	--
NAOH, 1 M	□	■	□
NAOH, 2.5 M	--	■	--
KOH, 1 M	□	■	□

	Silicone	EPDM	Fluoroelastomer
Solvents			
Acetone	--	--	--
Cyclohexanone	--	--	--
Methyl ethyl ketone	--	--	--
Methylisobutyketone	--	□	--
Diethylether	□	□	□
Methanol, 98 %	■	■	■
Ethanol, 10 %	■	■	■
Ethanol, 98 %	■	■	■
Isopropanol	■	■	■
n-Propanol	■	■	■
n-Amylalcohol	■	■	□
n-Butanol	■	■	■
Glycerol	■	■	■
Etyleneglycol	■	■	■
Methyleneglycol	■	■	■
Dioxane	--	--	--
Tetrahydrofuran	--	--	--
Dimethylsulfoxide	--	--	--
Dimethylformamide	--	--	--
Triethanolamine	□	□	■

Legend

■ = Compatible

□ = Limited compatibility depending on concentration, temperature etc.

-- = Not compatible

Test specifications

7 days contact at 20 °C

Important

Compatibility is influenced by various factors, such as temperature, concentration, etc.

If necessary, test the compatibility with the solution you wish to filter before performing the actual filtration run.

	Silicone	EPDM	Fluoroelastomer
Miscellanous			
Aniline	--	--	--
Sodium hypochlorite	□	■	■
Benzylalcohol	--	--	--
Phenol, 10%	--	--	--
Formalin, 30%	■	■	■
Hexane	□	□	■
Xylene	--	--	--
Toluene	--	--	--
Benzene	--	--	--
Tetralin	--	--	--
Dekalin	□	--	■
Methylenchloride	--	--	--
Chloroform	--	--	--
Carbontetrachloride	--	--	--
Trichloreethylene	--	--	--
Perchloreethylene	--	--	■
Monochlorbenzol	--	--	--
Methylacetate	--	--	--
Ethylacetate	--	--	--
Amylacetate	□	■	--
Propylacetate	□	■	--
Terpentine	□	--	■
H_2O_2, 0.3%	■	■	■
Ammoniumpersulfat, 25%	■	■	■
Sodiumhypochloride, 5%	■	■	■
Starch solution	■	■	■
Water	■	■	■

Legend

■ = Compatible

□ = Limited compatibility depending on concentration, temperature etc.

-- = Not compatible

Test specifications

7 days contact at 20 °C

Important

Compatibility is influenced by various factors, such as temperature, concentration, etc.

If necessary, test the compatibility with the solution you wish to filter before performing the actual filtration run.

5. Thermal Stability

5.1 Thermal Stability of Cartridges

The materials and construction of the Sartoguard PES filter cartridges allow for exposures to multiple steam sterilization cycles. Since multiple steam sterilization cycles may be required in actual practice, the influences of the thermo-mechanical stresses on the integrity of Sartoguard PES filter cartridges were examined. As a result, recommendations and limits for multiple in-line steam sterilization are given.

Test method
Sartoguard PES standard filter cartridges from a number of different production lots, were installed into stainless steel filter housing (Sartorius Part Number 340011P25TT112A) and were in-line sterilized with saturated steam at 2 bar | 29 psi for 30 minutes after reaching a steaming temperature of 134 °C (measured at the outlet of the housing). Additionally, the differential pressure was held constant and did not exceed 0.3 bar | 4 psi during steam sterilization. After the steam sterilization cycle, the steam pressure is allowed to drop to atmosphere (in about 3 to 5 minutes) and the system is cooled by filtration with water at a differential pressure of 0.2 to 0.3 bar (3 to 4 psi) for 5 minutes. The in-line steam cycle is then repeated. Before beginning these tests and after 25 in-line steam cycles, the integrity of the cartridges is verified through diffusion testing, as well as the water flow rates.

Important note for in-line steam sterilization
After the installation and wetting of the cartridges, the upstream vent valve on the filter housing, all drainage and inlet and outlet valves on the filter housing should be slightly opened and the steam inlet valve should be opened slowly to allow for a slow steam stream coming into the filter system. During the initial phase of pressure increase, the maximum differential pressure should not exceed 0.5 bar | 7 psi. As soon as steam is passing through the outlet valve of the housing, the inlet and outlet valves should be manipulated so that the outlet pressure is not more than 2 bar | 30 psi. Additionally, the inlet pressure should not be more than 0.2 to 0.3 bar (3 to 4 psi) above the sterilization pressure. After steam sterilization pressures have been achieved, the filters are steamed for 30 minutes under these conditions. After steaming and closing of the steam inlet valve, the upstream and downstream pressures are allowed to drop to atmospheric pressure, the drain valves are closed and the venting valve is opened. If cooling is required to be faster, the system can be rinsed with water at a differential pressure of 0.2 to 0.3 bar (3 to 4 psi). In order to assure that the filters are not chemically attached during steaming, only steam generated with pure water should be used. Water with corrosion reducing agents, which may produce hydrazine or an alkaline steam, should not be used.

In order to demonstrate that the Sartoguard PES cartridges have good thermal stability, three cartridges from three different manufacturing lots were tested under the following procedure:

1. **The new filter cartridges are wetted with water.**
2. **The filters are then integrity tested by diffusion and bubble point tests. The flow rates were also recorded for these new filters.**
3. **The filters are then steam sterilized 25 times.**
4. **After the 25 cycles, the filters are integrity tested by diffusion tests. The flow rates were also recorded.**

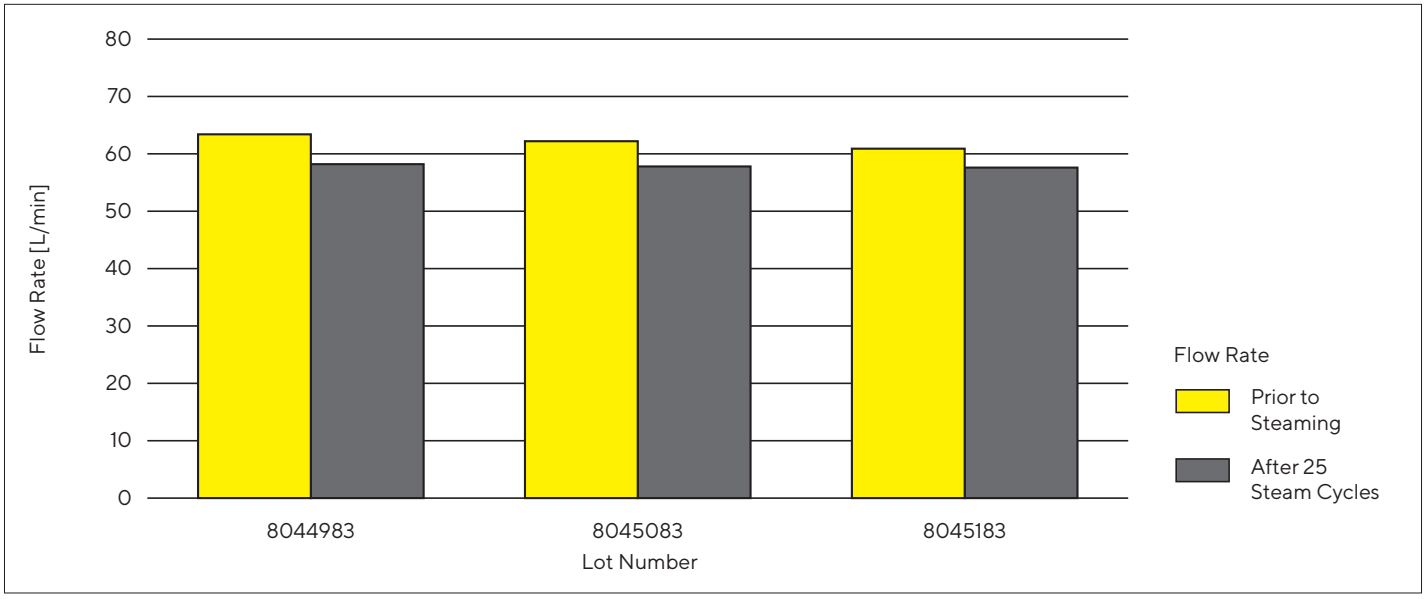
5.1.1 Effects on Water Flow Rates

Test procedure
Six Sartoguard PES standard cartridges from three different lot numbers were installed and wetted in standard filter housings. The flow rate was measured at a differential pressure of 0.5 bar | 7 psi. The following table contains the average values for the six cartridges tested.

Flow rate values have been standardized at 20 °C.

5.1.1.1 Standard Cartridges

Lot Number	Flow Rate Prior to Steaming [L/min]	Flow Rate After 25 Steam Cycles [L/min]
8044983	63.4	58.2
8045083	62.2	57.8
8045183	61.9	57.6



5.1.2 Effects on Diffusion Values

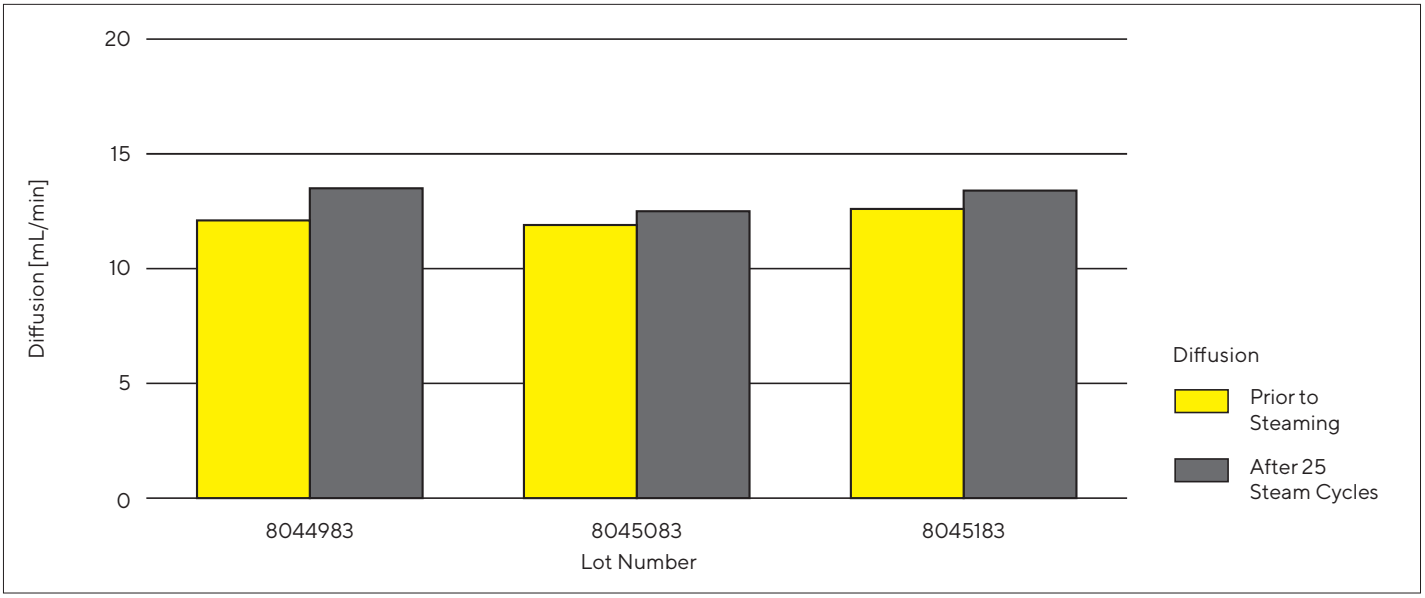
Test procedure
Six Sartoguard PES cartridges from three different production lots were wetted in standard filter housings. A Diffusion Test utilizing the following parameters was conducted utilizing an automated integrity test system, the Sartocheck®.

Test pressure: 1.5 bar | 22 psi
Stabilization time: 5 minutes
Test time: 5 minutes

The following results are the averages for the six cartridges tested.

5.1.2.1 Standard Cartridges

Lot Number	Diffusion Prior to Steaming [L/min]	Diffusion After 25 Steam Cycles [L/min]
8044983	11.1	12.6
8045083	10.9	12.5
8045183	11.0	12.4

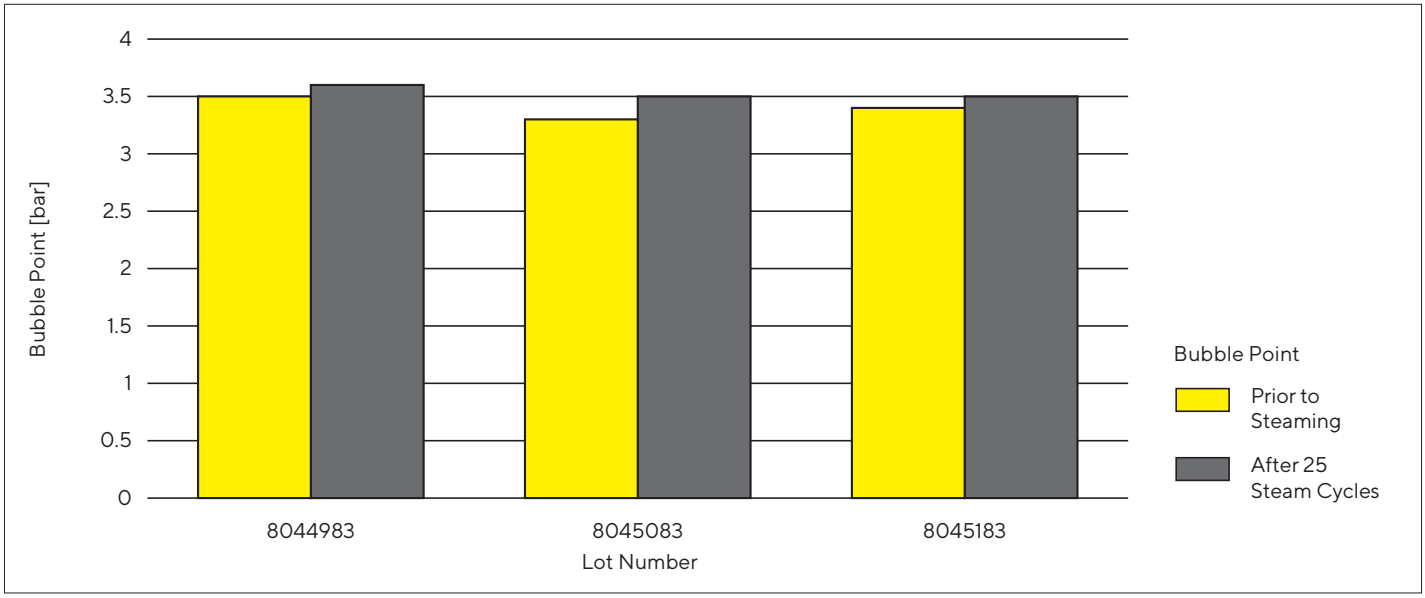


5.1.3 Effects on Bubble Point Values

Test procedure
After diffusion testing, the same Sartoguard PES cartridges are then tested by the bubble point test, utilizing the Sartocheck® automated integrity test system. The following results are the averages for the elements tested.

5.1.3.1 Standard Cartridges

Lot Number	Bubble Point Prior to Steaming [bar	psi]	Bubble Point After 25 Steam Cycles [bar	psi]
8044983	3.5	51	3.6	52
8045083	3.3	48	3.5	51
8045183	3.4	49	3.5	51



5.2 Sterilization of T-Style Maxicaps®, Midicaps® and Capsules

The materials and construction of the Sartoguard PES T-Style Maxicaps®, Midicaps® and capsules allow for exposures to multiple autoclaving cycles. Since multiple autoclaving cycles may be required in actual practice, the influences of the thermo-mechanical stresses on the integrity of Sartoguard PES T-Style Maxicaps®, Midicaps® and capsules were examined. As a result, recommendations and limits for multiple autoclaving are given.

Test method
Sartoguard PES T-Style Maxicaps®, Midicaps® and capsules, with a pore size of 0.2 µm from a number of different production lots, were installed and were autoclaved at 2 bar | 30 psi and a temperature of 134 °C for 30 minutes. Before beginning these tests and after 25 autoclaving cycles, the integrity of the T-Style Maxicaps®, Midicaps® and capsules is verified through diffusion and bubble point testing, as well as the water flow rates.

For T-Style Maxicaps®, tests have also been performed after sterilization by 50 kGy gamma irradiation (1 cycle).

In order to demonstrate that the Sartoguard PES T-Style Maxicaps®, Midicaps® and capsules have good thermal stability, multiple filter elements from three different manufacturing lots were tested under the following procedure:

1. **The new T-Style Maxicaps®, Midicaps® and capsules are wetted with water.**

2. **The filters are then integrity tested by bubble point and diffusion test. The flow rates were also recorded for these T-Style Maxicaps®, Midicaps® and capsules.**

3. **Autoclaving cycles:**
   - T-Style Maxicaps®: 5
   - Midicaps® and capsules: 5

4. **After autoclaving, the flow rates of the T-Style Maxicaps®, Midicaps® and capsules were recorded again.**

After autoclavig, the T-Style Maxicaps®, Midicaps® and capsules are integrity tested by bubble point and diffusion tests. The flow rates were also recorded.

T-Style Maxicaps® can be sterilized by gamma irradiation (max. 50 kGy) or alternatively by autoclaving.

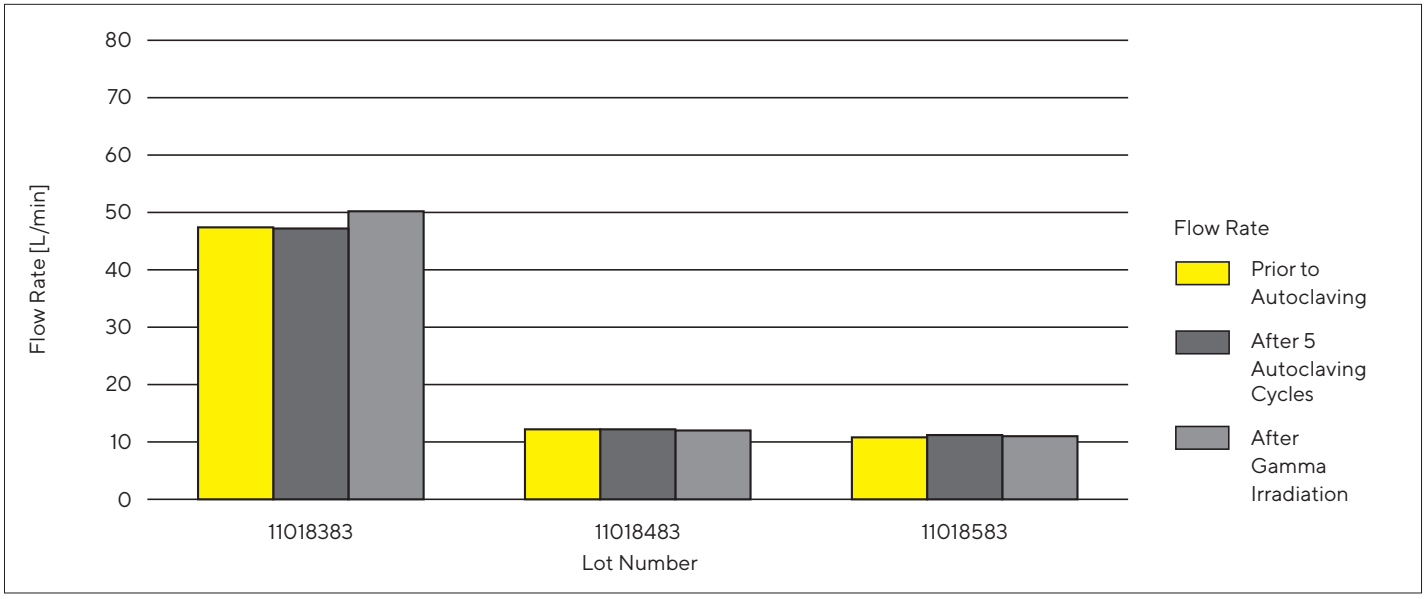
5.2.1 Effects on Water Flow Rates

Test procedure
Sartoguard PES T-Style Maxicaps® and Midicaps® each from three different lot numbers were installed and wetted. The flow rate was measured at a differential pressure of 0.5 bar | 7 psi. The following table contains the average values for the capsules tested.

Flow rate values have been standardized at 20 °C.

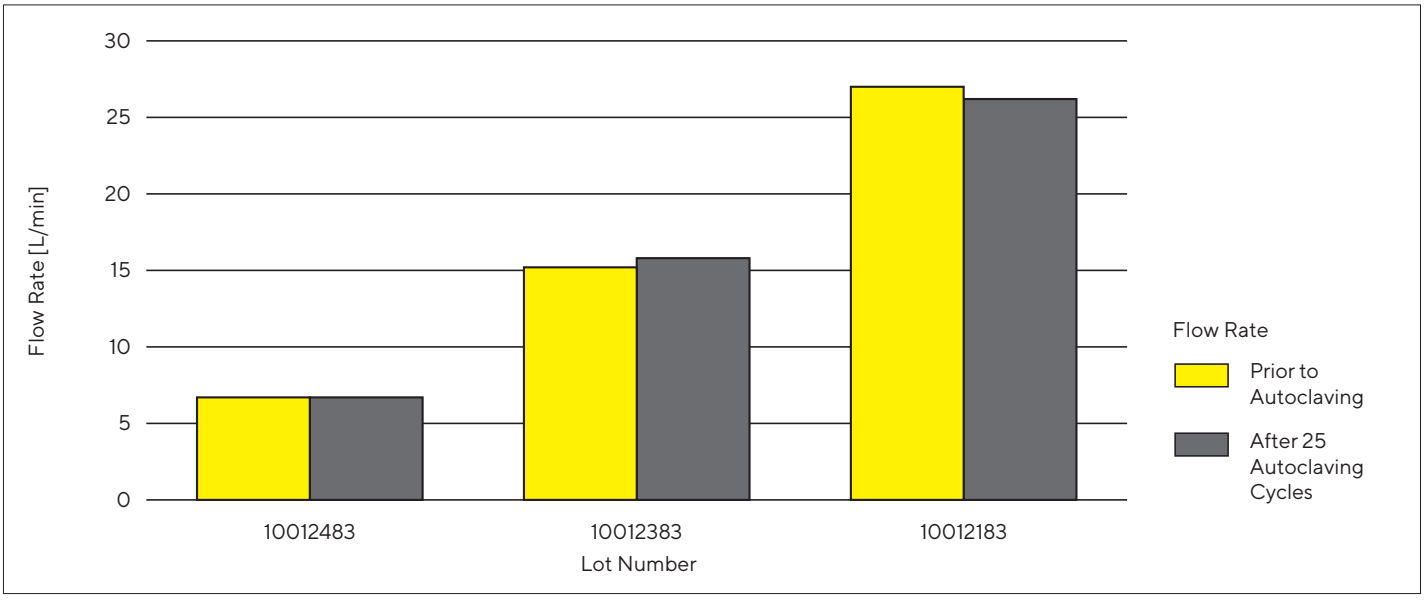
5.2.1.1 T-Style Maxicaps®

Lot Number	Flow Rate Prior to Autoclaving [L/min]	Flow Rate After 5 Autoclaving Cycles [L/min]	Flow Rate After Gamma Irradiation (50 kGy) [L/min]
11018383	47.4	47.2	50.2
11018483	12.2	12.2	12
11018583	10.8	11.2	11



5.2.1.2 Midicaps® 0.2 µm Nominally

Lot Number	Flow Rate Prior to Autoclaving [L/min]	Flow Rate After 25 Autoclaving Cycles [L/min]
10012483	6.7	6.7
10012383	15.2	15.8
10012183	27.0	26.2



5.2.2 Effects on Diffusion Values

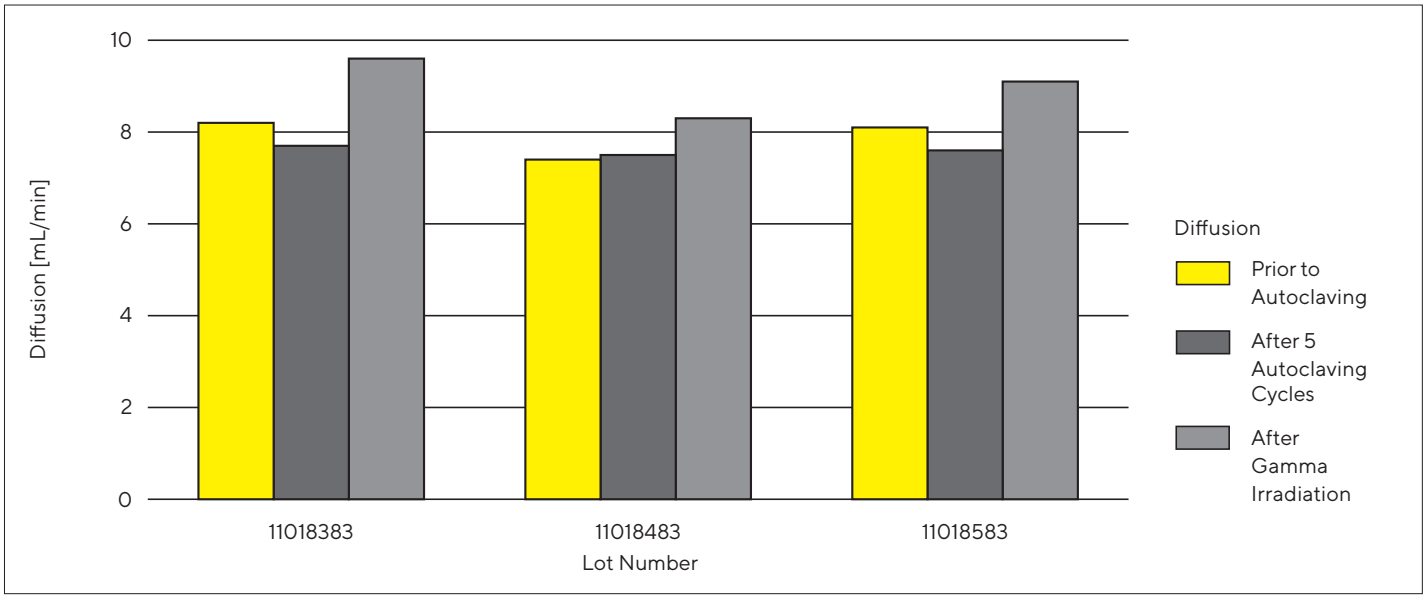
Test procedure
Sartoguard PES T-Style Maxicaps® and Midicaps® each from three different production lots were wetted. A Diffusion Test utilizing the following parameters was conducted utilizing an automated integrity test system, the Sartocheck®:

Test pressure: 1.2 bar | 17.5 psi
Stabilization time: 5 minutes
Test time: 5 minutes

The following results are the averages for the capsules tested.

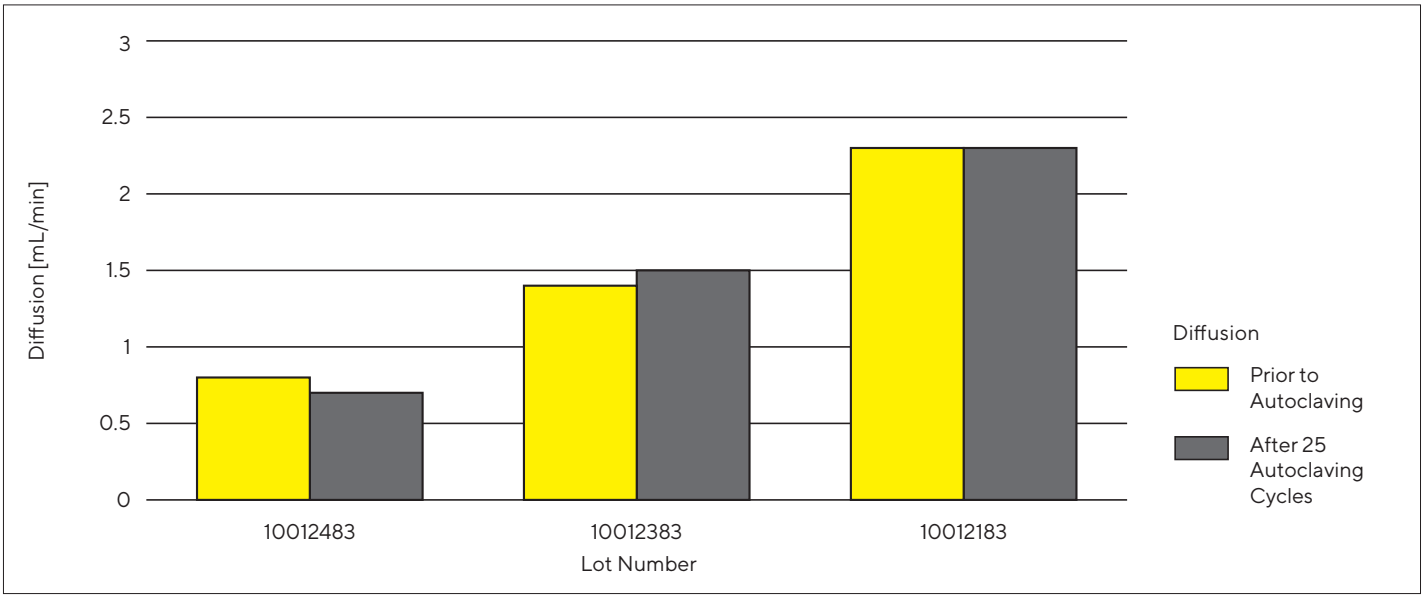
5.2.2.1 T-Style Maxicaps®

Lot Number	Diffusion Rate Prior to Autoclaving [L/min]	Diffusion Rate after 5 Autoclaving Cycles [mL/min]	Diffusion Values After Gamma Irradiation (50 kGy) [mL/min]
11018383	8.2	7.7	9.6
11018483	7.4	7.5	8.3
11018583	8.1	7.6	9.1



5.2.2.2 Midicaps® 0.2 µm Nominally

Lot Number	Diffusion Prior to Autoclaving [L/min]	Diffusion After 25 Autoclaving Cycles [L/min]
10012483	0.8	0.7
10012383	1.4	1.5
10012183	2.3	2.3

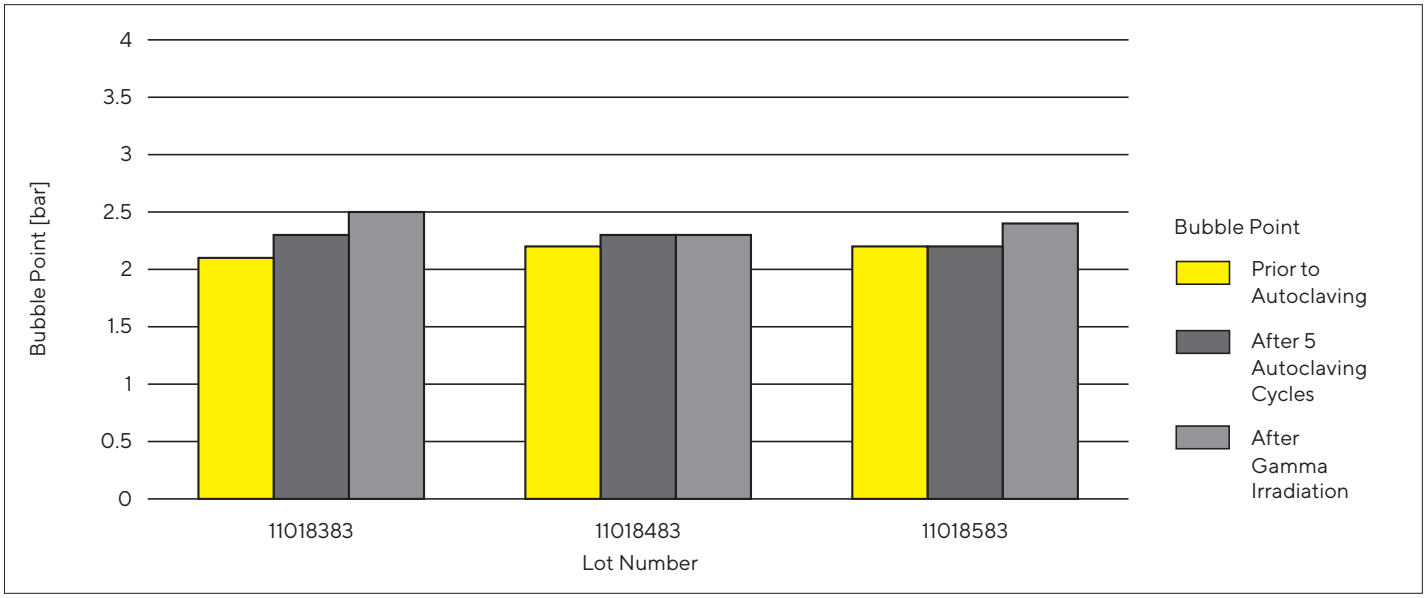


5.2.3 Effects on Bubble Point Values

Test procedure
After diffusion testing, the same Sartoguard PES T-Style Maxicaps® and Midicaps® are then tested by the Bubble Point Test, utilizing the Sartocheck® automated integrity test system. The following results are then averages for the elements tested.

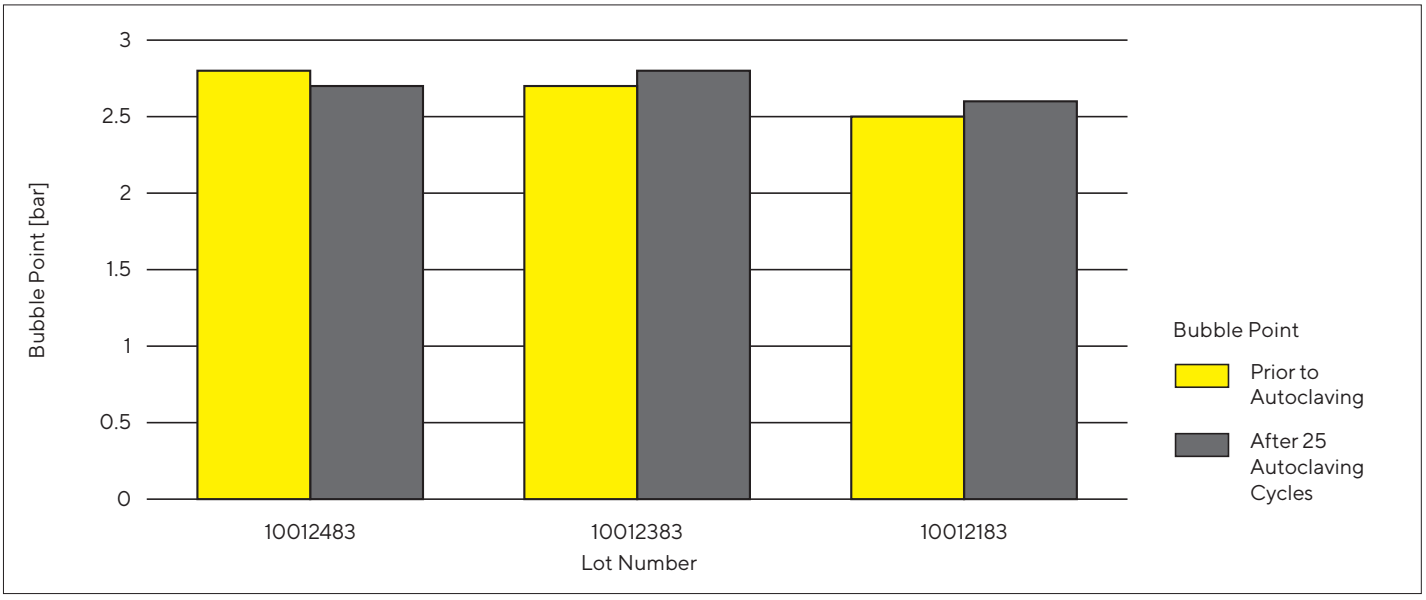
5.2.3.1 T-Style Maxicaps®

Lot Number	Bubble Point Prior to Autoclaving [bar | psi]	Bubble Point After 5 Autoclaving Cycles [bar | psi]	Diffusion Values After Gamma Irradiation (50 kGy) [bar | psi]
11018383	2.1 | 30.5	2.3 | 33.4	2.5 | 36.3
11018483	2.2 | 31.9	2.3 | 33.4	2.3 | 33.4
11018583	2.2 | 31.9	2.2 | 31.9	2.4 | 34.8



5.2.3.2 Midicaps® 0.2 µm Nominally

Lot Number	Bubble Point Prior to Autoclaving [bar | psi]	Bubble Point After 25 Autoclaving Cycles [bar | psi]
10012483	2.8 | 40.6	2.7 | 39.2
10012383	2.7 | 39.2	2.8 | 40.6
10012183	2.5 | 36.3	2.6 | 37.7



6. Testing According to USP

Test purpose
The tests for extractable substances and particle release of Sartoguard PES filter elements are performed in dynamic extraction mode. This methodology provides the best representative of actual filtration applications determining levels of extractable substances and particles present in varying filtrate volumes. The samples for all tests are taken after 1, 5 and 10 liters flush volume for standard filter elements.

According to the specifications given in section "Sterile Water for Injection" of the current USP, filtrate samples of Sartoguard PES filter elements are analyzed for particulate matter, oxidizable substances, pH and conductivity, ammonia, sulfate and chloride. The tests are performed according to the descriptions given in the current USP. The test results obtained are compared to the relevant USP specifications and for particulate matter also to the specifications of the European Pharmacopoeia (EP).

The following filter types were used for extractables and particle release testing of Sartoguard PES filters, representing the individual filter types available:

Standard filter elements:
5472558G1
5478307F1
5475307F9

6.1 Particle Content of the Filtrate

Purpose
In general, the particle release from the filters should be minimized. For parenteral solutions, the requirements are define in the USP Monographs, which set maximum limits for particle content based on defined particle sizes.

Limits
From the current USP, the following limits have been set as a maximum number of particles per mL of product (in this case, large volume injections for single dose infusion):

25 particles/mL ≥ 10 µm
3 particles/mL ≥ 25 µm

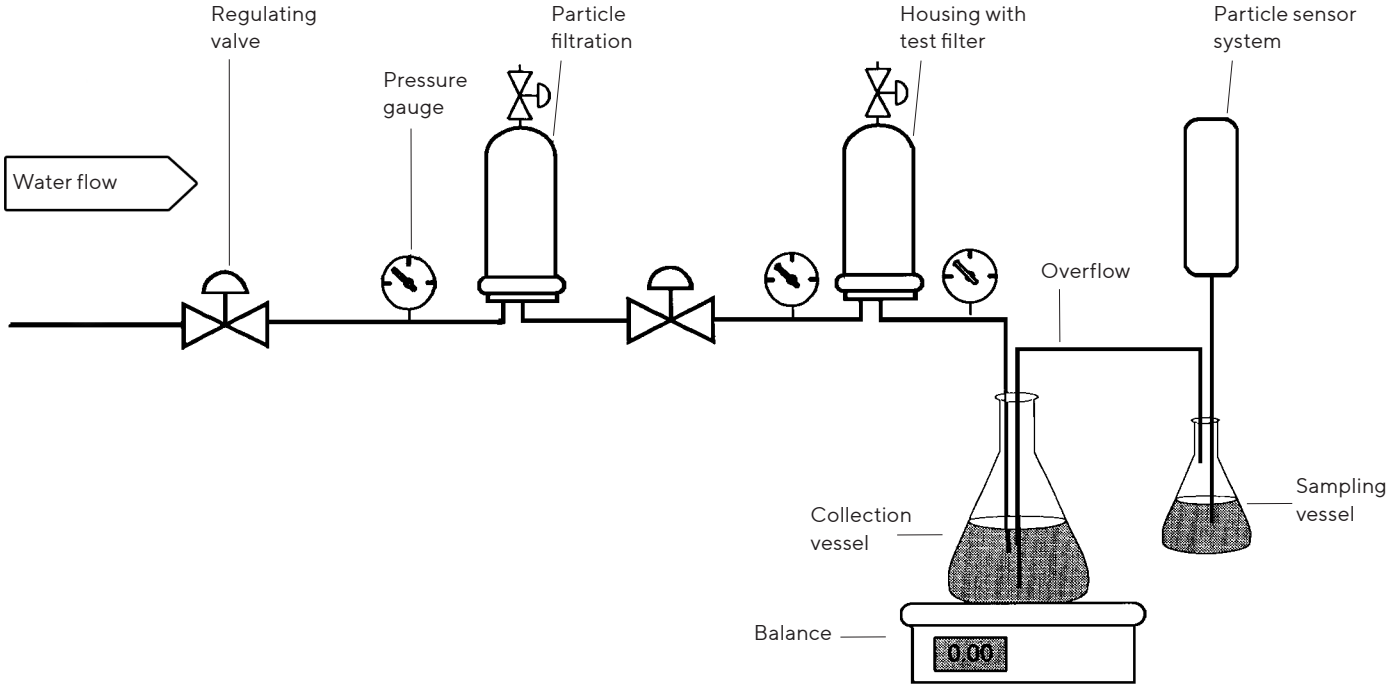
Test procedure
Two standard filter elements from three production lots were wetted and autoclaved prior to being tested. The wetting of the filters is achieved through a static soak, not through fluid flow, in order to avoid removing potential particles that may be present. As a wetting and flushing medium, Reverse Osmosis (RO) generated water is used during the testing. An integrity test is performed to assure that only integral filters are used for this testing. In order to generate particle-free water, the water is first filtered through two 0.2 µm membrane filter cartridges. This water is used to flush the filter housing and all contact surface to remove surface particles prior to testing. The filter elements that have been autoclaved and integrity tested are then installed in the pre-rinsed system.

After attachment of the collection vessel that was also pre-rinsed with the filtered water, the inlet valve is opened and the water is filtered through the test filter elements. The samples for all tests are taken after 1, 5 and 10 liters flush volume for all elements tested. The balance is used to determine gravimetrically when a sample should be taken. Particle analysis of the samples is conducted utilizing a particle sensor system. This system consists of a Pacific Scientific Hiac Royco sampler (Model 3000 SOS, serial No. 93023007), in which a particle sensor (Model HRLD 150, serial No. 9208-012) is installed to analyse the filtrate in accordance with the current USP requirements. The system also incorporates a particle counter (Model 8000, serial No. 91078805). The particle sensor system is calibrated twice a year in line with USP Standards.

A sampling vessel is placed into the sampler. The sample medium is drawn in through a glass bulb and a sample volume of 25 mL/min is set exactly on the sampler. The particle count begins automatically when the sampler is started. The average particle value is calculated from a total of six measurements, 25 mL each.

Summary of results
In order to have an overview of the particle content of filtrates of the tested filters the following table contains the average values for the test performed. These averages are for the three different production lots previously noted.

Test set-up



6.1.1 Standard Cartridges

Particle Size [µm]	Particle Count per mL After 1 L Flush	Particle Count per mL After 5 L Flush	Particle Count per mL After 10 L Flush	Limits according to USP
≥ 10	0	0	0	≥ 25
≥ 25	0	0	0	≥ 3

6.1.2 T-Style Maxicaps®

Particle Size [µm]	Particle Count per mL After 1 L Flush	Particle Count per mL After 5 L Flush	Particle Count per mL After 10 L Flush	Limits according to USP
≥ 10	0	0	0	≥ 25
≥ 25	0	0	0	≥ 3

6.1.3 T-Style Maxicaps®, Gamma Irradiated

Particle Size [µm]	Particle Count per mL After 1 L Flush	Particle Count per mL After 5 L Flush	Particle Count per mL After 10 L Flush	Limits according to USP
≥ 10	0	0	0	≥ 25
≥ 25	0	0	0	≥ 3

6.1.4 Midicaps®

Particle Size [µm]	Particle Count per mL After 1 L Flush	Particle Count per mL After 5 L Flush	Particle Count per mL After 10 L Flush	Limits according to USP
≥ 10	0	0	0	≥ 25
≥ 25	3	0	0	≥ 3

Conclusion
The table above shows that for Sartoguard PES filter, the requirements of the current USP and BP for particle content are met in the first liter of rinse volume. This shows that the initial filtrate conforms to these standards, as it is not technically feasible to test the first mL of solution filtered. Accordingly, the Sartoguard PES do not have to be rinsed prior to being able to produce a filtrate that conforms with the current USP and BP for particle content.

6.2 Determination of Oxidizable Substances of the Filtrate

Test procedure
Two Standard PES filter elements from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

As described in the current USP to the 100 mL samples 10 mL of 2 N sulfuric acid were added and heated to boiling.

Then 0.2 mL of 0.1 N potassium permanganate were added and the solution was boiled for 5 minutes. If a precipitate forms, it is cooled to room temperature. If the precipitate remains its color after cooling to room temperature, the test sample and respectively the tested filter element meets the USP specifications for oxidizable substances.

6.2.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

6.2.2 T-Style Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.2.3 T-Style Maxicaps®, gamma irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11004983	passed	passed	passed
11005483	passed	passed	passed
11005583	passed	passed	passed

6.2.4 Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10012183	passed	passed	passed
10012283	passed	passed	passed
10012383	passed	passed	passed

Conclusion
The Sartoguard PES filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for oxidizable substances for “Sterile Water for Injection”.

6.3 Determination of pH Values and Conductivity of the Filtrate

Test procedure
Two Sartoguard PES filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

Conductivity and pH value of the samples were measured using appropriate calibrated pH meters and conductivity meters according to the USP regulations.

Test limits
The following table lists the limits for pH and conductivity given by the current USP in conjunction with "Sterile Purified Water" and the filters were tested in the specified pH range of 5 to 7.

The relationship between the pH value and the maximum allowable conductivity for "Sterile Water for Injection" according to the current USP is:

pH Value	Maximum Allowable Conductivity [µS/cm]
5	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8–6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

6.3.1 Standard Cartridges

Results for the pH values

Blank	pH 5.8		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
8044983	5.6	5.7	5.8
8045083	5.7	5.8	5.8
8045183	5.7	5.7	5.7

6.3.2 T-Style Maxicaps®

Results for the pH values

Blank	pH 5.6		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
11018383	5.7	5.6	5.7
11018483	5.6	5.6	5.7
11018583	5.7	5.7	5.6

6.3.3 T-Style Maxicaps®, Gamma Irradiated

Results for the pH values

Blank	pH 5.7		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
11018383	5.6	5.6	5.7
11018483	5.6	5.7	5.7
11018583	5.5	5.6	5.7

6.3.4 Midicaps®

Results for the pH values

Blank	pH 5.9		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
10012183	5.4	5.9	5.9
10012283	5.3	5.9	5.9
10012383	5.4	5.9	5.9

Note

Due to the interrelationship between the pH value determination and the measurement of the conductivity, results for both tests must be viewed together.

6.3.5 Standard Cartridges

Results for conductivity

Blank	0.8 µS/cm		
Lot Number	Conductivity After 1 L Flush [µS/cm]	Conductivity After 5 L Flush [µS/cm]	Conductivity After 10 L Flush [µS/cm]
8044983	0.9	0.8	0.8
8045083	0.9	0.8	0.8
8045183	0.9	0.8	0.8

6.3.6 T-Style Maxicaps®

Results for conductivity

Blank	0.7 µS/cm		
Lot Number	Conductivity After 1 L Flush [µS/cm]	Conductivity After 5 L Flush [µS/cm]	Conductivity After 10 L Flush [µS/cm]
11018383	2.4	0.8	0.7
11018483	2.4	0.7	0.7
11018583	2.3	0.8	0.8

6.3.7 T-Style Maxicaps®, Gamma Irradiated

Results for conductivity

Blank	0.7 µS/cm		
Lot Number	Conductivity After 1 L Flush [µS/cm]	Conductivity After 5 L Flush [µS/cm]	Conductivity After 10 L Flush [µS/cm]
11018383	3.1	0.9	0.9
11018483	3.3	0.8	0.8
11018583	3.2	0.8	0.8

6.3.8 Midicaps®

Results for conductivity

Blank	0.7 µS/cm		
Lot Number	Conductivity After 1 L Flush [µS/cm]	Conductivity After 5 L Flush [µS/cm]	Conductivity After 10 L Flush [µS/cm]
10012183	2.7	0.8	0.8
10012283	2.7	0.8	0.8
10012383	2.9	0.8	0.8

Conclusion

Both parameters, pH and pH dependent conductivity of the filtrate, when filtering with the Sartoguard PES filter elements are well below the limit requirements of the current USP.

6.4 Determination of Chloride, Sulfate, Ammonia and Calcium in the Filtrate

6.4.1 Determination of Chloride

Test procedure
Two Sartoguard PES filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and 20 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 20 mL samples 5 drops of nitric acid and 1 mL of silver nitrate are added and gently mixed. If the turbidity formed within 10 minutes is below the control reagent consisting of 20 mL of high purity water containing 10 µg of chloride the test is passed.

6.4.1.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

6.4.1.2 T-Style Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.1.3 T-Style Maxicaps®, Gamma Irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.1.4 Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10012183	passed	passed	passed
10012283	passed	passed	passed
10012383	passed	passed	passed

Conclusion
Sartoguard PES standard filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for chloride for "Sterile Water for Injection".

6.4.2 Determination of Sulfate

Test procedure
Two Sartoguard PES filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 100 mL samples 1 mL of barium chloride is added. If no turbidity forms the test is passed.

6.4.2.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

6.4.2.2 T-Style Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.2.3 T-Style Maxicaps®, Gamma Irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.2.4 Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10012183	passed	passed	passed
10012283	passed	passed	passed
10012383	passed	passed	passed

Conclusion
Sartoguard PES filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for sulfate for "Sterile Water for Injection".

6.4.3 Determination of Ammonia

Test procedure
Two Sartoguard PES filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 100 mL samples 2 mL of alkaline mercuric-potassium iodide is added. If any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in high purity water the test is passed.

6.4.3.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

6.4.3.2 T-Style Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.3.3 T-Style Maxicaps®, Gamma Irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.3.4 Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10012183	passed	passed	passed
10012283	passed	passed	passed
10012383	passed	passed	passed

Conclusion
Sartoguard PES filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for ammonia for "Sterile Water for Injection".

6.4.4 Determination of Calcium

Test procedure
Two Sartoguard PES filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 100 mL samples 2 mL of alkaline mercuric-potassium iodide is added. If any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in high purity water the test is passed.

6.4.4.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

6.4.4.2 T-Style Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.4.3 T-Style Maxicaps®, Gamma Irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11018383	passed	passed	passed
11018483	passed	passed	passed
11018583	passed	passed	passed

6.4.4.4 Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10012183	passed	passed	passed
10012283	passed	passed	passed
10012383	passed	passed	passed

Conclusion
Sartoguard PES filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for calcium for "Sterile Water for Injection".

6.5 Biological Reactivity

Purpose
These tests are to determine that all components used in the manufacture of Sartoguard PES filter elements are biocompatible and meet or exceed the requirements for the current USP Class VI Plastics Tests.

Test method and results
Sartoguard PES filter were supplied to an independent testing facility for evaluation under the requirements of the current USP Class VI Plastics tests, including the following tests:

- Intracutaneous test (Extraction at 121 °C)
- Systemic injection test
- Implantation test (7 days)

The complete test report is available upon request.

Result
The following certificates were released as a result of the testing of Sartoguard PES filter elements. All material used in the construction of the Sartoguard PES meet or exceed the requirements of the USP Class VI–Plastics Tests.

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **SARTOGUARD PES**
Pat. No. US 4,900,449
Order-No.: 5472558G1
Retention rate: 0.1 µm nominal
Lot-No.: 8045083

Supplier: Sartorius Stedim Biotech GmbH
August-Spindler-Straße 11, D-37079 Göttingen

Studies performed: The following study was performed in order to determine the biocompatibility of the device. The material was produced according to the manufacturing process of Sartorius Stedim Biotech GmbH.

CYTOTOXICITY

USP BIOLOGICAL TEST
(CLASSIFICATION VI/121 °C)

Results: **The test item did not show any effect in the performed studies and meets the criteria of USP Biological Tests Classification VI. No leachable substances were released in cytotoxic concentrations from the test item.**

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6/8
D-82152 Planegg

Dr. Sandra Schmid
Biological Safety Testing
Date: 27 February 2009

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

Certificate T-Style housing

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Name:** **T-Style MaxiCaps**
Product Description: **T-Style Housing**

Supplier: Sartorius Stedim Biotech GmbH
August-Spindler-Straße 11, D-37079 Göttingen

Studies performed: The following studies were performed in order to determine the biocompatibility of the device. The material was produced according to the manufacturing process of Sartorius Stedim Biotech GmbH.

CYTOTOXICITY (BSL Project No. 113812)

USP BIOLOGICAL TEST
(CLASSIFICATION VI/121 °C) (BSL Project No. 113813)

Results: **The test item did not show any effect in the USP Class VI test and meets the criteria of USP Biological Tests Classification VI. No leachable substances were released in cytotoxic concentrations from the test item.**

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6/8
D-82152 Planegg

Dr. Sandra Schmid
Biological Safety Testing
Date: 15 September 2011

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **MidiCap® Housing***

Supplier: SARTORIUS AG
Weender Landstraße 94-108, D-37075 Göttingen

Studies performed: The following studies were performed in order to determine the biocompatibility of the device. The material was produced according to the manufacturing process of SARTORIUS AG.

USP BIOLOGICAL TESTS
(CLASSIFICATION VI/121 °C)

Results: **The test item did not show any effect in the performed studies and meets the criteria of USP Biological Tests Classification VI.**

* tested as combination with SARTOPORE 2 Order No.: 5445307H9--SO,
Lot No.: 414243

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6
D-82152 Planegg

Dr. Achim Albrecht
Biological Safety Testing
Date: August 28, 2004

BSL BIOSERVICE Scientific Laboratories GmbH
GLP
ISO 17025

7. Endotoxin Testing

Purpose
The goal of these tests is to determine that the amount of endotoxins released in the effluent of a Sartoguard PES filter.

Test method
Sartoguard PES filter elements from a variety of production lots were tested under the following conditions for endotoxins utilizing the LAL test method. 3.5 liters of endotoxin-free water for Sartoguard PES 10" filter cartridges, filtered through a Sartocon II Crossflow Ultrafiltration system, were filled into endotoxin free glass vessels. A physiological saline solution was produced by adding 31.5 g of NaCl. A sample of this solution is taken and tested with by the LAL test to assure that the extracting medium is non-endotoxenic. Sartoguard PES 10" filter cartridges are then placed into glass vessels and the vessels are placed on a shaker in order to free any endotoxins that may be present. The vessels are shaken for 60 minutes under the same procedure as for the other extraction tests. Samples are then taken and evaluated with the LAL test. In order to detect the presence of endotoxins, an LAL test is used with a sensitivity of 0.06 EU/mL. The test reagents are tested with a solution of known endotoxin content of
0.12 EU/mL prior to use. For an LAL test to pass, (no endotoxins detected), clot formation cannot be seen in the samples up to a dilution of 1:2 and the sample is considered to be below the 0.18 EU/mL endotoxin level.

Results

Standard cartridges

Lot Number	LAL Test Results
8044983	passed
8045083	passed
8045183	passed

T-Style Maxicaps®

Lot Number	LAL Test Results
11018383	passed
11018483	passed
11018583	passed

T-Style Maxicaps®, gamma irradiated

Lot Number	LAL Test Results
11018383	passed
11018483	passed
11018583	passed

Midicaps®

Lot Number	LAL Test Results
10012183	passed
10003883	passed

Conclusion
All Sartoguard PES filter tested, under the conditions of the extraction test described above, meet or exceed USP specifications.

8. Shelf Life

The shelf life of non-sterile filters is at least five years after manufacturing.

Sterile Maxicaps®, Midicaps®, capsules and T-Style Maxicaps® have been determined to have a shelf life of three years after manufacturing with regard to sterility.

The shelf life of Sartoguard PES T-Style Maxicaps®, Maxicaps®, gamma capsules and gamma Midicaps® after gamma irradiation (50 kGy), has been determined to be at least three years.

The recommendations regarding shelf life are valid for controlled storage conditions:
- Storage in a closed, dry area
- Temperature: 5 °C – 40 °C, frost-free
- Humidity: 10 % – 75 %
- No direct solar radiation
- No direct contact with moisture
- Prevention of any mechanical influence or damage

9. Document History

Version Number	Description of Change	Version Date
00	Update to new Sartorius brand design. Minor text and document structure adjustments. Harmonization of dimension data across filter families. Renaming of document to include DIR number.	October 2022
01	Removal of cGMP claim and update of chapter Quality Assurance (please refer to Change Notification of ECR 33619 "Removal of cGMP claim"). Addition of chapters 2.1.3 and 2.7.3 because the filter type Maxicaps® has not been mentioned before, even if Sartoguard PES is also available as this type of filter and this Validation Guide is applicable for them.	March 2024

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