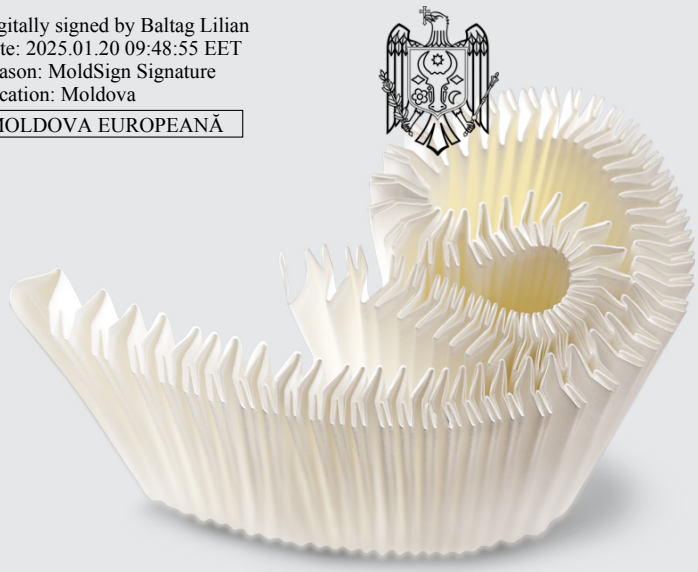
SARTORIUS

Product Datasheet



Sartopore® Platinum

Sterilizing-Grade Filter Elements

Product Information

- Highest product yield due to lowest adsorption
- Excellent wettability ensures to low flushing volumes and high reliability of integrity testing
- High filtration capacity enables use of less filter elements or smaller filter sizes
- Smaller dimensions of single-use assemblies necessary – smaller bags, less tubing

Unique Surface Modification

A patented membrane hydrophilization process is used to permanently modify the membrane surface.

This technology provides those membrane surface properties that are responsible for the outstanding wettability and low protein binding character of the Sartopore® Platinum membrane, even after extreme thermal and chemical stress, without affecting wettability and integrity testing.

Perfect Solution for Single-Use Processes

The perfect wettability of the PES membrane leads to drastic reduction of the required flushing volumes (up to 95% less water needed) which is highly beneficial especially for for single-use processes. Due to the low flushing volume the required waste bags can be significantly downsized by which costs are reduced and handling is optimized.

Maximum Yield for High-Value Products

Besides high filtration capacity the surface modification leads to lowest protein adsorption of any PES membrane in the market by which product yield can be maximized.

Reliable Integrity Testing

Imperfect wetting is the most frequent reason for failed integrity tests. Especially for single-use processes the re-wetting possibility is limited.

The extraordinary wetting behavior of Sartopore® Platinum thus helps to eliminate this important risk factor. Using Sartopore® Platinum leads to highly reliable integrity tests.

Flexible Cartridge Formats

Sartopore® Platinum filter cartridges are available in standard (0.6 m²/10″) and large membrane version (1 m²/10″). This allows highly economic filter sizing and also capacity adaptation without replacing stainless steel housings.

Applications

- Production of high-value biologicals like monoclonal antibodies
- Final conjugated bulk
- Point of fill filtration
- Especially beneficial for single-use filtration processes
- Blood & plasma processes
- Ophthalmics

Services

Sartorius Confidence® Validation Services is the perfect complement to Sartopore® Platinum filters.

Our services provide
- Extractables and leachables services
- Microbiological testing
- Physicochemical testing

in compliance with regulatory requirements. Our local teams of validation experts support you with our tailored and consultative approach to determine the most cost-effective solution and give you the confidence you need to succeed.

Technical Specifications

Available Sizes	Filtration Area	Max. Diffusion at 2.5 bar | 36 psi [ml/min]	Min. Bubble Point [bar | psi]
Cartridges standard pleated			
Size 1	0.6 m² | 6.5 ft²	15	3.5 | 51
Size 2	1.2 m² | 12.9 ft²	30	3.5 | 51
Size 3	1.8 m² | 19.4 ft²	45	3.5 | 51
Cartridges, T-Style Maxicaps®, Maxicaps®			
Size 1	1.0 m² | 10.8 ft²	25	3.5 | 51
Size 2	2.0 m² | 21.5 ft²	50	3.5 | 51
Size 3	3.0 m² | 32.3 ft²	75	3.5 | 51
Midicaps® | Gamma Midicaps®			
Size 7	0.065 m² | 0.7 ft²	4	3.5 | 51
Size 8	0.13 m² | 1.4 ft²	5	3.5 | 51
Size 9	0.26 m² | 2.8 ft²	7	3.5 | 51
Size 0	0.52 m² | 5.6 ft²	14	3.5 | 51
Capsules | Gamma Capsules			
Size 4	0.021 m² | 0.22 ft²	1.1	3.5 | 51

Max. Allowable Differential Pressure

Cartridges
5 bar | 72.5 psi at 20°C
2 bar | 29 psi at 80°C

T-Style Maxicaps®, Maxicaps®, Midicaps® | Gamma Midicaps®
5 bar | 72.5 psi at 20°C
3 bar | 43.5 psi at 50°C

Capsules | Gamma Capsules Size 4
4 bar | 58 psi at 20°C
2 bar | 29 psi at 50°C

Materials

Prefilter Membrane
Polyethersulfone, asymmetric

Endfilter Membrane
Polyethersulfone, asymmetric

Support Fleece
Polypropylene (In-line steam sterilizable & autoclavable)
Polyester (γ-irradiatable or γ-irradiatable | autoclavable)

Core
Polypropylene

End Caps
Polypropylene

Capsule Housing
Polypropylene

O-Ring
Silicone
(other materials on request)

Max. Allowable Back Pressure

2 bar | 29 psi at 20°C
(for all elements)

Pore Size Combination

0.45 µm + 0.2 µm

Regulatory Compliance

- For release, each individual element is tested for integrity by bubble point and diffusion test
- Fully validated as sterilizing-grade filters according to ASTM current F-838 guidelines
- Designed, developed and manufactured in accordance with an ISO 9001 certified Quality Management System
- Meet or exceed the requirements for WFI quality standards set by the current USP
- Non pyrogenic according to USP Bacterial Endotoxins
- USP Plastic Class VI Test
- Non fiber releasing according to 21 CFR

Sterilization

Cartridges
In-Line Steam Sterilization (dry or wet steaming)
Max. 134 °C, 0.3 bar, 20 min
Min. 25 Sterilization Cycles

or

Autoclaving
Max. 134°C, 2 bar, 30 min
Min. 25 Sterilization Cycles

Midicaps® & Capsules
Autoclaving
Max. 134°C, 2 bar, 30 min
Min. 25 Sterilization Cycles (Midicaps®)
Min. 5 Sterilization Cycles (Capsules)

Gamma Midicaps® & Gamma Capsules
Gamma Irradiation
≤ 50 kGy
1 Sterilization Cycle

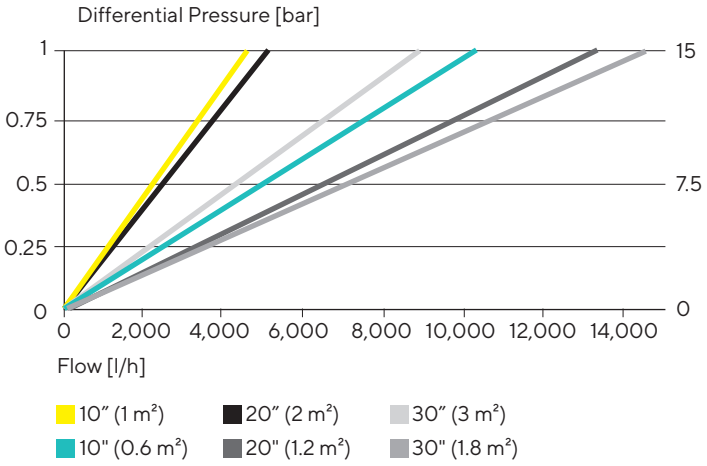
T-Style Maxicaps® & Maxicaps®
Autoclaving
Max. 134°C, 2 bar, 30 min
Min. 5 Sterilization Cycles

or

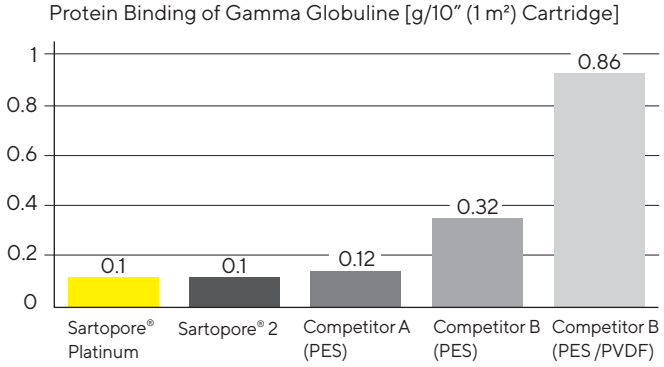
Gamma Irradiation
≤ 50 kGy
1 Sterilization Cycle

Performance

Water Flow Rates 10", 20", 30"



Unspecific Protein Binding



Technical References

Validation Guide	2665259
Extractables Guide	2650008

Ordering Information

Cartridge

549	25	07	H	■

Adapter
25: 2 flange bayonet adapter with 226 double o-ring

Filter Size
1: 1.0 m² | 10.8 ft² (10″)
2: 2.0 m² | 21.5 ft² (20″)
3: 3.0 m² | 32.3 ft² (30″)
1-S: 0.6 m² | 6.5 ft² (10″)
2-S: 1.2 m² | 12.9 ft² (20″)
3-S: 1.8 m² | 19.4 ft² (30″)

(Standard with silicone o-ring optional with EPDM or Fluoroelastomer o-ring).

T-Style Maxicaps®

549	83	07	H	■	G-	■	■

Filter Size
1: 1.0 m² | 10.8 ft² (10″)
2: 2.0 m² | 21.5 ft² (20″)
3: 3.0 m² | 32.3 ft² (30″)

Sterilization
G-: γ-irradiatable and autoclavable

Connector Inlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
Y: 1″single stepped hose barb

Connector Outlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
Y: 1″ single stepped hose barb

Maxicaps®

549	73	07	H	■	G-	■	■

Filter Size
1: 1.0 m² | 10.8 ft² (10″)
2: 2.0 m² | 21.5 ft² (20″)
3: 3.0 m² | 32.3 ft² (30″)

Sterilization
G-: γ-irradiatable and autoclavable

Connector Inlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
F: ¾″ tri-clamp 25 mm

Connector Outlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
F: ¾″ tri-clamp 25 mm

(Optional with vent valve design for connection of integrity tester. Example: 5497307H1G-SOIT)

Midicaps® | Gamma Midicaps®

549	53	07	H	■	■	■	■	--	■

Filter Size
7: 0.065 m² | 0.7 ft²
8: 0.13 m² | 1.4 ft²
9: 0.26 m² | 2.8 ft²
0: 0.52 m² | 5.6 ft²

Sterilization
G-: γ-irradiatable
--: autoclavable

Connector Inlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
F: ¾″ tri-clamp 25 mm
H: ¼″ multiple stepped hose barb (only size 7 with filling bell)

Connector Outlet
S: 1½″ tri-clamp 50.5 mm
O: ½″ single stepped hose barb
F: ¾″ tri-clamp 25 mm
H: ¼″ multiple stepped hose barb (only size 7 with filling bell)

Packing Size
A: box of 4 (size 7, 8, 9)
V: box of 2 (size 0)

Capsules | Gamma Capsules

549	13	07	H	4	■	■	■	--	B

Filter Size
4: 0.021 m² | 0.22 ft²

Sterilization
G-: γ-irradiatable
--: autoclavable

Connector Inlet
S: ¾″ tri-clamp 25 mm
O: ¼″ multiple stepped hose barb

Connector Outlet
S: ¾″ tri-clamp 25 mm
O: ¼″ multiple stepped hose barb

Packing Size
B: box of 5

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For more information, visit
www.sartorius.com

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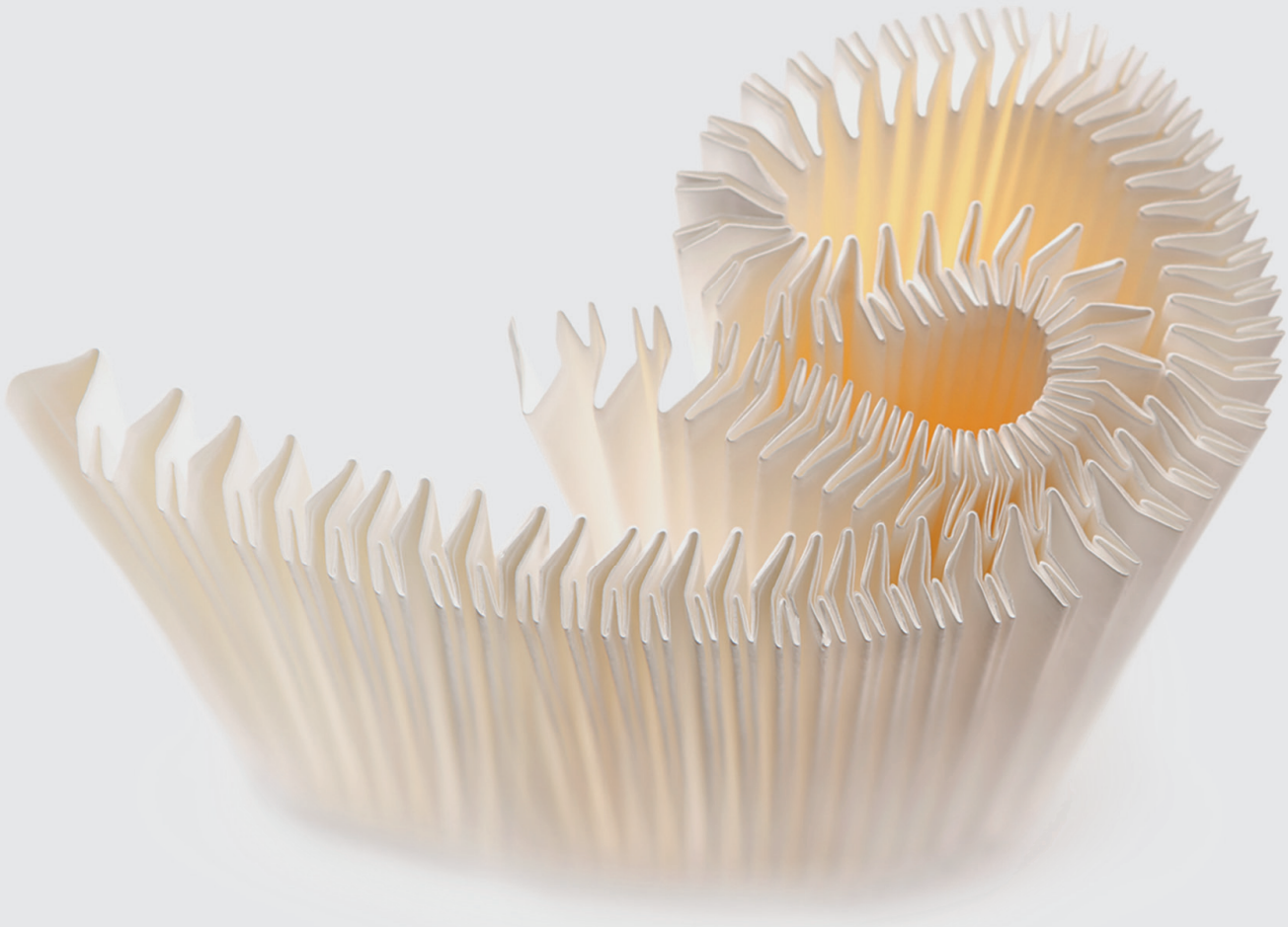


Sartopore® Platinum Family

Validation Guide

SARTORIUS

Table of Contents

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 accordingn to the European Pharmacopeia 6) 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.

Sartopore® Platinum family, pleated membrane filter elements with a heterogeneous membrane, reliably fulfills the product-specific requirements which have to be imposed on a sterilizing grade filter. 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 ofIndustrial 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 Sartopore® Platinum family filter elements can plan, implement and document their own validation procedures.

1.1 cGMP Quality from Sartorius

Consistent high quality of Sartorius membrane filters, capsules (ready-to-connect filtration units) and filter cartridges is assured by careful selection of the raw materials, well-planned and validated production technologies and an exceptionally efficient Quality Assurance Department, all of which results in high batch-to-batch reproducibility. The test procedures used are based both on external standard methods, such as the USP, EP and ASTM, and on in-house methods which are the result of Sartorius' experience over the past 60 years.

1.2 Quality Assurance

For quality assurance, all materials are selected carefully in accordance with current regulations, such as the FDA CFR's, cGMP's in-house guidelines and the specifications of our Research and Development Department including the terms of delivery and acceptance of our Purchasing Department. Documentation begins with the inspection of the incoming raw materials including in-process materials, molded parts and sealing materials, etc. for manufacture. Adherence to cGMP requirements (clean-room conditions, gowning and employee hygiene, etc.) which are monitored by documented in-process controls, ensures optimal quality control in standard operating procedures for production. Finished Sartorius capsules and filter cartridges undergo final product quality control. This involves 100 % non-destructive testing of each individual product and other individual tests carried out on a representative number of samples. A lot is not released until all in-process and final quality control data are available.

1.3 Prevention of Contamination

Sartopore® Platinum (HB) filter cartridges, gamma Midicaps® and gamma capsules size 4 are double wrapped in protective plastics bags in a controlled production area. During production those filters are dried to reliably prevent microbial growth, and thus rule out the possibility of pyrogen synthesis during shipping and storage.

Sartopore® Platinum (HB) Midicaps®, T-Style Maxicaps®, Maxicaps® and capsules size 4 are sealed in steam permeable protective plastic bags are double wrapped 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.

1.4 Complete Traceability

The pore size, type, used before date 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 the information about filter type, pore size, lot number and individual number are indicated on the top adapter of the cartridges, housing of Midicaps®, Maxicaps®, capsules and banderole of T-Style Maxicaps®. A data matrix code offers the possibility to use a barcode scanner for error-free and easy data transfer. The traceable lot number allows convenient retrieval of all data complied on the materials used, production steps and QC tests.

1.5 Sartorius Drug Master File – DMF

This product is registered with the Food and Drug Adminstration (FDA). The DMF number is available upon request.

1.6 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 ISO 9001

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

1.7 Test Methods for the Quality Assurance of Sartorius Sartopore® Platinum Family Filter Elements

Lot Related Tests – 100 % Individual Testing

- Bubble point of the element
- Diffusion value of the element
- Flow rate and throughput of the membrane
- Bacterial challenge testing of every Lot of final filter membrane

Routine Testing of Randomly Sampled Filter Elements

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

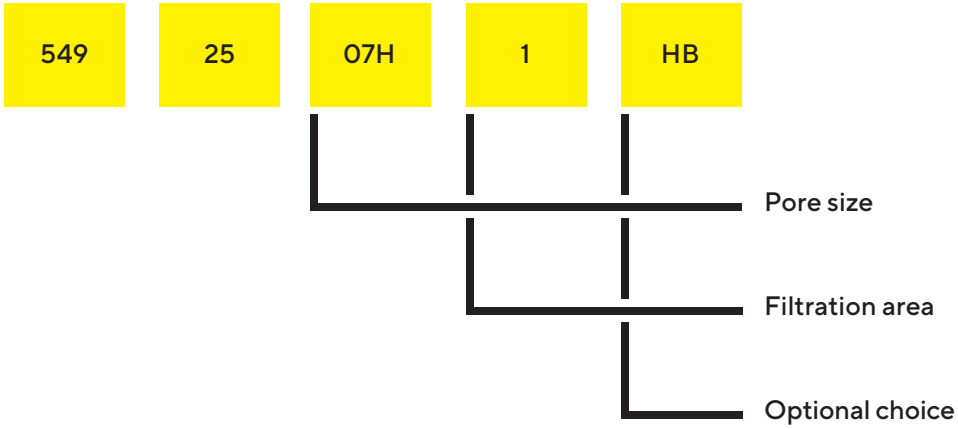
Testing Conducted for Validation of the Filter Elements

- Correlation of diffusion and bubble point values with the ASTM bacterial challenge tests
- 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
- Evaluation of integrity test values after long term storage
- In-line steam sterilization
- Autoclavability
- γ-sterilization

2. Technical Specifications

2.1 Type and Part Number Overview

2.1.1 Standard Cartridges



Explanation

549
Sartopore® Platinum, heterogeneous double layer Polyethersulfone membrane filter

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

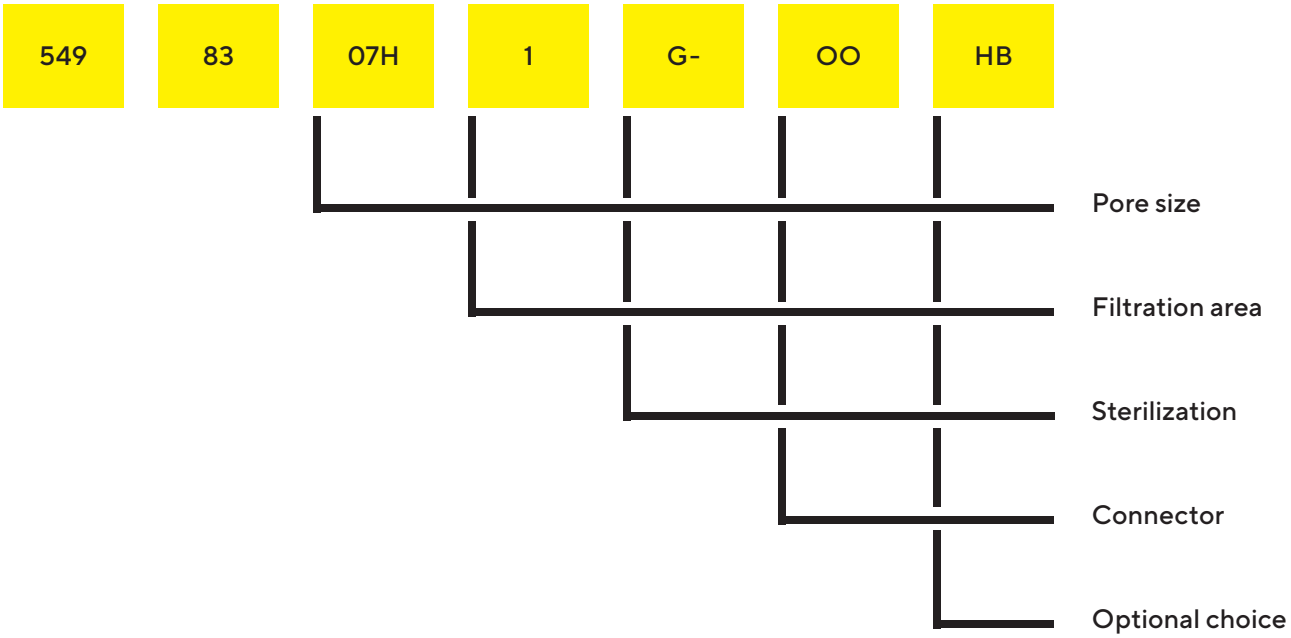
Pore size
07 0.2 µm final membrane
H 0.45 µm prefilter membrane

Effective filtration area
1 1.0 m^2 | 10.8 ft^2
2 2.0 m^2 | 21.5 ft^2
3 3.0 m^2 | 32.3 ft^2
1-S 0.6 m^2 | 6.5 ft^2
2-S 1.2 m^2 | 12.9 ft^2
3-S 1.8 m^2 | 19.4 ft^2

Optional Choice
HB Sartopore® Platinum version with a higher bubble point than the standard version filtration area

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

2.1.2 T-Style Maxicaps®



Explanation

549
Sartopore® Platinum, heterogeneous double layer polyethersulfone membrane filter

Pore size
07 0.2 µm final membrane
H 0.45 µm prefilter membrane

Effective filtration area
1 1.0 m^2 | 10.8 ft^2
2 2.0 m^2 | 21.5 ft^2
3 3.0 m^2 | 32.3 ft^2

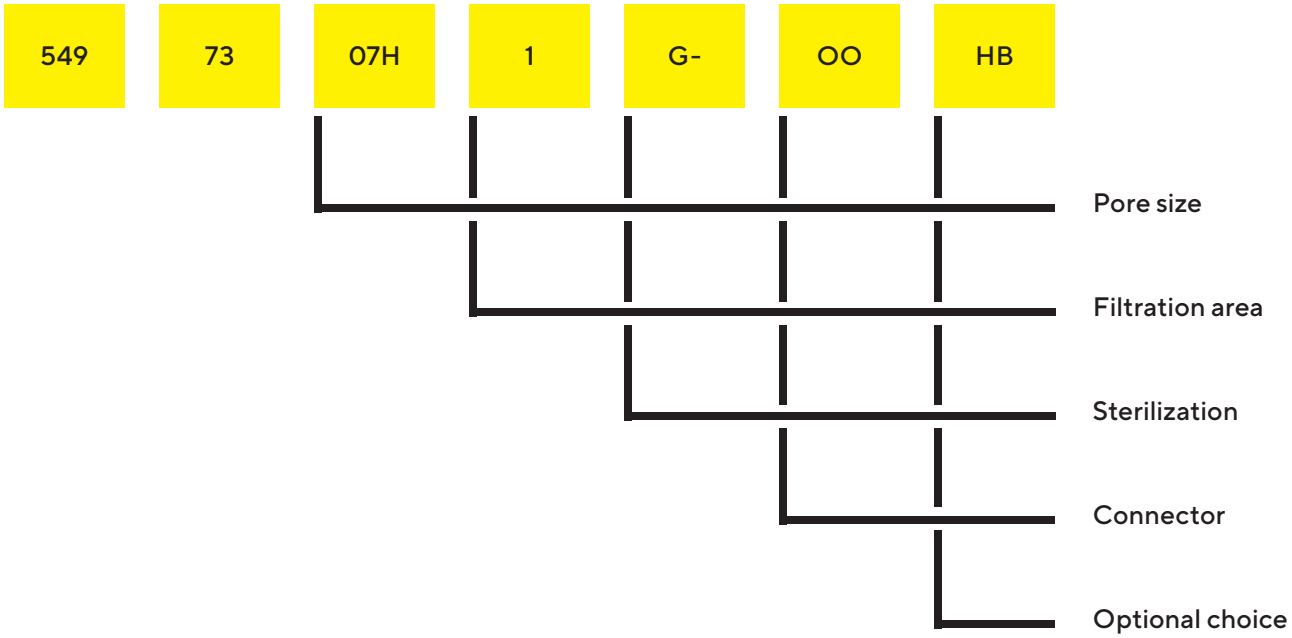
Sterilization
G- γ-irradiatable & autoclavable

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

Optional choice
HB Sartopore® Platinum version with a higher bubble point than the standard version

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

2.1.3 Maxicaps®



Explanation

549
Sartopore® Platinum, heterogeneous double layer polyethersulfone membrane filter

Pore size
07 0.2 µm final membrane
H 0.45 µm prefilter membrane

Effective filtration area
1 1.0 m^2 | 10.8 ft^2
2 2.0 m^2 | 21.6 ft^2
3 3.0 m^2 | 32.4 ft^2

Sterilization
G- γ-irradiatable & autoclavable

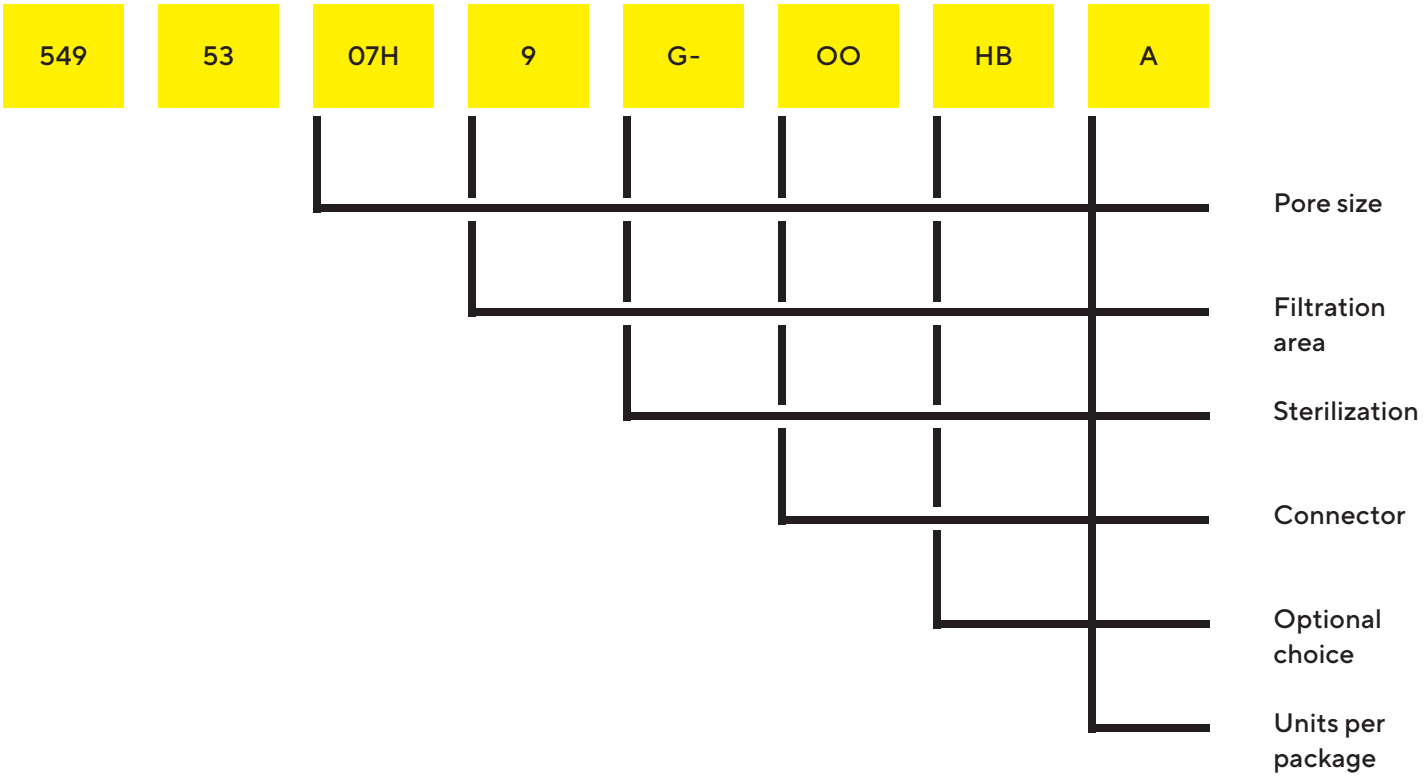
Connectors
S 1½" Tri-clamp
O ½" single-stepped hose barb
F ¾" Tri-clamp (sanitary)

Vent valve design
IT Design suitable for connection of integrity tester standard

Optional choice
HB Sartopore® Platinum version with a higher bubble point than the standard version

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

2.1.4 Midicaps® | Gamma Midicaps®



Explanation

549
Sartopore® Platinum, heterogeneous double layer polyethersulfone membrane filter

Pore size
07 0.2 µm final membrane
H 0.45 µm prefilter membrane

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

Sterilization
G- γ-irradiatable
-- autoclavable

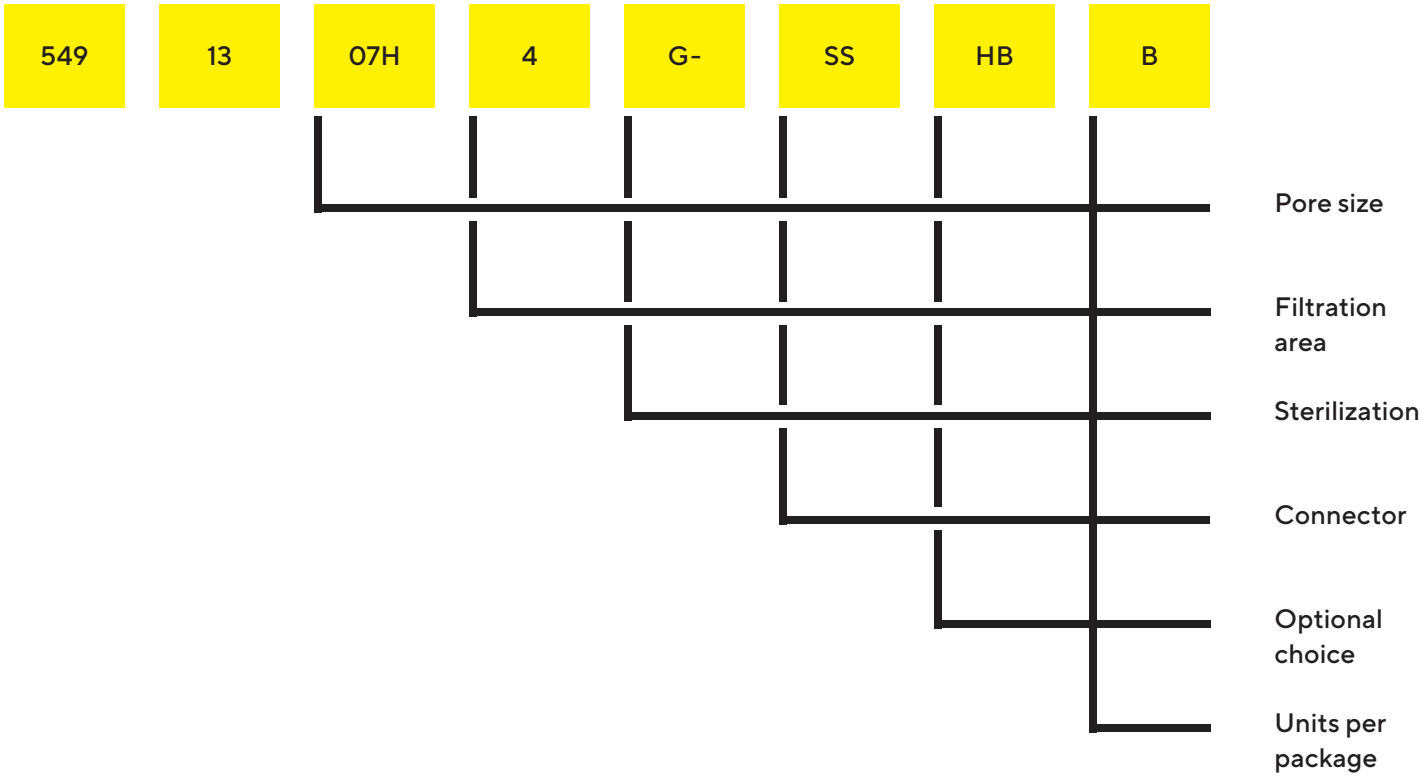
Connectors
S 1½" Tri-clamp (sanitary)
O ½" single-stepped hose barb
F ¾" Tri-clamp (sanitary)
H ¼" multiple-stepped hose barb (only size 7)

Optional choice
HB Sartopore® Platinum version with a higher bubble point than the standard version

Units per package
A Box of 4 (size 7-9)
V Box of 2 (size 0)

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

2.1.5 Capsules | Gamma Capsules



Explanation

549
Sartopore® Platinum, heterogeneous double layer polyethersulfone membrane filter

Pore size
07 0.2 µm final membrane
H 0.45 µm prefilter membrane

Effective filtration area
4 0.021 m² | 0.22 ft²

Sterilization
G- γ-irradiatable
-- autoclavable

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

Optional choice
HB Sartopore® Platinum version with a higher bubble point than the standard version

Units per package
B Box of 5

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 asymmetric; 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 optimized filter membrane combinations where the two membranes have different retention ratings.

2.4 Available Pore Size Combination

0.45 µm + 0.2 µm
(optional with high bubble point (HB))

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, is also met and exceeded.

Upstream support layer:
- Polypropylene
  (in-line steam sterilizable and autoclavable).
- Polyesther
  (γ-irradiatable and γ-irradiatable | autoclavable).

Filter membrane:
Polyethersulfone, double layer

Downstream support:
- Polypropylene
  (in-line steam sterilizable and autoclavable).
- Polyesther
  (γ-irradiatable and γ-irradiatable | autoclavable).

Outer cage:
Polypropylene

Inner core:
Polypropylene

Endcaps:
Polypropylene

O-Rings | Gaskets
Silicone; Optional:
EPDM or Fluoroelastomer

Filling bell:
Polycarbonate

2.6 Fiber Release

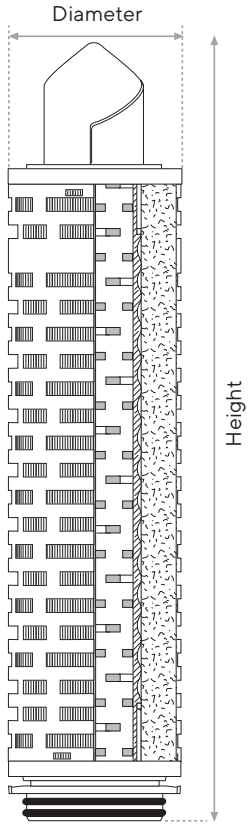
Sartopore® Platinum family filter membranes comply with Title 21 Code of Federal Regulations, Section 211.72 and 210.3 (b) (6) for non-fiber releasing filters.

2.7 Dimensions

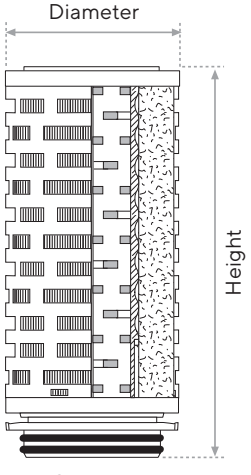
2.7.1 Standard Cartridges

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

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



10"–30" Cartridge

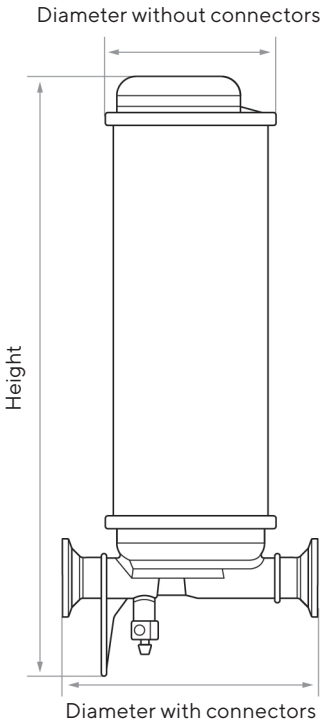


5" Cartridge

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	110.2
20	110.2
30	110.2

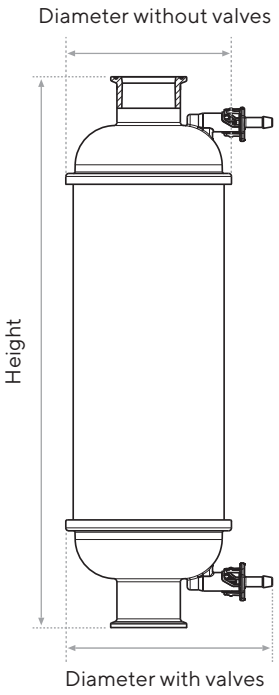
2.7.3 Maxicaps®

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	110
20	137	110
30	137	110

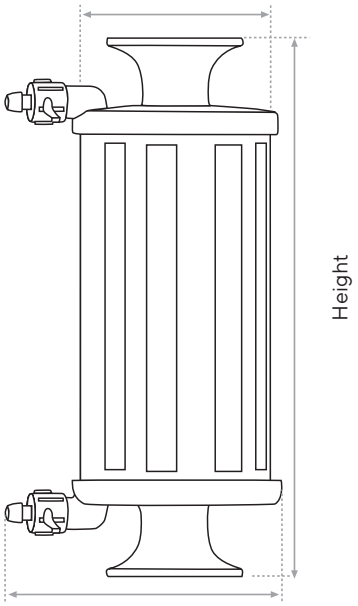


2.7.4 Midicaps® | Gamma Midicaps®

Total height

Size	Connector Combinations [mm]						
	SS	SO	OO	FF	FO	FH	HH
7	115	121	128	114	121	118	121
8	149	156	162	148	155	–	–
9	199	206	212	198	205	–	–
0	332	339	345	331	339	–	–

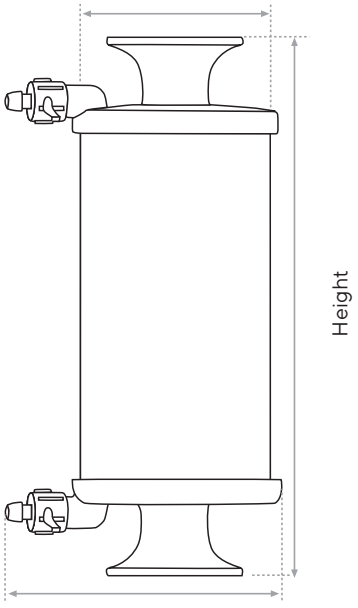
Midicaps® Design:
Diameter without valves



Total diameter

Size	All Connector Combinations [mm]	
	including valves	without valves
7	109	70.9
8	109	70.9
9	109	70.9
0	109	70.9

Gamma Midicaps® Design:
diameter without valves



2.7.5 Capsules | Gamma Capsules Size 4

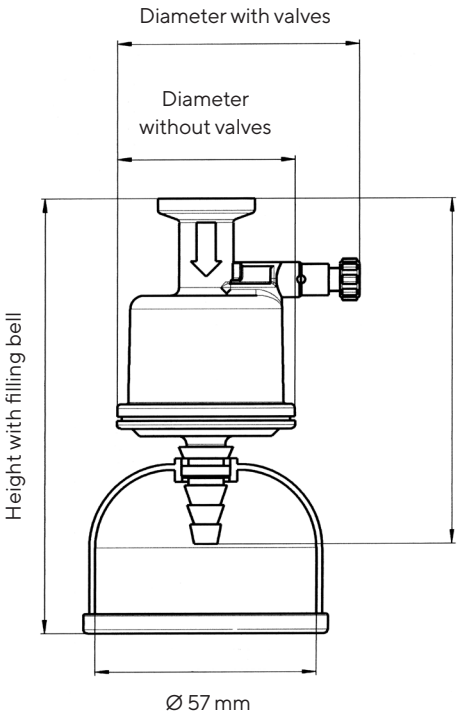
Total height

Connector Combinations [mm] with filling bell		
SO	OO	SS
88	101	85

Connector Combinations [mm] without filling bell		
SO	OO	SS
111	124	–

Total diameter

All Connector Combinations [mm]	
without valves	with valves
46	61



2.8 Maximum 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 Standard Cartridges

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

2.8.2 T-Style Maxicaps®, Maxicaps® and Midicaps® | Gamma Midicaps®

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

2.8.3 Capsules | Gamma Capsules Size 4

Temperature [°C]	20	50
Pressure [bar]	4	2
Pressure [psi]	58	29

2.9 Maximum Back Pressure

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

2.9.1 T-Style Maxicaps®, Maxicaps®, Midicaps® | Gamma Midicaps® and Capsules | Gamma Capsules Size 4

Temperature [°C]	20	50
Pressure [bar]	2	1.5
Pressure [psi]	29	21.8

2.10 Sterilization

Autoclaving of wet and dry filter cartridges, T-Style Maxicaps®, Maxicaps®, Midicaps® and capsules size 4 (also applies to the HB version) up to a maximum temperature of 134 °C, for 30 minutes

or

in-line steam sterilization of wetted and dry cartridges (also applies to the HB version) 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)

or

gamma irradiation of T-Style Maxicaps®, Maxicaps®, gamma Midicaps® and gamma capsules (also applies to the HB version) with ≤ 50 kGy.

Note

Only cartridges (also applies to the HB version) can be in-line steam sterilized.

2.11 Rinsing Volumes of Capsule Filters

2.11.1 Background

Sterilizing-grade filtration is an essential unit operation in pharmaceutical and biopharmaceutical manufacturing. Sartorius filter cartridges and capsules are designed for the lowest possible release of substances into the process stream to meet the regulatory requirements applied to these processes. Consequently, filter elements can be used without any pretreatment ('out-of-box') for most applications. This includes filtration processes where a pre-use, post-sterilization integrity test (PUPSIT) is performed followed by a rinsing step or when filter elements are conditioned with the process stream before use. Standardized rinsing tests are performed routinely during filter qualification. Results are available in the Validation Guide for selected volumes and representative filter sizes.

The effectiveness of rinsing can be monitored by measuring the total organic carbon (TOC) content of the filtrate.[1] A TOC level of < 500 ppb (ng/mL) corresponds to the quality of water for injection (WFI) according to the USP monograph 'Sterile Water for Injection' and is a commonly employed safety threshold in bioprocess validation. Compounds removed in the flushing step are considered as "rinsables". They are specific for each filter type and mainly consist of wetting agents or volatiles formed during gamma sterilization.[2] Their quantity scales directly with the effective filtration area (EFA).[3]

In-depth information on the rinsing behavior is relevant when limitations in rinsing volumes exist, such as small bulk filtration volume in high-risk final filling applications.

In general, there are two common filtration types for which rinsing recommendations can be provided (Figure 1): **Bulk filtration** and **fractionized filling filtration**.

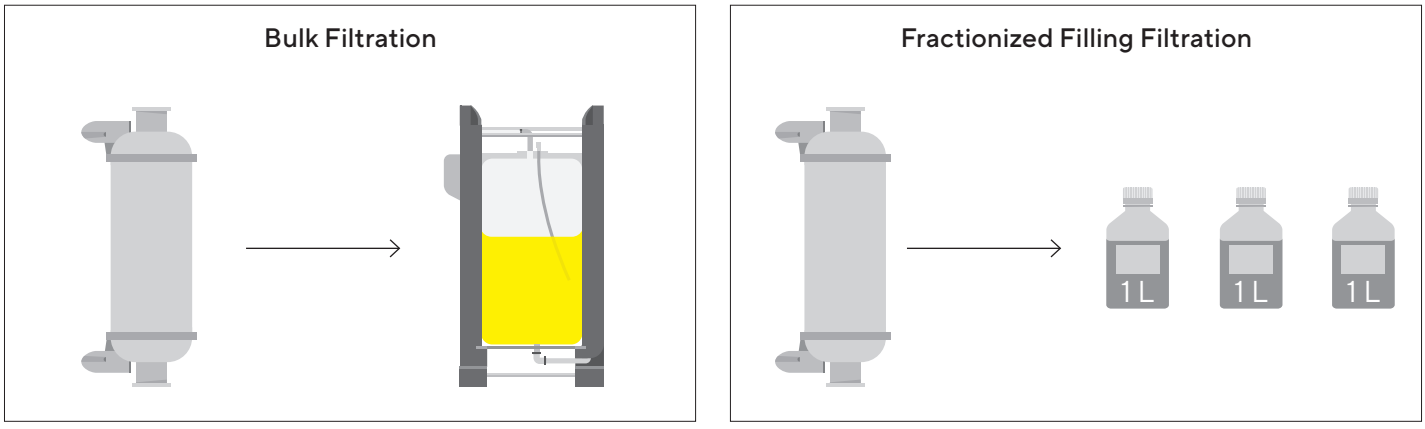


Figure 1: During bulk filtration into larger reservoirs the TOC is diluted in the bulk volume. In case of fractionized filling filtration, rinsables can accumulate within the first fractions.

Sartorius has developed a methodology to determine the filter-specific parameters Bulk Volume per Surface (BVS) and Rinsing Volume per Surface (RVS).[2] Based on these parameters and the EFA of the filter element the **minimum bulk** or **rinsing volume** can be calculated for each filter element and size. The minimum bulk volume refers to the volume that is required to dilute the TOC below the threshold of 500 ppb. The minimum rinsing volume represents the initial flush volume that is required to reduce the TOC level of the filtrate to less than 500 ppb.

[1] Jenke, D.; Couch, T. R.; Robinson, S. J.; Volz, T. J.; Colton, R. H. The Use of TOC Reconciliation as a Means of Establishing the Degree to Which Chromatographic Screening of Plastic Material Extracts for Organic Extractables Is Complete. PDA J. Pharm. Sci. Technol. **2014**, 68 (3), 256–270. https://doi.org/10.5731/pdajpst.2014.00977.
[2] Menzel, R.; Pahl, I.; Loewe, T.; Stuetzer, A.; Hauk, A. Rinsing Recommendations for Membrane Filters and Identification of Rinsables. Eur. J. Pharm. Sci. **2022**, 168, 105982. https://doi.org/https:/ doi.org/10.1016/j.ejps.2021.105982.
[3] Pahl, I.; Menzel, R.; Hauk, A.; Loewe, T. Using Extractables Data of Sterile Filter Components for Scaling Calculations. PDA J. Pharm. Sci. Technol. **2019**, 73, 523–537. https://doi.org/10.5731/ pdajpst.2018.009647.

2.11.2 Filtration Use Cases

To illustrate how these volumes can support the design of filtration processes three representative use cases are discussed with generic values (Figure 2).

In case A, a total volume of 50 L is filtered into a storage bag for further processing. The comparison of the filtrate volume (50 L) to the filter-specific minimum bulk volume (30 L) shows that the filter can be used 'out-of-box' without any rinsing as the filtrate bulk volume is larger than the minimum bulk volume. Hence, the TOC of the filtrate is diluted to less than 500 ppb without a rinsing step. In case B, an initial rinsing of the filter is performed, and the required minimum flushing volume should be based on the filter-specific minimum rinsing volume (200 mL). The third use case C refers to a filling filtration process into vials where the minimum bulk volume of the filter (17 L) is larger than the vial volume (1 L). Here, the filter should be rinsed with the minimum rinsing volume (1.5 L). Alternatively, if no rinsing is feasable, the first two fractions (2 L) must be discarded. The minimum volume to be discarded is equal to the minimum rinsing volume of the filter if a rinsing step is omitted.

The presented use cases demonstrate the benefit of minimum bulk and rinsing volumes for optimization of single-use filtration systems with respect to small flushing volumes and waste bag sizes.

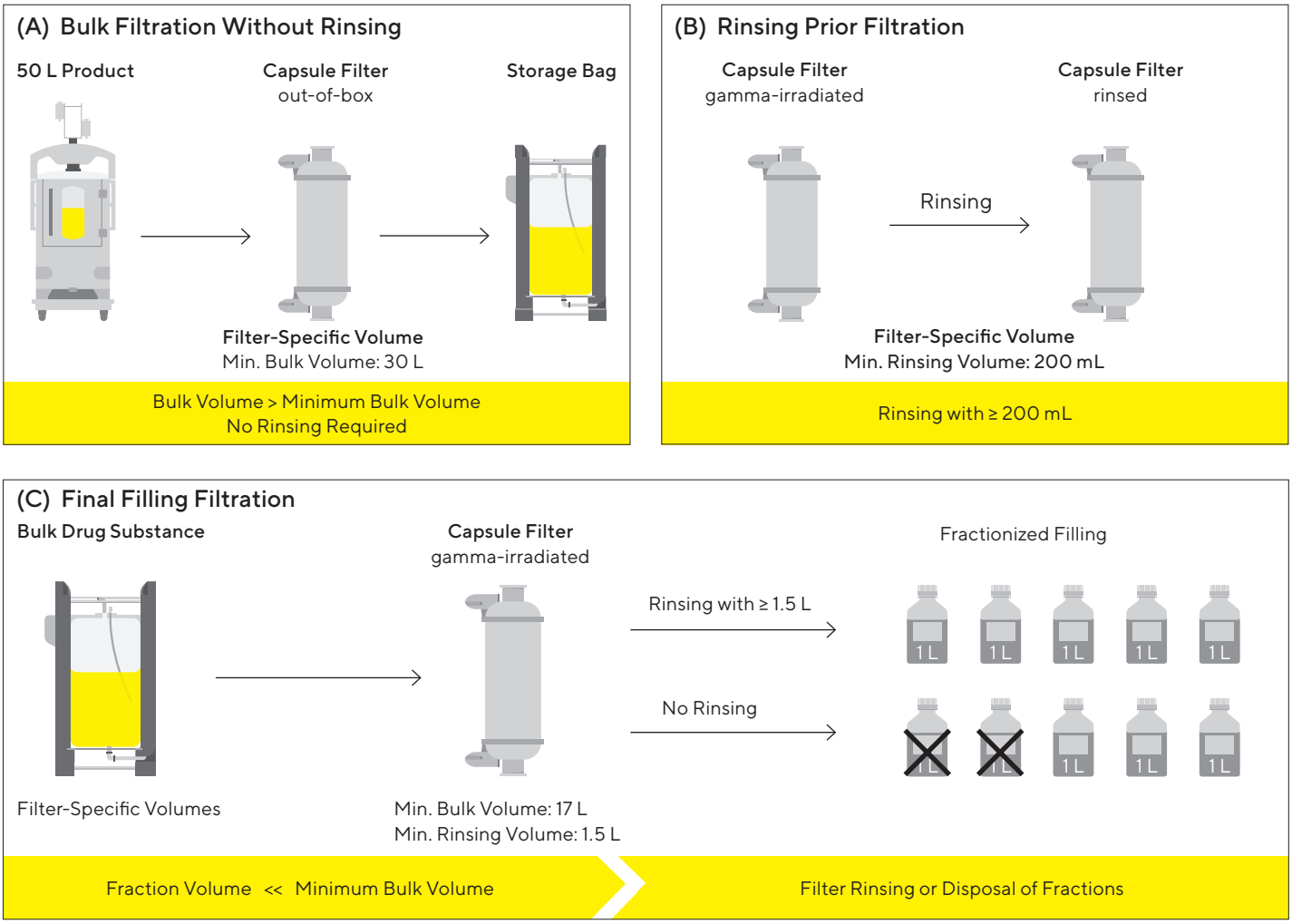


Figure 2: Filtration examples demonstrating the use of filter-specific minimum bulk and rising volumes. Volumes are representative and must be adapted to the used filter type, size, and sterilization method.

2.11.3 Minimum Bulk and Rinsing Volumes

Based on TOC rinsing curves of Sartopore® Platinum (HB) capsule filters the minimum bulk and rinsing volumes were determined. Volumes are shown for autoclavable, gamma and hybrid filter capsules. Hybrid filter elements can be either autoclaved or sterilized by gamma irradiation.

The recommended minimum volumes are valid for capsule filters and filter cartridges with identical EFA.[2] The volumes are based on the filter-specific parameters RVS and BVS obtained from representative test items and can be used as the minimum values in process qualification.

Table 7: Minimum rinsing and bulk volumes of autoclavable Sartopore® Platinum (HB) capsule filters

Filter Type	Size	EFA [cm^2]	Min. Rinsing Volume [L] untreated | autoclaved	Min. Bulk Volume [L] untreated | autoclaved
Midicaps®	0	5,200	0.57	14
	9	2,600	0.29	6.8
	8	1,300	0.14	3.4
	7	650	0.072	1.7
Capsules	4	210	0.023	0.55

Table 8: Minimum rinsing and bulk volumes of gamma | hybrid Sartopore® Platinum (HB) capsule filters

Filter Type	Size	EFA [cm^2]	Min. Rinsing Volume [L]		Min. Bulk Volume [L]	
			untreated | autoclaved	gamma irradiated	untreated | autoclaved	gamma irradiated
Maxicaps® (Hybrid)	30	30,000	11	22	200	360
	20	20,000	7	15	130	240
	10	10,000	3.5	7.4	66	120
T-Style Maxicaps® (Hybrid)	30	30,000	11	22	200	360
	20	20,000	7	15	130	240
	10	10,000	3.5	7.4	66	120
Gamma Midicaps®	0	5,200	1.8	3.8	34	62
	9	2,600	0.91	1.9	17	31
	8	1,300	0.46	0.96	8.6	16
	7	650	0.23	0.48	4.3	7.8
Gamma Capsules	4	210	0.074	0.16	1.4	2.5

2.12 Wetting the Filters for Integrity Testing

Standard integrity test methods essentially require a completely wetted membrane. The surface coating used for Sartopore® Platinum (HB) lead to a permanently hydrophilic membrane even after thermal stress. In order to determine the minimum quantity of water for getting reliable wetting, filters were flushed with different water volumes (0.1 bar differential pressure) and standard diffusion test and bubble point test were used to verify sufficient wetting. The following table gives an overview about minimum quantities of water for complete wetting:

Type	Filter Area [m^2]	Flush Volume [L]
Size 4	0.021	0.1
Size 7	0.065	0.4
Size 8	0.13	0.5
Size 9	0.26	1.0
Size 0	0.52	3.0
10"	1.0	5.0
10"	0.6	3.5

2.13 Integrity Tests Limits for Sartopore® Platinum

The bubble point and diffusion limits for water were established during filter validation and are correlated with bacterial retention studies as described in section "5. Integrity Test Limits" of this validation guide.

The bubble point limits for isopropanol (IPA)-water mixtures are correlated with the bubble point limits for water. Bubble point limits for IPA-water mixtures were determined using 10" cartridge filters in accordance with the approach defined in the PDA Technical Report No. 26 (Sterilizing Filtration of Liquids, PDA Vol 62, No. S-5, 2008) under "7.2.1 Product-Wetted Bubble Point Tests".

2.13.1 Standard Cartridges

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	2.5 | 36	15	3.5 | 50.8
	10	2.5 | 36	25	3.5 | 50.8
	20	2.5 | 36	30	3.5 | 50.8
	20	2.5 | 36	50	3.5 | 50.8
	30	2.5 | 36	45	3.5 | 50.8
	30	2.5 | 36	75	3.5 | 50.8

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	1 | 14.5	11	1.3 | 18.85
	10	1 | 14.5	17	1.3 | 18.85
	20	1 | 14.5	22	1.3 | 18.85
	20	1 | 14.5	34	1.3 | 18.85
	30	1 | 14.5	33	1.3 | 18.85
	30	1 | 14.5	51	1.3 | 18.85

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	–	n.a.	1.3 | 18.85
	10	–	n.a.	1.3 | 18.85
	20	–	n.a.	1.3 | 18.85
	20	–	n.a.	1.3 | 18.85
	30	–	n.a.	1.3 | 18.85
	30	–	n.a.	1.3 | 18.85

2.13.2 T-Style Maxicaps® & Maxicaps®

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	Height ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	2.5 | 36	25	3.5 | 50.8
	20	2.5 | 36	50	3.5 | 50.8
	30	2.5 | 36	75	3.5 | 50.8

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Height ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	1 | 14.5	17	1.3 | 18.85
	20	1 | 14.5	34	1.3 | 18.85
	30	1 | 14.5	51	1.3 | 18.85

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Height ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	–	n.a.	1.3 | 18.85
	20	–	n.a.	1.3 | 18.85
	30	–	n.a.	1.3 | 18.85

2.13.3 Midicaps® | Gamma Midicaps®

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	7	2.5 | 36	4	3.5 | 50.8
	8	2.5 | 36	5	3.5 | 50.8
	9	2.5 | 36	7	3.5 | 50.8
	0	2.5 | 36	14	3.5 | 50.8

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	7	1 | 14.5	3	1.3 | 18.85
	8	1 | 14.5	4	1.3 | 18.85
	9	1 | 14.5	5	1.3 | 18.85
	0		10	1.3 | 18.85

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	7	–	n.a.	1.3 | 18.85
	8	–	n.a.	1.3 | 18.85
	9	–	n.a.	1.3 | 18.85
	0	–	n.a.	1.3 | 18.85

2.13.4 Capsules | Gamma Capsules

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	4	2.5 | 36	1.1	3.5 | 50.8

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	4	1 | 14.5	1	1.3 | 18.85

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	4	–	n.a.	1.3 | 18.85

2.14 Integrity Tests Limits for Sartopore® Platinum HB

The bubble point and diffusion limits for water were established during filter validation and are correlated with bacterial retention studies as described in section "5. Integrity Test Limits" of this validation guide.

The bubble point limits for isopropanol (IPA)-water mixtures are correlated with the bubble point limits for water. Bubble point limits for IPA-water mixtures were determined using 10" cartridge filters in accordance with the approach defined in the PDA Technical Report No. 26 (Sterilizing Filtration of Liquids, PDA Vol 62, No. S-5, 2008) under "7.2.1 Product-Wetted Bubble Point Tests".

2.14.1 Standard Cartridges

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	2.5 | 36	25	4.1 | 59.5
	20	2.5 | 36	50	4.1 | 59.5
	30	2.5 | 36	75	4.1 | 59.5

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size ["]**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

2.14.2 T-Style Maxicaps® & Maxicaps®

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	Size ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	2.5 | 36	25	4.1 | 59.5
	20	2.5 | 36	50	4.1 | 59.5
	30	2.5 | 36	75	4.1 | 59.5

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

2.14.3 Midicaps® | Gamma Midicaps®

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	Size	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	7	2.5 | 36	4	4.1 | 59.5
	8	2.5 | 36	5	4.1 | 59.5
	9	2.5 | 36	7	4.1 | 59.5
	0	2.5 | 36	14	4.1 | 59.5

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	Size ["]	Test Pressure [bar | psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar | psi]
0.2	10	–	n.a.	1.5 | 21.8
	20	–	n.a.	1.5 | 21.8
	30	–	n.a.	1.5 | 21.8

2.14.4 Capsules | Gamma Capsules

Wetting Liquid: Water				
Pore Size of the Final Membrane [µm]	**Size**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	4	2.5 | 36	1.1	4.1 | 59.5

Wetting Liquid: 60/40 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	4	–	n.a.	1.5 | 21.8

Wetting Liquid: 70/30 IPA-Water Mixture				
Pore Size of the Final Membrane [µm]	**Size**	**Test Pressure [bar | psi]**	**Maximum Diffusion [mL/min]**	**Minimum Bubble Point [bar | psi]**
0.2	4	–	n.a.	1.5 | 21.8

Note:
Due to limited pressure resistance of single-use filter housing (in particular capsules | gamma capsules size 4) the recommended integrity test method for Sartopore® Platinum HB is diffusion test (Please note the information letter in the scope of delivery).

3. Flow Rates

Background
Test filter elements are installed into the piping system.The piping system to and from the filters has an inner diameter of 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.

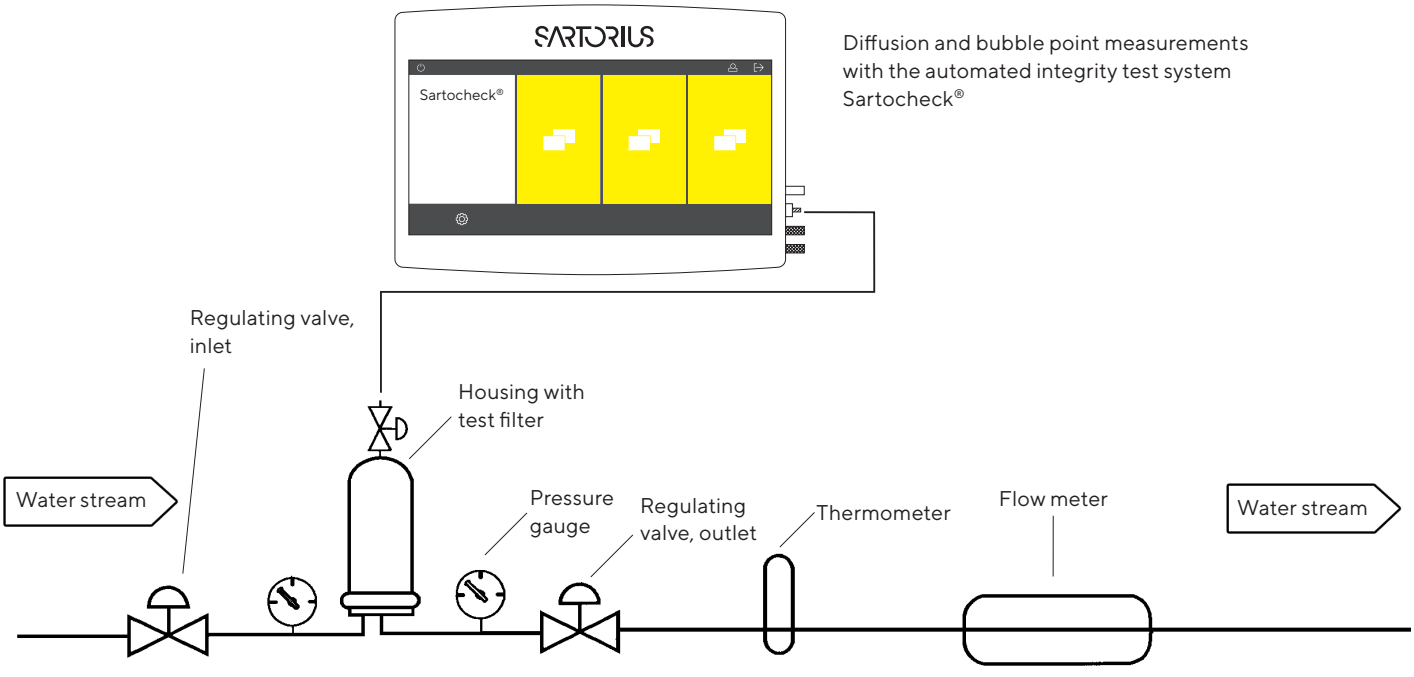
Through the adjustment of valves on the downstream side of the filter housing, the required differential pressure for the test measurements is established. After achieving a constant differential pressure, the flow rate is recorded from the flow meter and the temperature is noted. The flow meter used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

Results
The flow rate curves for water through Sartopore® Platinum family 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.

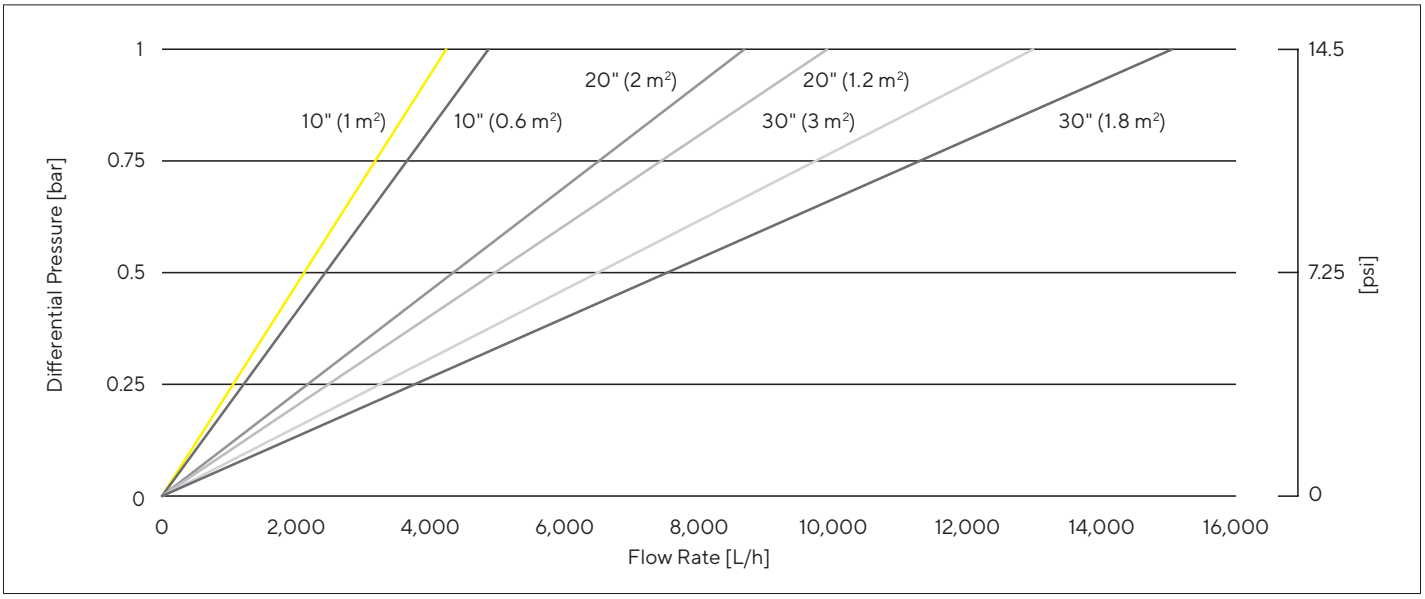
For flow rate measurements of 20" and 30" filter elements, the flow rates reach a point where the geometry of the piping and the filter housing begin to contribute to the overall differential pressure (resistance to flow). At a flow rate of approximately 7000 L/h (120 L/min), the filter membrane surface 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

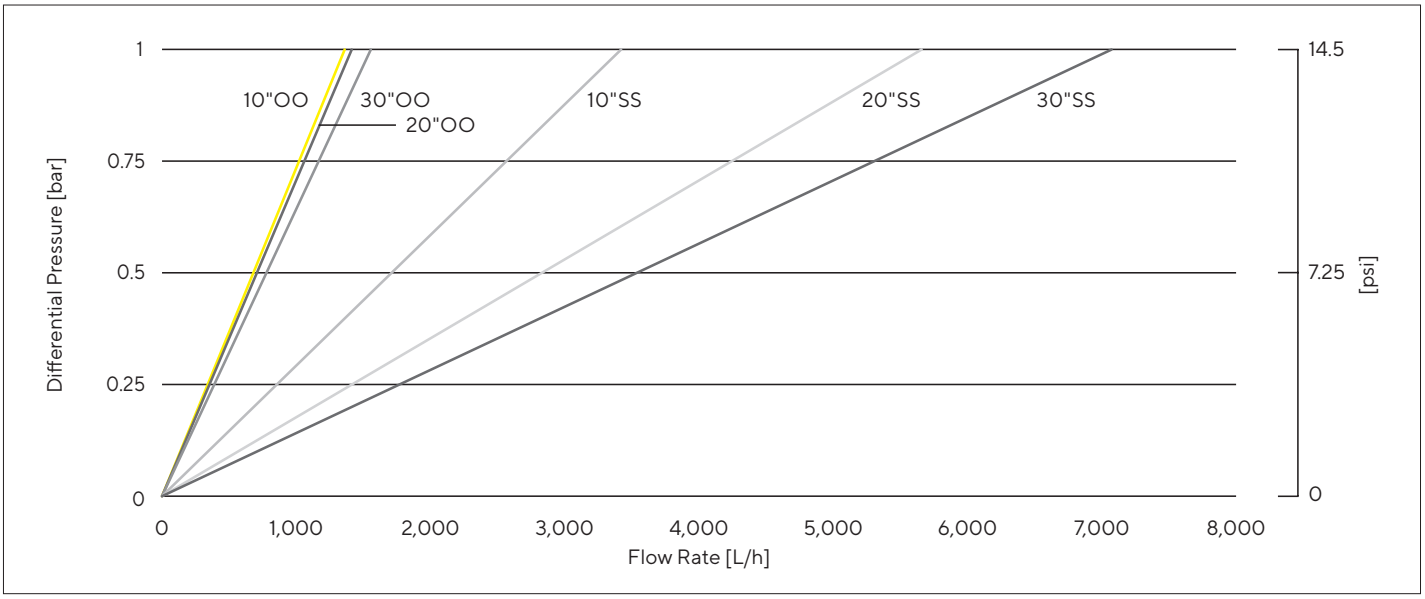


3.1 Water Flow Rates

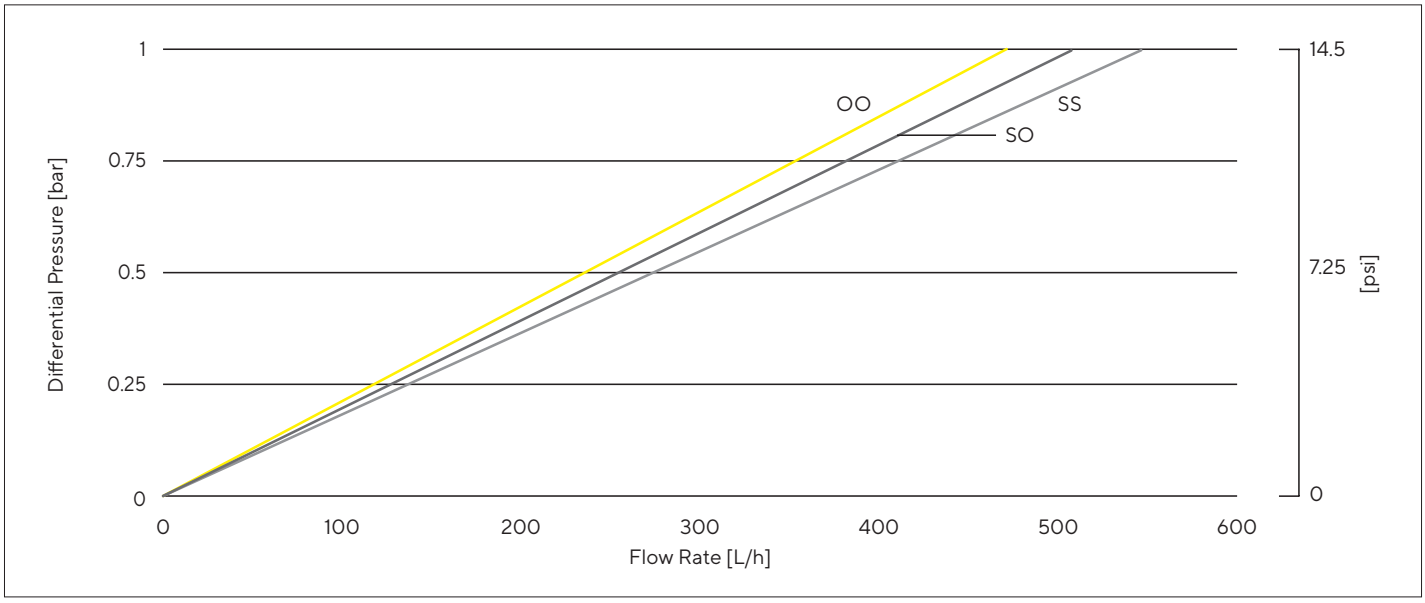
for Standard cartridges



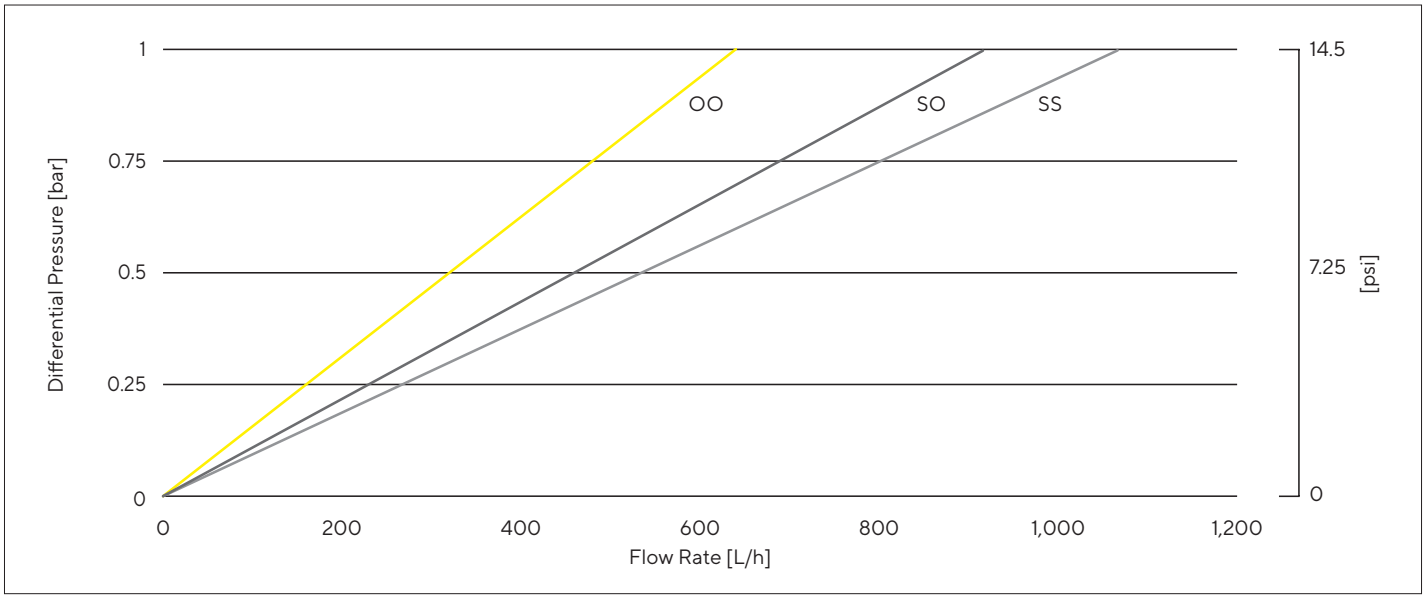
for T-Style Maxicaps® and Maxicaps®



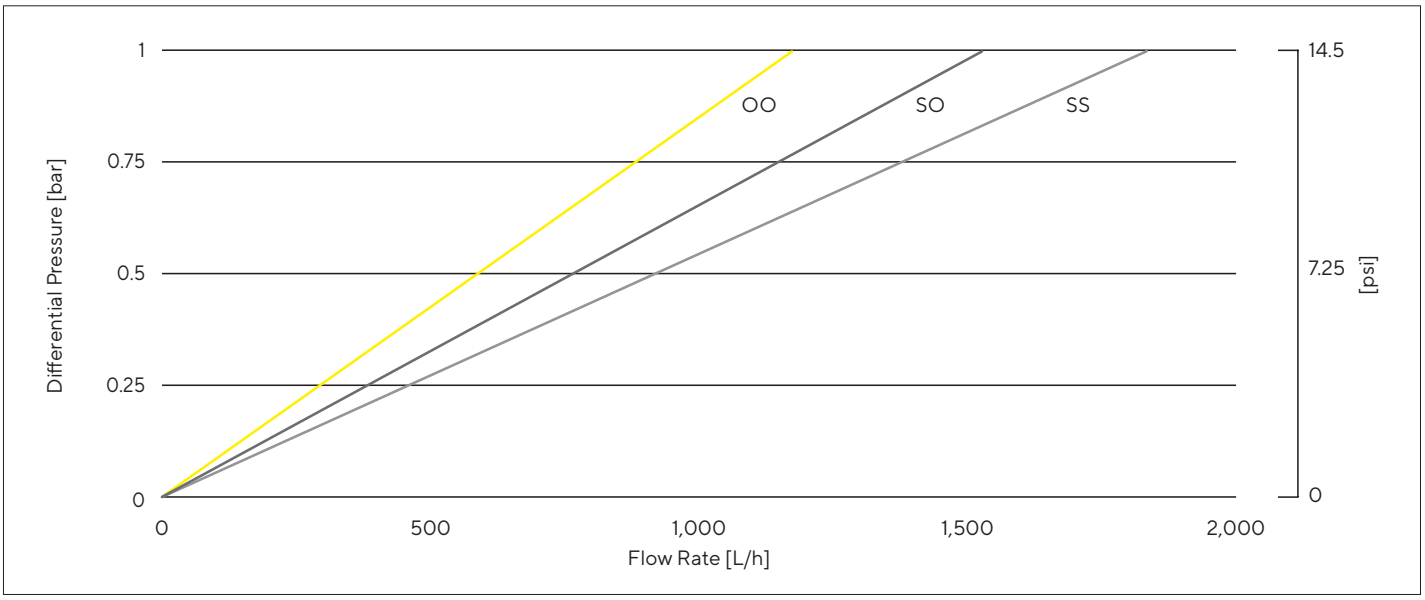
for Midicaps® | gamma Midicaps® size 7



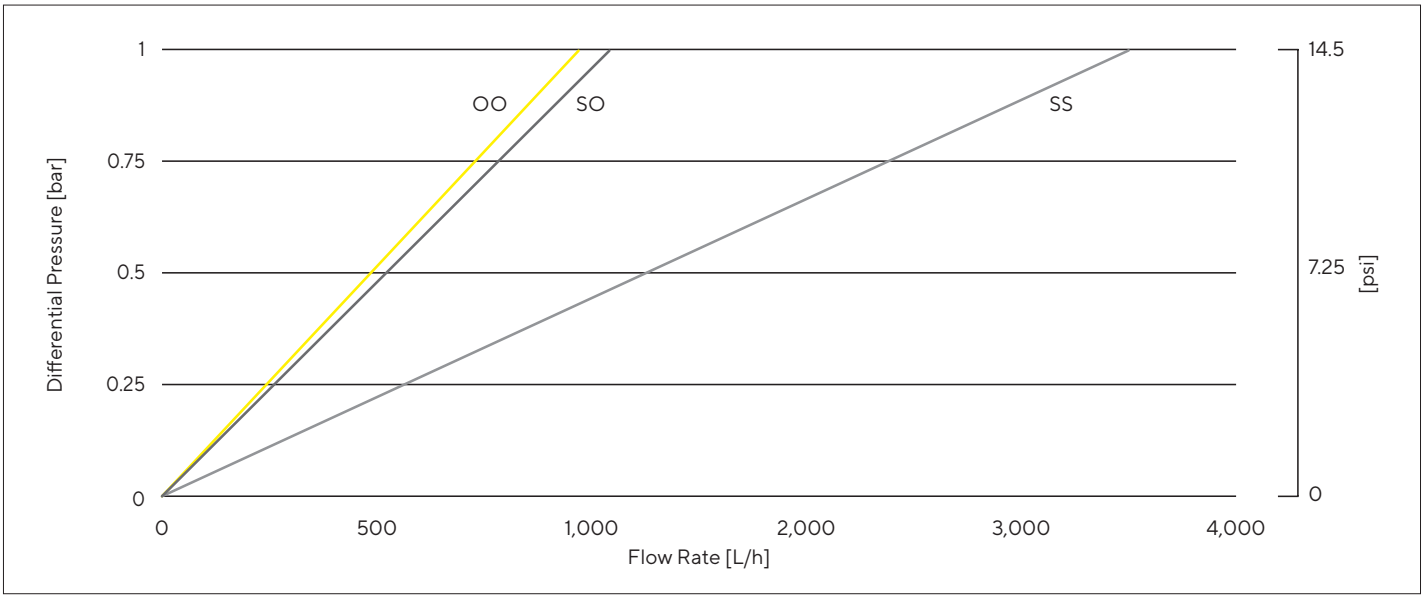
for Midicaps® | gamma Midicaps® size 8



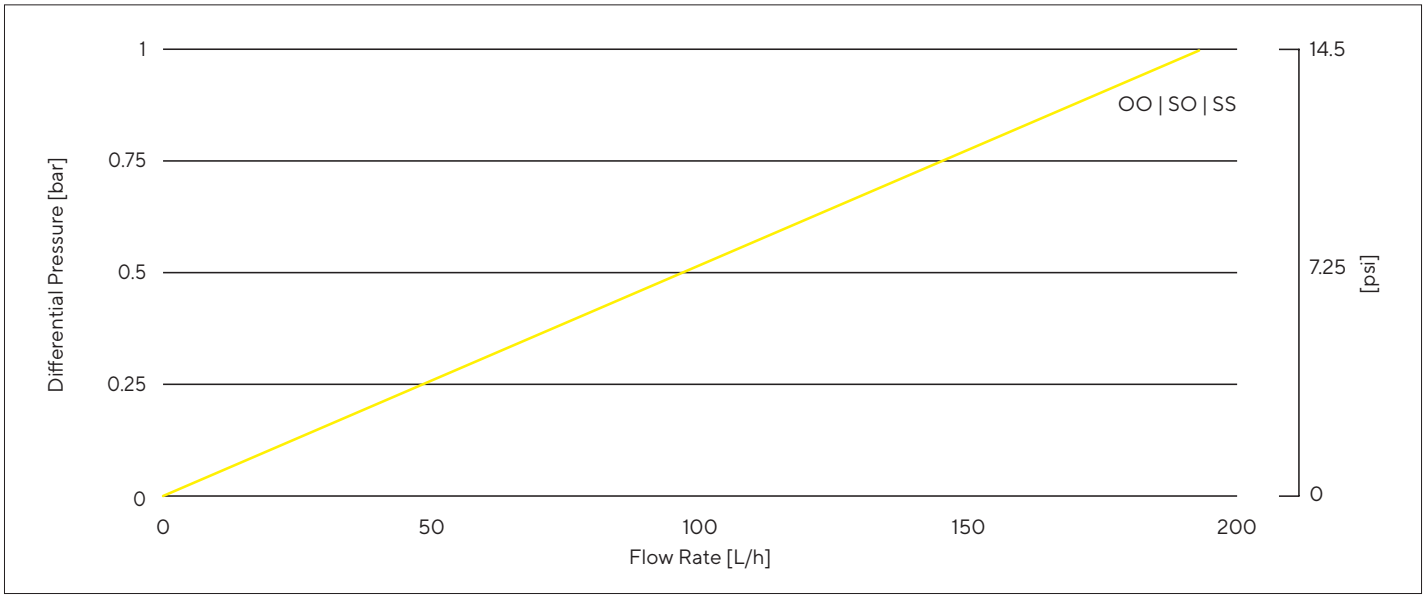
for Midicaps® | gamma Midicaps® size 9



for Midicaps® | gamma Midicaps® size 0



for capsules | gamma capsules size 4



4. Chemical Stability

Under normal operating conditions, Sartopore® Platinum family filter elements are resistant to commonly-used aqueous solutions within pH 1–14, biochemicals and most solvents, with the exception of aromatic and chlorinated compounds. Certain operating conditions and elevated temperatures, can effect the membrane's compatibility. Sartorius advises an own compatibility studies under specific operation conditions and temperatures.

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

	Silicone	EPDM	Fluoroelastomer
Acids			
HCl, 30%	■	■	■
HNO3, 10%	■	■	■
HNO3, 65%	– –	– –	– –
H2SO4, conz.	– –	– –	– –
H2SO4, 25%	□	■	■
H3PO4, 25%	□	■	■
Formic acid, conc.	– –	□	– –
Formic acid, 25%	□	■	□
Acetic acid, conc.	□	■	□
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	– –	– –	– –
Ethers	– –	– –	– –
Methanol, 98%	■	■	■
Ethanol, 10%	■	■	■
Ethanol, 98%	■	■	■
Isopropanol	■	■	■
n-Propanol	■	■	■
n-Amyl alcohol	■	■	□
n-Butanol	■	■	■
Glycerol	■	■	■
Ethylene glycol	■	■	■
Dioxane	– –	– –	– –
Tetrahydrofuran	– –	– –	– –
Dimethylsulfoxide	– –	– –	– –
Dimethylformamide	– –	– –	– –
Pyridine	– –	– –	– –
Acetonitril	– –	– –	– –
Methyl isobutyl keton (MIBK)	– –	– –	– –

■ = Compatible
□ = Limited compatibility
depending on concentration, temperature etc.
– – = Not compatible

Test specifications
24 hours contact at 20 °C

	Silicone	EPDM	Fluoroelastomer
Miscellaneous:			
Aniline	--	--	--
Sodium hypochlorite ≤ 5%	□	■	■
Benzyl alcohol	--	--	--
Phenol, 10%	--	--	--
Formalin, 30%	■	■	■
Hexane	□	□	■
Xylene	--	--	--
Toluene	--	--	--
Benzene	--	--	--
Tetralin	--	--	--
Decalin	□	--	■
Methylene chloride	--	--	--
Chloroform	--	--	--
Carbon tetrachloride	--	--	--
Trichloroethylene	--	--	--
Perchloroethylene	--	--	--
Monochlorobenzene	--	--	--
Methyl acetate	--	--	--
Ethyl acetate	--	--	--
Amyl acetate	□	■	--
Propyl acetate	□	□	--
H_2O_2, 0.3%	■	■	■
Ammoniumpersulfat, 25%	□	□	□
Starch solution	■	■	■
Water	■	■	■
Oil (peanut, sesame, cottonseed, silicone)	■	■	■

■ = Compatible

□ = Limited compatibility
depending on concentration, temperature etc.

-- = Not compatible

Test specifications

24 hours contact at 20 °C

5. Integrity Test Limits

5.1 Basis for the Determination of Integrity Test Values

Establishing a correlation between bacterial retention of a sterilizing grade filter and a non-destructive integrity test is decisive for the reliability of a sterile filtration process.

According to the current ASTM F838 Guideline, and the FDA "Guidelines on Sterile Drug Products Produced by Aseptic Processing", June 1987, a sterilizing grade filter cartridge should produce a sterile effluent when challenged with a minimum concentration of 10^7 *Brevundimonas diminuta* organisms/cm^2 of filter area.

The FDA "Guidelines on Sterile Drug Products Produced by Aseptic Processing", June 1987 states:

"After a filtration process is properly validated for a given product, process and filter, it is important to assure that identical filter replacements (membrane or cartridge) used in production runs will perform in the same manner." One way of achieving this is to correlate filter performance data with filter integrity testing data. Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilized prior to use. More importantly, however, such testing should be conducted after the filter is used in order to detect any filter leaks or perforations that may have occurred during filtration.

Test method
Several Sartopore® Platinum family filter cartridges and capsules, with 0.2 µm pore size membranes, from numerous production lots were tested according to a bacterial challenge test in accordance with the current ASTM F838 Guideline, and DIN 58356, Part 1.
.

Test organism
Brevundimonas diminuta (0.2 µm) (ATCC 19146)

Note
For validation studies of the Sartopore® Platinum family filter elements, a minimum concentration of 1×10^7 *B. diminuta* per cm^2 filtration area for each tested element was used.

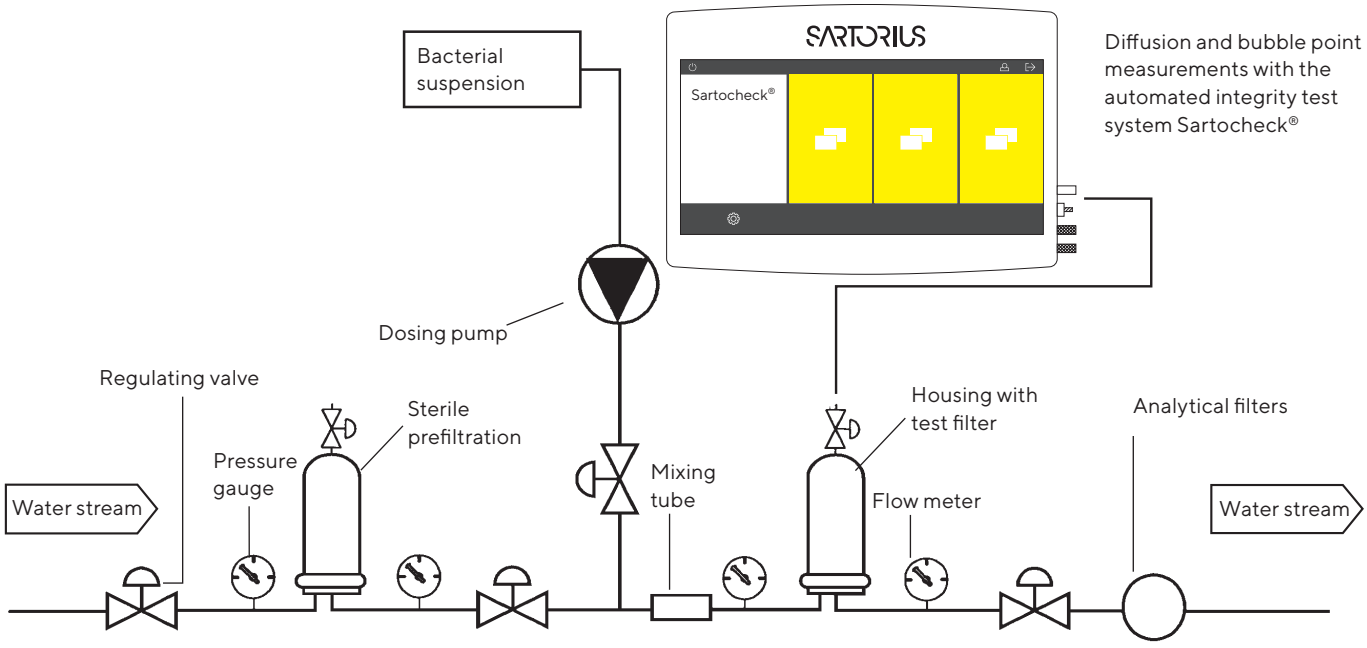
Integrity test
The Sartopore® Platinum family filter elements were integrity tested by diffusion and bubble point test methods in order to correlate the results of the destructive bacterial challenge test with these non-destructive integrity tests.

The diffusion test and the bubble point test are performed utilizing a Sartocheck® automated integrity test unit.

The diffusion values are determined at a test pressure of 2.5 bar | 36 psi for 0.2 µm rated filters and 3.0 bar | 44 psi for 0.1 µm rated filters. For the determination of the bubble point, air pressure is slowly increased on the upstream side of the filter housing by the Sartocheck® integrity tester until the bubble point is automatically detected (overproportional flow).

5.2 Bacterial Retention Test

Test set-up



Water flow is initiated and the water stream first passes through a sterilizing grade filter cartridge. The purpose of this filter is to remove particles and bacteria to assure the test filter is only challenged with the bacterial load as described in the ASTM Document.

Sterilizing Filter Cartridge:
Sartopore® Platinum 0.45 + 0.2 µm
Membrane Filter 5492507H1

The bacterial challenge bioburden that will be introduced to the test filter cartridge is controlled by dosing of the bacterial suspension into the water stream with a peristaltic pump. After the bacterial suspension is added to the water stream, the flow is directed through a mixing tube to ensure that proper mixing of the bacterial suspension has occurred. For the control and monitoring of the differential pressure during the bacterial challenge test, pressure gauges and valves have been installed on the upstream and downstream side of the filter cartridges. The filtrate that passes through the test filter then flows through the analytical filters. After the completion of the bacterial challenge test, these analytical filters can be examined according to the analytical methods described in the ASTM document.

Test procedure
The Sartopore® Platinum family filter cartridges or capsules are installed and wetted as described in the operating instructions. The filter system is then sterilized.

The system is then rinsed with water and the test filter is integrity tested with the Sartocheck®. The water flow is controlled with the valving of the system and set so that the bacterial suspension can be dosed into the water stream. After the bacterial challenge test, the analytical filters are incubated on agar plates to determine if there was passage of bacteria through the test filter. The analysis of the analytical filters is conducted according to the ASTM Method.

5.3 Diffusion Test Limits

5.3.1 Standard Cartridges, T-Style Maxicaps® and Maxicaps® 10" (1.0 m^2 | 10.8 ft^2)

Note
Since most of the filters tested during the validation studies had low diffusion values and produced a sterile filtrate, the following data is a sampling from all filters tested during the validation testing indicating results near the diffusion | sterile filtrate limits.

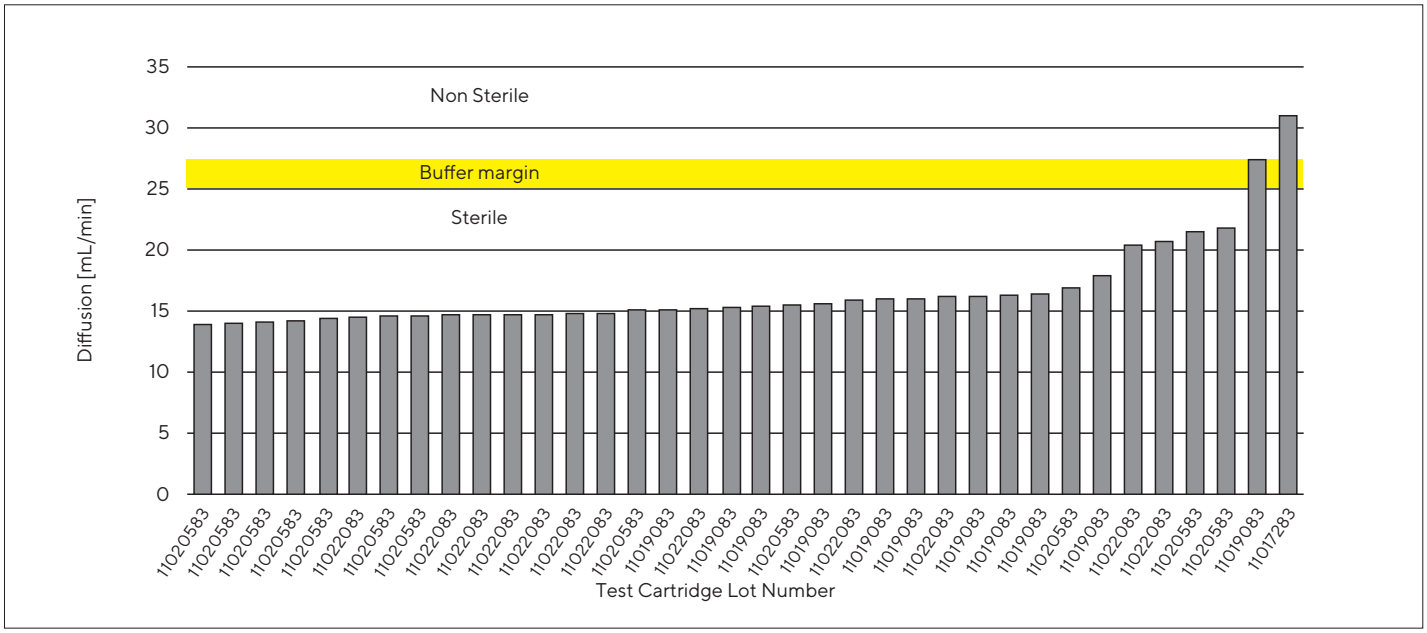
Results

Lot Number	Diffusion [mL/min]	Bioburden [CFU]*	Filtrate Quality
11020583	13.9	1.85×10^{11}	sterile
11020583	14	1.85×10^{11}	sterile
11020583	14.1	1.85×10^{11}	sterile
11020583	14.2	1.53×10^{11}	sterile
11020583	14.4	1.53×10^{11}	sterile
11022083	14.5	1.44×10^{11}	sterile
11020583	14.6	1.85×10^{11}	sterile
11020583	14.6	1.53×10^{11}	sterile
11022083	14.7	1.49×10^{11}	sterile
11022083	14.7	1.49×10^{11}	sterile
11022083	14.7	1.49×10^{11}	sterile
11022083	14.7	1.44×10^{11}	sterile
11022083	14.8	1.44×10^{11}	sterile
11022083	14.8	1.49×10^{11}	sterile
11020583	15.1	1.85×10^{11}	sterile
11019083	15.1	1.53×10^{11}	sterile
11022083	15.2	1.49×10^{11}	sterile
11019083	15.3	1.53×10^{11}	sterile
11019083	15.4	1.53×10^{11}	sterile
11020583	15.5	1.53×10^{11}	sterile
11019083	15.6	1.53×10^{11}	sterile
11022083	15.9	1.44×10^{11}	sterile
11019083	16	1.53×10^{11}	sterile
11019083	16	1.53×10^{11}	sterile
11022083	16.2	1.11×10^{11}	sterile
11019083	16.2	1.53×10^{11}	sterile
11019083	16.3	1.53×10^{11}	sterile
11019083	16.4	1.53×10^{11}	sterile

Lot Number	Diffusion [mL/min]	Bioburden [CFU]*	Filtrate Quality
11020583	16.9	1.53×10^{11}	sterile
11019083	17.9	1.62×10^{11}	sterile
11022083	20.4	1.13×10^{11}	sterile
11022083	20.7	1.13×10^{11}	sterile
11020583	21.5	1.44×10^{11}	sterile
11020583	21.8	1.44×10^{11}	sterile
11019083	27.4	1.62×10^{11}	sterile
11017283	31	1.96×10^{11}	non sterile
130051283	16.7	–	sterile
130047583	14.6	–	sterile

Note
The diffusion values shown can also be assumed for the HB version.

* CFU = Colony Forming Units



Conclusion

The data shows that Sartopore® Platinum filter cartridges 10" exemplarily for T-Style Maxicaps® and Maxicaps® have diffusion values < 27.4 mL/min always produced a sterile filtrate with 100% retention of the test organism, *Brevundimonas diminuta*. In order to have a high degree of caution when evaluating the test results, and considering that other filter integrity test units or other test methods may be used, a buffer margin of 2.4 mL/min has been defined. For a thoroughly water wetted 10" Sartopore® Platinum 0.2 µm filter cartridge, (keeping in mind this buffer margin), the maximum allowable diffusion value at a test pressure of 2.5 bar | 36.2 psi at 20 °C is:

25 mL/min.

Note

The maximal allowable diffusion values for Sartopore® Platinum HB filters are the same as for the standard Sartopore® Platinum filters.

Sartopore® Platinum 0.2 µm filter cartridges, T-Style Maxicaps® and Maxicaps® of various lengths have the following maximum allowable diffusion values at a test pressure of 2.5 bar | 36 psi at 20 °C:

for 10" (1.0 m² | 10.8 ft²): 25 mL/min
for 20" (2.0 m² | 21.5 ft²): 50 mL/min
for 30" (3.0 m² | 32.3 ft²): 75 mL/min

Min. bubble point for standard version: ≥ 3.5 bar | 50.8 psi
Min. bubble point for HB version: ≥ 4.1 bar | 59.5 psi

Note

The diffusion and bubble point test results are influenced by the nature of the wetting medium. The diffusion and bubble point values listed in this validation guide are for Sartopore® Platinum (HB) filters wetted with water at 20 °C. It should be noted, that a variation of the test conditions such as temperature, wetting liquid or type of gas may require a different integrity test limit related to those mentioned above.

If a different test method is selected, for example an integrity test device that measures the values by monitoring the upstream pressure drop, this test method must be verified to the direct methods described above. The upstream pressure drop (pressure hold) test is not only influenced by the diffusion of gas through the wetted filter membranes, but also the upstream volume of the filtration system. Without exact values for the upstream volume of the filtration systems, maximum allowable pressure drop values cannot be calculated for a particular filter system.

5.3.2 Standard Cartridges 10" (0.6 m² | 6.5 ft²)

Sartopore® Platinum 0.2 µm filter cartridges of various lengths have the following maximum allowable diffusion values at a test pressure of 2.5 bar | 36 psi at 20 °C:

for 10" (0.6 m² | 6.5 ft²): 15 mL/min
for 20" (1.2 m² | 12.9 ft²): 30 mL/min
for 30" (1.8 m² | 19.4 ft²): 45 mL/min

Min. Bubble Point: ≥ 3.5 bar | 50.8 psi

5.3.3 Midicaps® | Gamma Midicaps® Size 9 and Capsules | Gamma Capsules Size 4

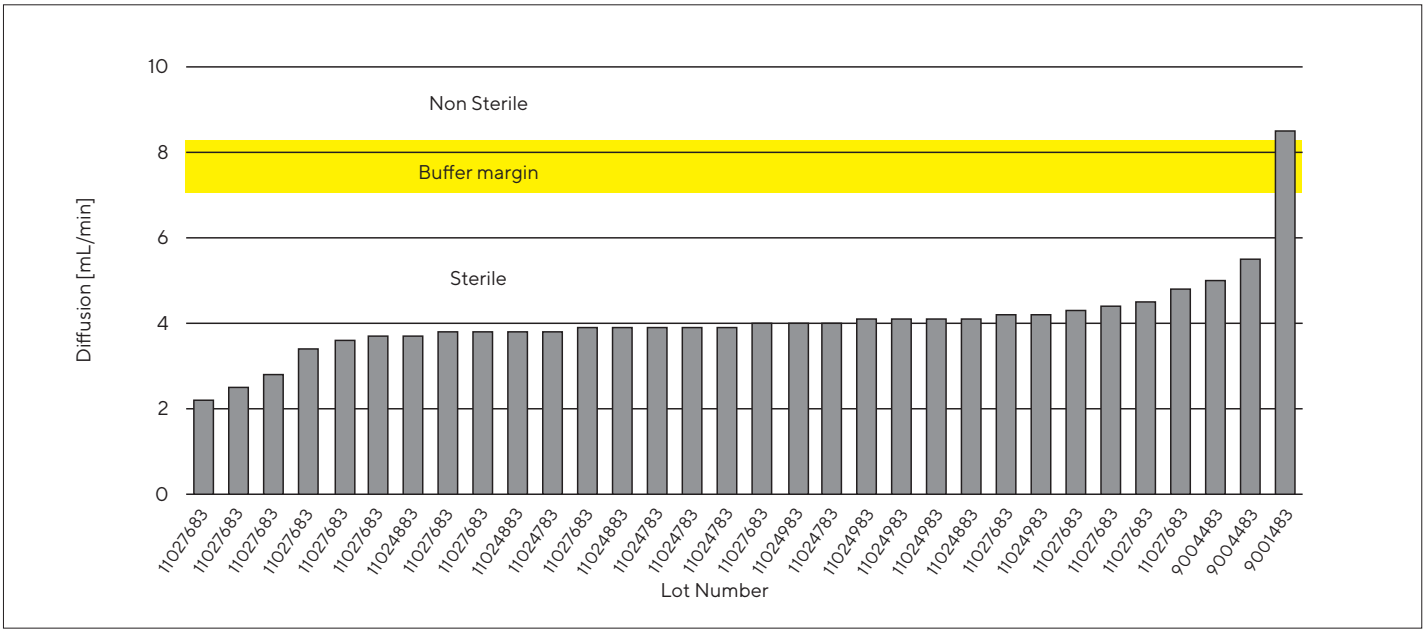
Lot Number	Diffusion [mL/min]	Bioburden [CFU]	Filtrate Quality
11027683	2.2	1.27×10^{10}	sterile
11027683	2.5	1.81×10^{10}	sterile
11027683	2.8	1.33×10^{10}	sterile
11027683	3.4	1.81×10^{10}	sterile
11027683	3.6	1.08×10^{10}	sterile
11027683	3.7	1.08×10^{10}	sterile
11024883	3.7	3.45×10^{10}	sterile
11027683	3.8	1.08×10^{10}	sterile
11027683	3.8	1.27×10^{10}	sterile
11024883	3.8	3.45×10^{10}	sterile
11024783	3.8	3.45×10^{10}	sterile
11027683	3.9	1.28×10^{10}	sterile
11024883	3.9	3.45×10^{10}	sterile
11024783	3.9	3.75×10^{10}	sterile
11024783	3.9	3.75×10^{10}	sterile
11024783	3.9	3.75×10^{10}	sterile
11027683	4	1.28×10^{10}	sterile
11024983	4	4.05×10^{10}	sterile
11024783	4	3.75×10^{10}	sterile
11024983	4.1	4.05×10^{10}	sterile
11024983	4.1	4.05×10^{10}	sterile
11024983	4.1	4.05×10^{10}	sterile
11024883	4.1	3.45×10^{10}	sterile
11027683	4.2	1.08×10^{10}	sterile
11024983	4.2	4.05×10^{10}	sterile
11027683	4.3	1.33×10^{10}	sterile
11027683	4.4	1.27×10^{10}	sterile
11027683	4.5	1.23×10^{10}	sterile
11027683	4.8	1.23×10^{10}	sterile
9004483	5.0	4.05×10^{10}	sterile
9004483	5.5	3.75×10^{10}	sterile
9001483	8.5	3.45×10^{10}	sterile

Lot Number	Diffusion [mL/min]	Bioburden [CFU]	Filtrate Quality
170004583	4.2	–	sterile
170017983	4.4	–	sterile

Note

The diffusion values shown can also be assumed for the HB version.

* CFU = Colony Forming Units



Conclusion

The data shows that Sartopore® Platinum Midicaps® | gamma Midicaps® size 9 exemplarily for capsules | gamma capsules size 4 have diffusion values ≤ 8.5 mL/min always produced a sterile effluent with 100 % retention of the test organism, *Brevundimonas diminuta*. In order to have a high degree of caution when evaluating the test results, and considering that other filter integrity test units or other test methods may be used, a buffer margin of 1.5 mL/min has been defined. For a thoroughly water wetted Sartopore® Platinum Midicaps® | gamma Midicaps® with 0.26 m^2 filtration area, (keeping in mind this buffer margin), the maximum allowable diffusion value at a test pressure of 2.5 bar | 36.2 psi at 20 °C is:

7 mL/min.

Note

The maximal allowable diffusion values for Sartopore® Platinum HB filters are the same as for the standard Sartopore® Platinum filters.

Sartopore® Platinum 0.2 µm Midicaps®| gamma Midicaps® and capsules| gamma capsules of various lengths have the following maximum allowable diffusion values at a test pressure of 2.5 bar| 36 psi at 20 °C:

for size 4: 1.1 mL/min
for size 7: 4 mL/min
for size 8: 5 mL/min
for size 9: 7 mL/min
for size 0: 14 mL/min

Min. bubble point for standard version: 3.5 bar | 50.8 psi
Min. bubble point for HB Version: ≥ 4.1 bar | 59.5 psi

Note

The diffusion and bubble point test results are influenced by the nature of the wetting medium. The diffusion and bubble point values listed in this validation guide are for Sartopore® Platinum (HB) filter capsules wetted with water at 20 °C. It should be noted, that a variation of the test conditions such as temperature, wetting liquid or type of gas may require a different integrity test limit related to those mentioned above.

If a different test method is selected, for example an integrity test device that measures the values by monitoring the upstream pressure drop, this test method must be verified to the direct methods described above. The upstream pressure drop (pressure hold) test is not only influenced by the diffusion of gas through the wetted filter membranes, but also the upstream volume of the filtration system. Without exact values for the upstream volume of the filtration systems, maximum allowable pressure dropvalues cannot be calculated for a particular filter system.

5.4 Manual Determination of Maximal Allowable Pressure Drop

Test protocol
Slowly pressurize the filter housing containing the wetted filter cartridge. The test pressure which you need to use is dependent upon the pore size of the membrane to be tested. (See integrity test data table). Once the correct pressure is attained, allow for a 5 minute stabilization period and then close the pressure supply. During the 5 minute test period, the pressure drop should not exceed the permissible value. This maximum pressure drop is dependent upon a variety of criteria, including the upstream volume of the special filter housing at a constant temperature, and must be calculated according to the general gas equation:

$$P_A - P_E = \frac{V_D \cdot t \cdot P_O}{V}$$

$P_A - P_E$: Pressure drop in mbar after test period (t)

V_D: Gas diffusion [mL/min] (see table)

t: Test time [min]

P_O: Atmospheric pressure (= 1,000 mbar | 14.5 psi)

V: Volume of housing on the inlet side in mL
(net volume of housing with installed cartridge
+ volume of the inlet line to the stop valve
+ volume of the gas tubing)

Note
With the use of the Sartorius automated integrity test system, Sartocheck®, the upstream volume is calculated during every integrity test. In order to have a reliable determination of the integrity of the filtration system without the influence of the upstream volume, it is suggested that the diffusion test is used. This test is not dependent on the upstream volume of the filter system.

5.4.1 Examples of the Maximum Allowable Pressure Drop for:

T-Style Maxicaps®

Filter Capsule	Max. Diffusion at 20 °C and 2.5 bar | 36 psi [mL/min]	Upstream Volume [mL]	Max. Allowable Pressure Drop at 20 °C and 2.5 bar | 36 psi
5498307H1G-**	25	1,100	113.6 mbar/5 min (1.65 psi/5 min)
5498307H2G-**	50	2,000	125 mbar/5 min (1.81 psi/5 min)
5498307H3G-**	75	2,900	129.3 mbar/5 min (1.88 psi/5 min)

Maxicaps®

Filter Capsule	Max. Diffusion at 20 °C and 2.5 bar | 36 psi [mL/min]	Upstream Volume [mL]	Max. Allowable Pressure Drop at 20 °C and 2.5 bar | 36 psi
5497307H1G-**	25	1,096	114.1 mbar/5 min (1.65 psi/5 min)
5497307H2G-**	50	1,874	133.4 mbar/5 min (1.93 psi/5 min)
5497307H3G-**	75	2,630	142.6 mbar/5 min (2.07 psi/5 min)

Midicaps® | gamma Midicaps® and capsules | gamma capsules

Filter Capsule	Max. Diffusion at 20 °C and 2.5 bar | 36 psi [mL/min]	Upstream Volume [mL]	Max. Allowable Pressure Drop at 20 °C and 2.5 bar | 36 psi
5495307H0--** 5495307H0G-**	14	530	132.1 mbar/5 min (1.91 psi/5 min)
5495307H9--** 5495307H9G-**	7	320	109.4 mbar/5 min (1.58 psi/5 min)
5495307H8--** 5495307H8G-**	5	240	104.2 mbar/5 min (1.51 psi/5 min)
5495307H7--** 5495307H7G-**	4	180	111.1 mbar/5 min (1.61 psi/5 min)
5491307H4--** 5491307H4G-**	1.1	78	70.5 mbar/5 min (1.02 psi/5 min)

** = All available connector | adapter types

6. Thermal Stability

6.1 Steam Sterilization

The materials and construction of the Sartopore® Platinum (HB) 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 Sartopore® Platinum (HB) filter cartridges were examined. As a result, recommendations and limits for multiple in-line steam sterilization are given.

Test method
Sartopore® Platinum standard filter cartridges, with a pore size of 0.2 µm from a number of different production lots, were installed into stainless steel filter housing (Sartorius Part Number 340011P25TT112A or 331019P15TT112A) and were in-line sterilized with saturated steam at 2 bar | 30 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 and bubble point testing, as well as the water flow rates. After 25 steam cycles, the filters are tested by the ASTM bacterial challenge test to verify that the filters could still produce a sterile effluent.

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 Sartopore® Platinum 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 test and bubble point. The flow rates were also recorded for these filters.**

3. **The filters are in-line steam sterilized using different methods:**
   - **wet forward (25 ×)**
   - **wet reverse (5 ×)**
   - **dry forward (5 ×)**
   - **dry reverse (5 ×)**

4. **After the first in-line steam sterilization cycle, the filters are integrity tested by diffusion and bubble point. The flow rates were also recorded.**

5. **The filters are then steam sterilized 25 times or 5 times (see above).**

6. **After having performed the complete number of sterilization cycles, the filters are integrity tested by diffusion and bubble point. The flow rates were also recorded.**

7. **The cartridges are then bacterial challenge tested to determine if the steam sterilization cycles had any effect on the bacteria retention properties of the Sartopore® Platinum (HB) filter cartridges.**

Note
The tests described in this chapter have been performed on 10" cartridges with 1.0 m^2 effective filtration area. The conclusion for this cartridge is valid for the 0.6 m^2 cartridge as well.

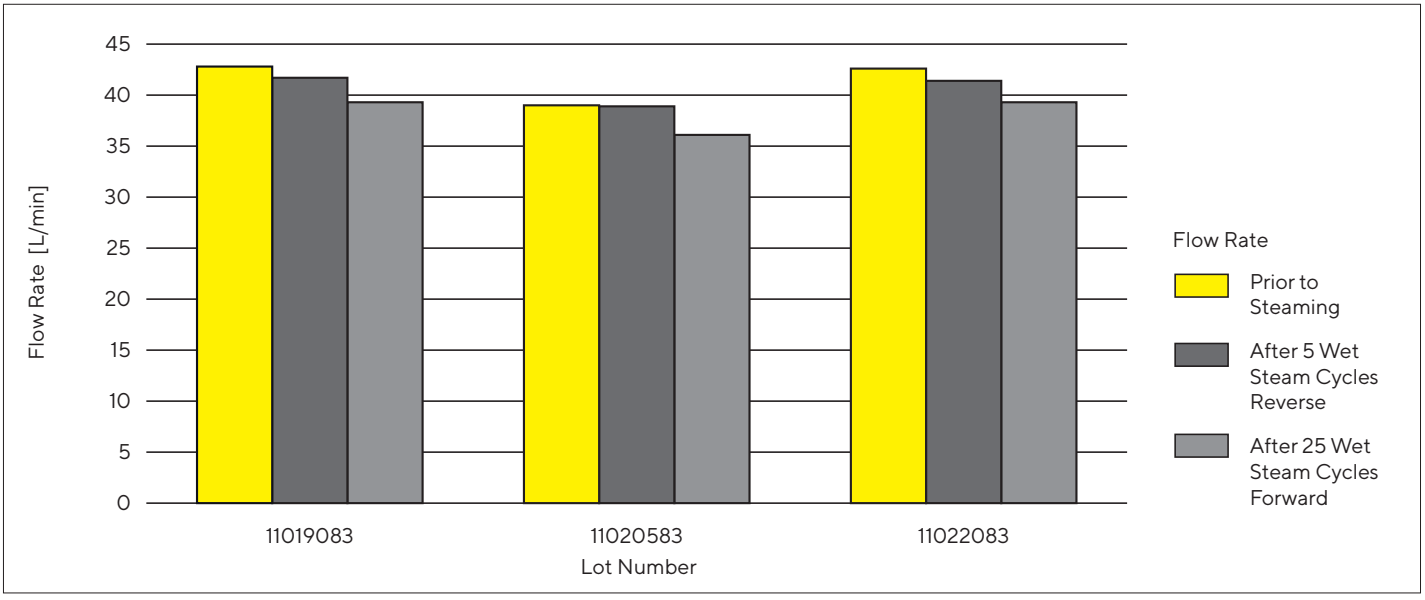
6.1.1 Effects on Water Flow Rates

Test procedure
Six Sartopore® Platinum 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.

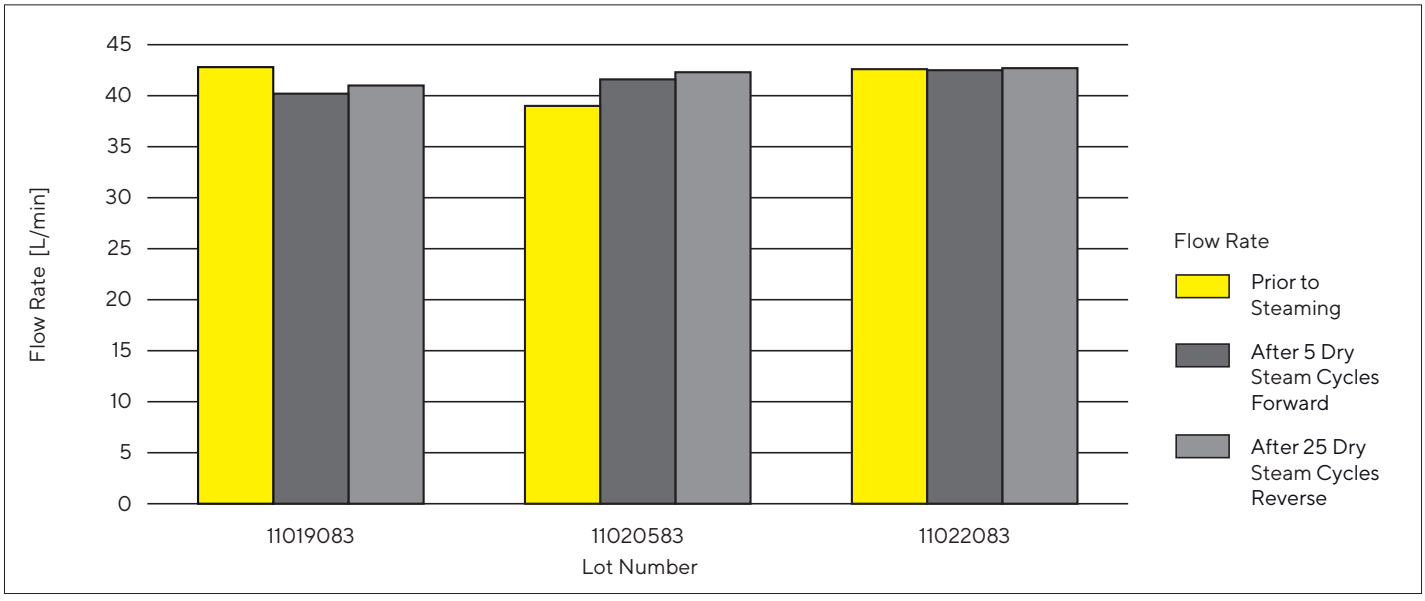
6.1.1.1 Standard Cartridges 10" (1 m^2) 0.2 µm – Wet Steaming

Lot Number	Flow Rate Prior to Steaming [L/min]	Flow Rate After 5 Wet Steam Cycle Reverse [L/min]	Flow Rate After 25 Wet Steam Cycles Forward [L/min]
11019083	42.8	41.7	39.3
11020583	39	38.9	36.1
11022083	42.6	41.4	39.3



6.1.1.2 Standard Cartridges 10" (1 m^2) 0.2 µm – Dry Steaming

Lot Number	Flow Rate Prior to Steaming [L/min]	Flow Rate After 5 Dry Steam Cycles Forward [L/min]	Flow Rate After 5 Dry Steam Cycles Reverse [L/min]
11019083	42.8	40.2	41
11020583	39	41.6	42.3
11022083	42.6	42.5	42.7



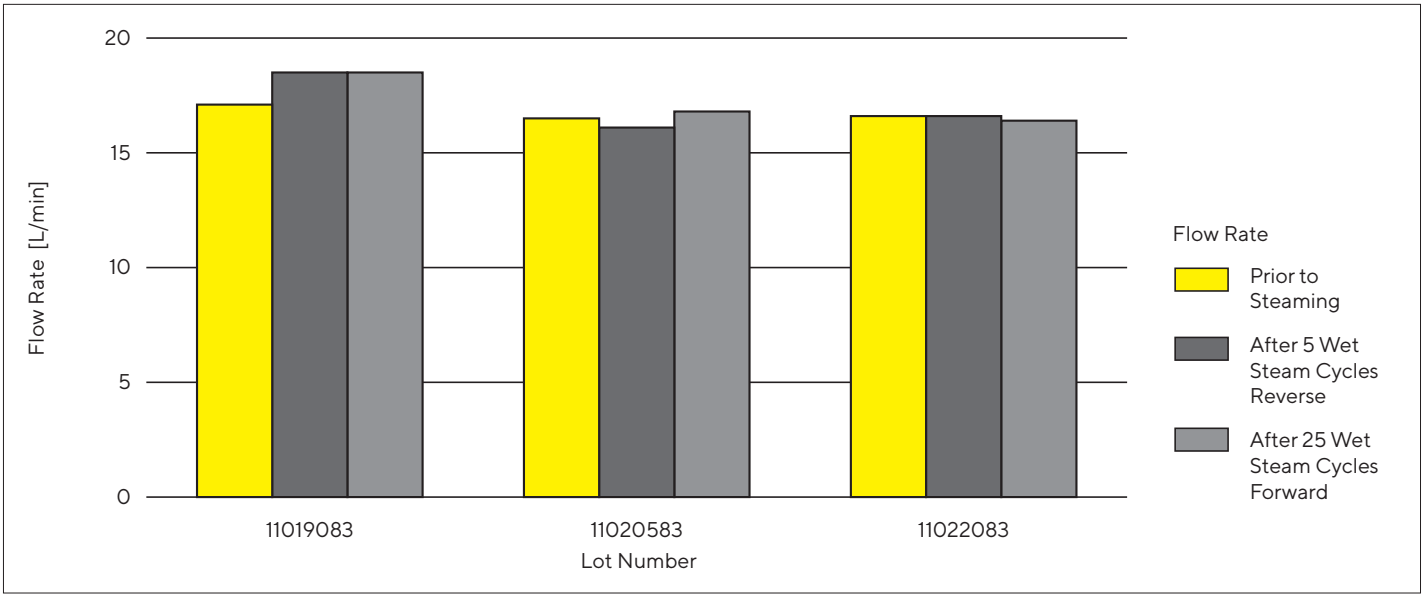
6.1.2 Effects on Diffusion Values

Test procedure
Six Sartopore® Platinum standard 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: 2.5 bar | 36 psi
Stabilization time: 5 minutes
Test time: 5 minutes

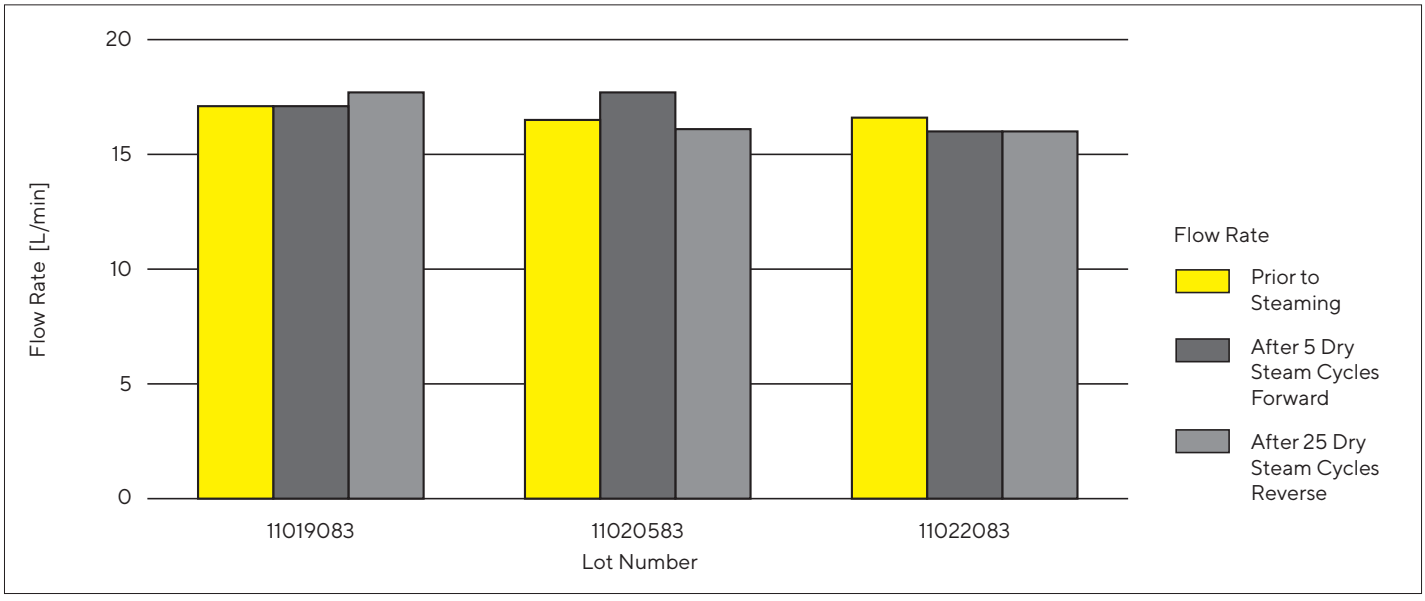
6.1.2.1 Standard Cartridges 10" (1 m^2) 0.2 µm – Wet Steaming

Lot Number	Diffusion Prior to Steaming [mL/min]	Flow Rate After 5 Wet Steam Cycles Reverse [mL/min]	Flow Rate After 25 Wet Steam Cycles Forward [mL/min]
11019083	17.1	18.5	18.2
11020583	16.5	16.1	16.8
11022083	16.6	16.6	16.4



6.1.2.2 Standard Cartridges 10" (1 m²) 0.2 µm – Dry Steaming

Lot Number	Diffusion Prior to Steaming [L/min]	Diffusion After 5 Dry Steam Cycles Forward [L/min]	Diffusion After 5 Dry Steam Cycles Reverse [L/min]
11019083	17.1	17.1	17.7
11020583	16.5	17.7	16.1
11022083	16.6	16	16

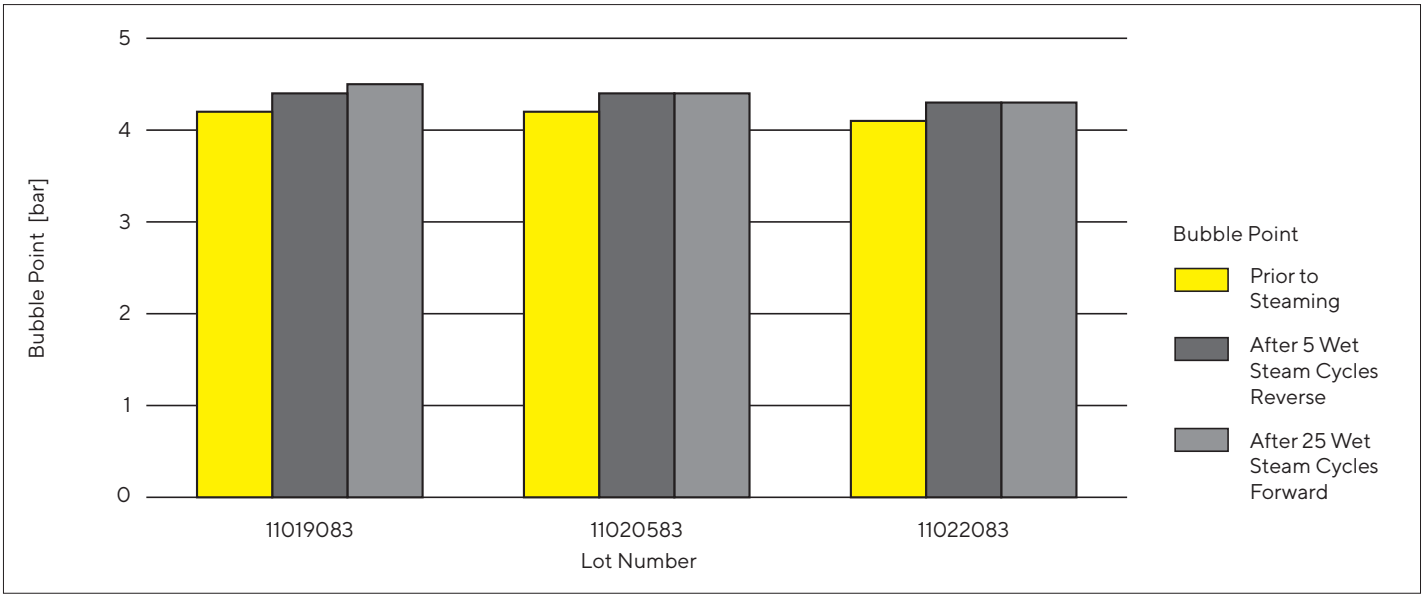


6.1.3 Effects on Bubble Point Values

Test procedure
After diffusion testing, the same Sartopore® Platinum standard 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.

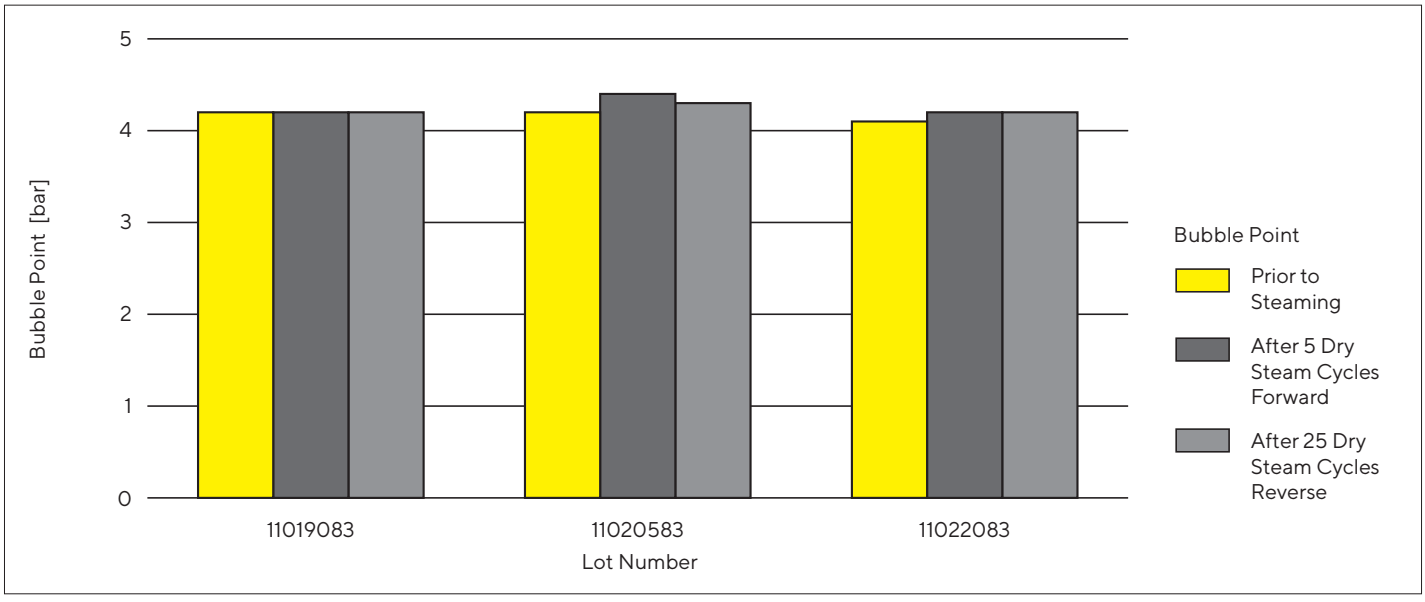
6.1.3.1 Standard Cartridges 10" (1 m^2) 0.2 µm – Wet Steaming

Lot Number	Bubble Point Prior to Steaming [mL/min]	Bubble Point After 5 Wet Steam Cycles Reverse [mL/min]	Bubble Point After 25 Wet Steam Cycles Forward [mL/min]
11019083	4.2	4.4	4.5
11020583	4.2	4.4	4.4
11022083	4.1	4.3	4.3



6.1.3.2 Standard Cartridges 10" (1 m²) 0.2 µm – Dry Steaming

Lot Number	Bubble Point Prior to Steaming [mL/min]	Bubble Point After 5 Dry Steam Cycles Forward [mL/min]	Bubble Point After 25 Dry Steam Cycles Reverse [mL/min]
11019083	4.2	4.2	4.2
11020583	4.2	4.4	4.3
11022083	4.1	4.2	4.2



6.1.4 Bacterial Challenge Test Values

Test procedure
With the Sartopore® Platinum standard cartridges previously mentioned, a bacterial challenge test was performed. This test was conducted according to the current ASTM F838 Guideline. The following bacteria concentrations are averages for the elements tested.

6.1.4.1 Standard Cartridges 10" (1 m^2) 0.2 µm

Lot Number	Bioburden [CFU]	Bacterial Challenge Test After 25 Steam Sterilization Cycles
11019083	1.76×10^{11}	sterile filtrate
11020583	1.76×10^{11}	sterile filtrate
11022083	1.76×10^{11}	sterile filtrate

Lot Number	Bioburden [CFU]	Bacterial Challenge Test After 5 Wet Steam Sterilization Cycles Reverse
11019083	1.71×10^{11}	sterile filtrate
11020583	1.44×10^{11}	sterile filtrate
11022083	1.49×10^{11}	sterile filtrate

Lot Number	Bioburden [CFU]	Bacterial Challenge Test After 5 Dry Steam Sterilization Cycles Reverse
11019083	1.62×10^{11}	sterile filtrate
11020583	1.17×10^{11}	sterile filtrate
11022083	1.17×10^{11}	sterile filtrate

Lot Number	Bioburden [CFU]	Bacterial Challenge Test After 5 Dry Steam Sterilization Cycles Forward
11019083	1.62×10^{11}	sterile filtrate
11020583	1.44×10^{11}	sterile filtrate
11022083	1.71×10^{11}	sterile filtrate

Conclusion
The results indicate that the integrity and bacterial retentive properties of the Sartopore® Platinum (HB) standard cartridges are not effected by 25 in-line steam sterilization (wet forward) cycles at 134 °C for 30 minutes (12.5 hours total) and 5 cycles wet reverse and 5 cycles dry steaming in both directions.

Note
The service life of the filter elements is determined by process conditions, for instance the particle load of the solution being filtered. The service life can also be influenced by the steaming conditions. Different qualities of steam and steam process conditions may lead to variations in the service life of the filters when filters are in-line steam sterilized repeatedly. Additional service life can be affected by product residues which are not removed completely from the membrane by flushing.

6.2 Sterilization of T-Style Maxicaps®, Maxicaps®, Midicaps® | Gamma Midicaps® and Capsules | Gamma Capsules

The materials and construction of the Sartopore® Platinum (HB) T-Style Maxicaps®, Maxicaps®, Midicaps® and capsules size 4 allow for exposures to multiple autoclaving cycles. T-Style Maxicaps® and Maxicaps® can be either autoclaved or gamma irradiated. Gamma Midicaps® and gamma capsules can be gamma irradiated (no autoclaving). Since multiple autoclaving cycles may be required in actual practice, the influences of the thermomechanical stress on the integrity of Sartopore® Platinum (HB) elements was examined. As a result, recommendations and limits for multiple autoclaving are given.

Test method
Sartopore® Platinum T-Style Maxicaps®, Maxicaps®, Midicaps® and capsules size 4 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 of the Midicaps® and after 5 autoclaving cycles of the T-Style Maxicaps®, Maxicaps® and capsules size 4 the integrity is verified through diffusion and bubble point testing, as well as the water flow rates.

For the gamma irradiatable products, tests have also been performed after sterilization by 50 kGy gamma irradiation (1 cycle).

In order to demonstrate that the Sartopore® Platinum (HB) T-Style Maxicaps®, Maxicaps®, Midicaps® | gamma Midicaps® and capsules | gamma capsules have good thermal stability, multiple capsules from different manufacturing lots were tested under the following procedure:

1. **All filter elements are wetted with water.**

2. **The filters are then integrity tested by diffusion and bubble point. The flow rates were also recorded.**

3. **Sterilization of:**
   - **T-Style Maxicaps® and Maxicaps® by autoclaving 5 times or 50 kGy γ-irradiation 1 cycle**
   - **Midicaps® by autoclaving 25 times**
   - **Gamma Midicaps® by 50 kGy γ-irradiation 1 cycle**
   - **Capsules size 4 by autoclaving 5 times**
   - **Gamma capsules size 4 by 50 kGy γ-irradiation 1 cycle**

4. **After the sterilization, the elements are integrity tested by bubble point and diffusion tests. The flow rates were also recorded.**

5. **The elements are then bacteria challenge tested to determine if the autoclaving cycles and gamma irradiation had any effect on the bacteria retention properties of the Sartopore® 2 Platinum products.**

6.2.1 Effects on Water Flow Rates

Test procedure
Sartopore® Platinum filter elements from 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.

6.2.1.1 T-Style Maxicaps® 10"

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 5 Autoclaving Cycles [L/min]	Flow Rate After 50 kGy γ-Irradiation [L/min]
111021583 (SS Connector)	31	27.3	29.4
111022183 (OO Connector)	11.6	11.8	13.4

6.2.1.2 Maxicaps® 10"

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 5 Autoclaving Cycles [L/min]	Flow Rate After 50 kGy γ-Irradiation [L/min]
140018483 (SS Connector)	37.4	25.0	32.3
140018583 (OO Connector)	11.3	11.8	11.4

6.2.1.3 Midicaps® | Gamma Midicaps® Size 9

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 5 Autoclaving Cycles [L/min]
11024783 (SS Connector)	15.6	15.6

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 50 kGy γ-irradiation [L/min]
11027683 (SO Connector)	10.6	10.0
11024783 (SS Connector)	16.8	16.5

6.2.1.4 Capsules | Gamma Capsules Size 4

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 5 Wet Autoclaving Cycles [L/min]	Flow Rate After 5 Dry Autoclaving Cycles [L/min]
10018383	1.46	1.4	1.48
10018483	1.41	1.35	1.44
10018583	1.45	1.34	1.32

Lot Number	Flow Rate Prior Sterilization [L/min]	Flow Rate After 50 kGy γ-irradiation [L/min]
120043483	1.8	2.0
120043583	1.9	2.0
120043683	2.3	2.4

6.2.2 Effects on Diffusion Values

Test procedure
Sartopore® Platinum filter elements from different production lots were wetted. A diffusion test utilizing the following parameters was conducted utilizing an automated integrity test system, the Sartocheck®:

Test pressure: 2.5 bar | 36 psi
Stabilization time: 5 minutes
Test time: 5 minutes

The following results are the averages for the capsules tested.

6.2.2.1 T-Style Maxicaps® 10"

Lot Number	Diffusion Prior Sterilization [mL/min]	Diffusion After 5 Autoclaving Cycles [mL/min]	Diffusion After 50 kGy γ-Irradiation [mL/min]
111021583	16.7	18.1	17
111022183	16	15.4	16

6.2.2.2 Maxicaps® 10"

Lot Number	Diffusion Prior Sterilization [mL/min]	Diffusion After 5 Autoclaving Cycles [mL/min]	Diffusion After 50 kGy γ-Irradiation [mL/min]
140018483	20.5	19.8	19.2
140018583	19.8	19.3	19.2

6.2.2.3 Midicaps® | Gamma Midicaps® Size 9

Lot Number	Diffusion Prior Sterilization [mL/min]	Diffusion After 25 Autoclaving Cycles [mL/min]
11024783	4.2	4.2
11024883	4.3	4.0

Lot Number	Diffusion Prior Sterilization [mL/min]	Diffusion After 50 kGy γ-irradiation [mL/min]
11027583	5.2	4.3
11027683	5.0	5.0

6.2.2.4 Capsules | Gamma Capsules Size 4

Lot Number	Diffusion Prior Sterilization [L/min]	Diffusion After 5 Wet Autoclaving Cycles [L/min]	Diffusion After 5 Dry Autoclaving Cycles [L/min]
10018383	0.4	0.5	0.6
10018483	0.4	0.5	0.5
10018583	0.4	0.5	0.5

Lot Number	Diffusion Prior Sterilization [L/min]	Diffusion After 50 kGy γ-irradiation [L/min]
120043483	0.4	0.4
120043583	0.3	0.4
120043683	0.4	0.5

6.2.3 Effects on Bubble Point Values

Test procedure
After diffusion testing, the same Sartopore® Platinum filter elements 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.

6.2.3.1 T-Style Maxicaps® 10"

Lot Number	Bubble Point Prior Sterilization [mL/min]	Bubble Point After 5 Autoclaving Cycles [mL/min]	Bubble Point After 50 kGy γ-Irradiation [mL/min]
111021583	4.1	4.3	4.4
111022183	4.0	4.2	4.3

6.2.3.2 Maxicaps® 10"

Lot Number	Bubble Point Prior Sterilization [mL/min]	Bubble Point After 5 Autoclaving Cycles [mL/min]	Bubble Point After 50 kGy γ-Irradiation [mL/min]
140018483	4.0	3.9	4.0
140018583	4.0	4.3	4.0

6.2.3.3 Midicaps® | Gamma Midicaps® Size 9

Lot Number	Bubble Point Prior Sterilization [mL/min]	Bubble Point After 25 Autoclaving Cycles [mL/min]
11024783	4.5	4.7
11024883	4.2	4.6

Lot Number	Bubble Point Prior Sterilization [mL/min]	Bubble Point After 50 kGy γ-irradiation [mL/min]
11027583	4.8	4.3
11027683	4.2	4.2

6.2.3.4 Capsules | Gamma Capsules Size 4

Lot Number	Bubble Point Prior Sterilization [L/min]	Bubble Point After 5 Wet Autoclaving Cycles [L/min]	Bubble Point After 5 Dry Autoclaving Cycles [L/min]
10018383	3.8	4.5	4.1
10018483	3.9	4.6	4.1
10018583	3.9	4.6	4.4

Lot Number	Bubble Point Prior Sterilization [L/min]	Bubble Point After 50 kGy γ-irradiation [L/min]
120043483	3.2	3.9
120043583	3.5	3.9
120043683	3.3	4.0

6.2.4 Bacterial Challenge Test Values

Test procedure
With the Sartopore® Platinum family filter elements previously mentioned, a bacterial challenge test was performed. This test was conducted according to the current ASTM F838 Guideline. The following bacteria concentrations are averages for the elements tested.

6.2.4.1 T-Style Maxicaps® 10"

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After 5 Autoclaving Cycles
111022283	1.17×10^7	sterile filtrate
111022183	1.17×10^7	sterile filtrate

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After Gamma Sterilization
111022283	1.17×10^7	sterile filtrate

6.2.4.2 Maxicaps® 10"

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After 5 Autoclaving Cycles
140018483	1.38×10^7	sterile filtrate
140018583	1.57×10^7	sterile filtrate

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After Gamma Sterilization
140018483	1.46×10^7	sterile filtrate
140018583	1.46×10^7	sterile filtrate

6.2.4.3 Midicaps® | Gamma Midicaps® Size 9

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After 5 Autoclaving Cycles
11024983	1.84×10^7	sterile filtrate
11024683	1.9×10^7	sterile filtrate
11025283	1.79×10^7	sterile filtrate

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After Gamma Sterilization
11027583	1.5×10^7	sterile filtrate
11027683	1.5×10^7	aterile filtrate

6.2.4.4 Capsules | Gamma Capsules Size 4

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After 5 Autoclaving Cycles
10018383	1.84×10^7	sterile filtrate
10018483	1.9×10^7	sterile filtrate
10018583	1.79×10^7	sterile filtrate

Lot Number	Bioburden [CFU/cm²]	Bacterial Challenge Test After Gamma Sterilization
120043483	1.71×10^7	sterile filtrate
120043583	1.14×10^7	aterile filtrate
120043683	1.38×10^7	

Conclusion

The results indicate that the integrity and bacterial retentive properties of the Sartopore® Platinum (HB) filter elements are not effected by multiple sterilization cycles.

Note

The service life of the filter elements is determined by process conditions, for instance the particle load of the solution being filtered. The service life can also be influenced by the steaming conditions. Different qualities of steam and steam process conditions may lead to variations in the service life of the filters when filters are in-line steam sterilized repeatedly. Service life can be affected by product residues which are not removed completely from the membrane by flushing.

7. Testing According to USP

The tests for extractable substances and particle release of Sartopore® Platinum (HB) 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.

According to the specifications given in section "Sterile Water for Injection" of the current USP, filtrate samples of Sartopore® Platinum (HB) 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 British Pharmacopoeia (BP).

The following filter types were used for extractables and particle release testing of Sartopore® Platinum (HB) filters, representing the individual filter types available:

Standard filter cartridges:
5492507H1 (1 m^2)

T-Style Maxicaps®:
5498307H1G-SS

Maxicaps®:
5497307H1G-SSIT

Midicaps®:
5495307H9- -SS

Gamma Midicaps®:
5495307H9G-SS

Capsules size 4:
5491307H4- -SS

Gamma capsules size 4:
5491307H4G-SS

Note:
The tests described in this chapter have been performed on 10" cartridges with 1.0 m^2 effective filtration area. The conclusion for this cartridge is valid for the 0.6 m^2 cartridge (5492507H1-S) as well.

7.1 Particle Content of the Filtrate

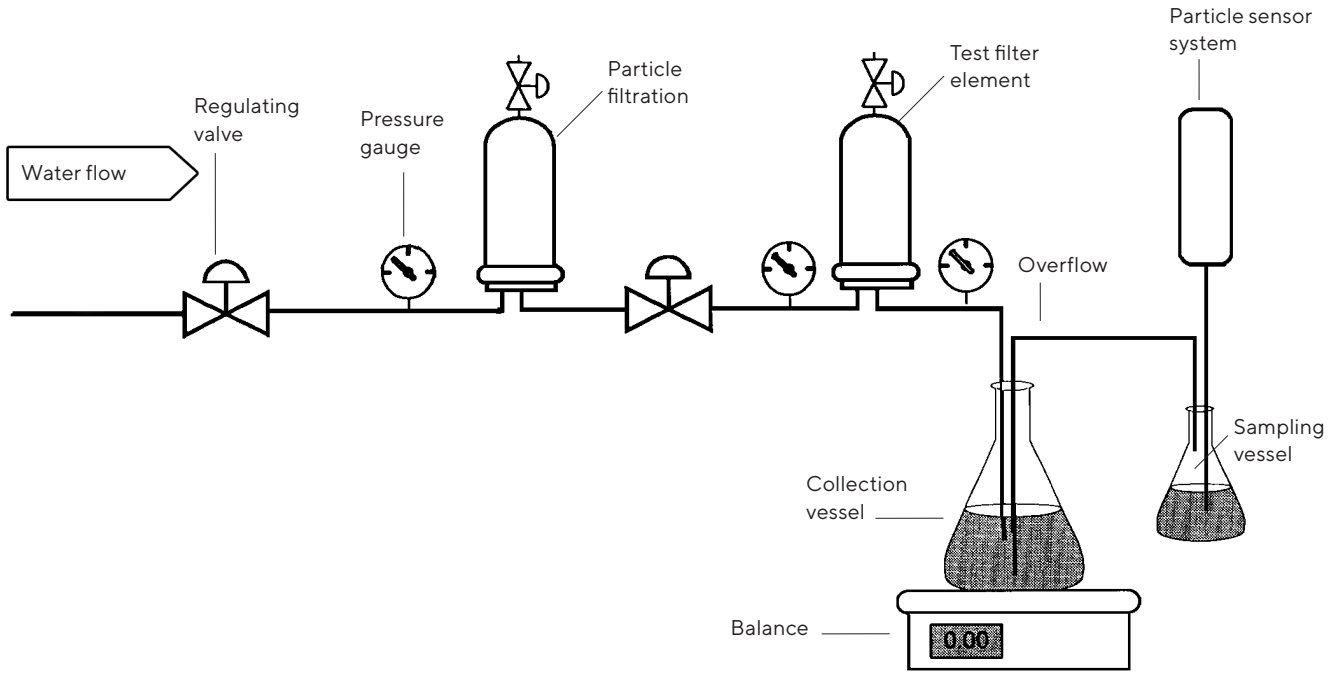
Purpose
In general, the particle release from the filters should be minimized. For parenteral solutions, the requirements are define in the USP Monographs, which set maximum limits for particle content based on defined particle sizes. The particle release of Sartopore® Platinum family filter elements should lie well below the limits set forth in the current USP for "Large Volume Parenterals for Single Dose Infusion".

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
Standard filter cartridges, T-Style Maxicaps®, Maxicaps® Midicaps® | gamma Midicaps® and capsules | gamma capsules from different production lots were being tested. As a wetting and flushing medium, deionized water (DI 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 cartridges are then installed in the pre-rinsed system

Test set-up



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 cartridges. The samples are taken after 1, 5 and 10 liters for standard cartridges, T-Style Maxicaps®, Maxicaps®, Midicaps® | gamma Midicaps®, and capsules | gamma capsules for analysis. 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.

7.1.1 Standard Cartridges 10"

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

7.1.2 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

7.1.3 Maxicaps® | Gamma 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

7.1.4 Midicaps® | Gamma 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	0	0	0	3

7.1.5 Capsules | Gamma Capsules

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

Conclusion
The tables above show that for Sartopore® Platinum family filter elements the requirements of the current USP 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 Sartopore® Platinum family filter elements produce a filtrate that conforms with the current USP for particle content.

7.2 Determination of Oxidizable Substances of the Filtrate

Test procedure
Three Sartopore® Platinum standard cartridges, Midicaps®, Maxicaps®, T-Style Maxicaps® and capsules from different production lots were wetted (by soaking) and autoclaved, T-Style Maxicaps®, Maxicaps® and gamma Midicaps® and gamma capsules of different production lots were gamma irradiated. After installation the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes.

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

Than 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.

7.2.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11019083	passed	passed	passed
11022083	passed	passed	passed
11020583	passed	passed	passed

7.2.2 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**
111021583	passed	passed	passed
111022183	passed	passed	passed

7.2.3 Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
140018483	passed	passed	passed
140018583	passed	passed	passed

7.2.4 Midicaps® | Gamma Midicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11027583	passed	passed	passed
11027783	passed	passed	passed
11027583	passed	passed	passed

HB Version

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11024783	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11027583	passed	passed	passed
11027783	passed	passed	passed
11027583	passed	passed	passed

7.2.5 Capsules® | Gamma Capsules® Size 4

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
10018483	passed	passed	passed
10018383	passed	passed	passed
10018583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
120043483	passed	passed	passed
120043583	passed	passed	passed
120043683	passed	passed	passed

Conclusion

The Sartopore® Platinum family products 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".

7.3 Determination of pH Values and Conductivity of the Filtrate

Test procedure
After installation the filter elements were flushed with water for injection and samples were taken after 1, 5 and 10 L flush volumes.

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

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

7.3.1 Standard Cartridges

Results for the pH values

Blank	pH 5.85		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
11019083	5.3	5.5	5.55
11022083	5.4	5.65	5.75
11020583	5.45	5.7	5.7

Results for the conductivity

Blank	0.832 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]
11019083	3.12	1.55	1.33
11019083	2.55	1.08	0.97
11020583	3.11	0.99	1.0

7.3.2 T-Style Maxicaps®

Results for the pH values

Autoclaved

Blank	pH 5.75		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
111021583	4.6	5.5	5.6
111022183	4.5	5.5	5.6

γ-irradiated

Blank	pH 5.8		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
111021583	3.95	5.4	5.6
111022183	4	5.2	5.45

Results for the conductivity

Autoclaved

Blank	0.89 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]
111021583	4.6	5.5	5.6
111022183	4.5	5.5	5.6

γ-irradiated

Blank	9.4 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]
111022183	44.8	2.44	1.59
111021583	11.84	1.55	1.28

7.3.3 Maxicaps®

Results for the pH values

γ-irradiated

Blank	pH 5.95		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
140018483	5.05	5.7	5.8
140018583	4.9	5.35	5.55

Results for conductivity

γ-irradiated

Blank	0.93 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]
140018483	6.01	1.45	1.29
140018583	6.32	2.8	1.85

7.3.4 Midicaps® | Gamma Midicaps®

Results for the pH values

Autoclaved

Blank	pH 5.85		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
11024983	5.45	5.85	5.85
11024683	5.3	5.75	5.75
11025283	4.85	5.5	5.65

γ-irradiated

Blank	pH 5.9		
Lot Number	pH After 1 L Flush	pH After 5 L Flush	pH After 10 L Flush
11027583	5	5.9	5.9
11027783	5.1	5.8	5.9
11027583	5.1	5.7	5.7

Results for conductivity

Blank	0.9 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]
11024983	2.13	0.84	0.85
11024683	2.74	1.0	1.13
11025283	7.49	1.49	1.24

γ-irradiated

Blank	0.92 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]
11027583	5.02	0.98	0.96
11027783	3.71	1.03	0.93
11027583	4.48	1.21	1.19

7.3.5 Capsules | Gamma Capsules

Results for the pH values

Autoclaved

Blank	pH 5.95		
Lot Number	pH After 0.5 L Flush	pH After 1 L Flush	pH After 1.5 L Flush
10018483	5.85	5.85	5.85
10018383	5.85	5.85	5.85
10018583	5.6	5.7	5.7

γ-irradiated

Blank	0.68 µS/cm		
Lot Number	Conductivity After 0.5 L Flush [µS/cm]	Conductivity After 1 L Flush [µS/cm]	Conductivity After 1.5 L Flush [µS/cm]
10018483	1.1	0.73	0.73
10018383	1.48	0.86	0.78
10018583	1.37	0.89	0.83

Conclusion

Both parameters, pH and pH dependent conductivity of the filtrate, when filtering with the Sartopore® Platinum family products are well below the limit requirements of the current USP.

7.4 Determination of Chloride, Sulfate, and Ammonia in the Filtrate

7.4.1 Determination of Chloride

Test procedure
After installation the filter elements were flushed with water for injection and 20 mL samples were taken after 1, 5 and 10 L flush volumes.

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.

7.4.1.1 Standard Cartridges

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11019083	passed	passed	passed
11022083	passed	passed	passed
11020583	passed	passed	passed

7.4.1.2 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**
111021583	passed	passed	passed
111022183	passed	passed	passed
111021583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
111021583	passed	passed	passed
111022183	passed	passed	passed
111021583	passed	passed	passed

7.4.1.3 Maxicaps®

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
140018483	passed	passed	passed
140018583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
140018483	passed	passed	passed
140018583	passed	passed	passed

7.4.1.4 Midicaps® | Gamma Midicaps®

Autoclaved

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11024983	passed	passed	passed
11024683	passed	passed	passed
11025283	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**	**Test Results After 10 L Flush**
11027583	passed	passed	passed
11027783	passed	passed	passed
11027583	passed	passed	passed

7.4.1.5 Capsules | Gamma Capsules Size 4

Autoclaved

Blank	passed		
Lot Number	**Test Results After 0.5 L Flush**	**Test Results After 1 L Flush**	**Test Results After 1.5 L Flush**
10018483	passed	passed	passed
10018383	passed	passed	passed
10018583	passed	passed	passed

Test procedure

Sartopore® Platinum family products 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".

7.4.2 Determination of Sulfate

Test procedure
After installation the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes.

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

7.4.2.1 Standard Cartridges

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11019083	passed	passed	passed
11022083	passed	passed	passed
11020583	passed	passed	passed

7.4.2.2 T-Style Maxicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
111021583	passed	passed	passed
111022183			
111021583			

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
111021583	passed	passed	passed
111022183			
111021583			

7.4.2.3 Maxicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
140018483	passed	passed	passed
140018583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
140018483	passed	passed	passed
140018583	passed	passed	passed

7.4.2.4 Midicaps® | Gamma Midicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11024983	passed	passed	passed
11024683	passed	passed	passed
11025283	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11027583	passed	passed	passed
11027783	passed	passed	passed
11027583	passed	passed	passed

7.4.2.5 Capsules | Gamma Capsules Size 4

Autoclaved

Blank	passed		
Lot Number	**Test Results After 0.5 L Flush**	**Test Results After 1 L Flush**	**Test Results After 5 L Flush**
10018483	passed	passed	passed
10018383	passed	passed	passed
10018583	passed	passed	passed

Conclusion

Sartopore® Platinum family products 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".

7.4.3 Determination of Ammonia

Test procedure
After installation the filter elements were flushed with water for injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes.

To 100 mL of each of the recirculation samples and sample blank, added 2 mL of ammonium oxalate (2 %). A sample passed the test, if no turbidity was produced.

7.4.3.1 Standard Cartridges

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11019083	passed	passed	passed
11022083	passed	passed	passed
11020583	passed	passed	passed

7.4.3.2 T-Style Maxicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
111021583	passed	passed	passed
111022183	passed	passed	passed
111021583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
111021583	passed	passed	passed
111022183	passed	passed	passed
111021583	passed	passed	passed

7.4.3.3 Maxicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
140018483	passed	passed	passed
140018583	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
140018483	passed	passed	passed
140018583	passed	passed	passed

7.4.3.4 Midicaps® | Gamma Midicaps®

Autoclaved

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11024983	passed	passed	passed
11024683	passed	passed	passed
11025283	passed	passed	passed

γ-irradiated

Blank	passed		
Lot Number	Test Results After 1 L Flush	Test Results After 5 L Flush	Test Results After 10 L Flush
11027583	passed	passed	passed
11027783	passed	passed	passed
11027583	passed	passed	passed

7.4.3.5 Capsules | Gamma Capsules Size 4

Autoclaved

Blank	passed		
Lot Number	**Test Results After 0.5 L Flush**	**Test Results After 1 L Flush**	**Test Results After 1.5 L Flush**
11024983	passed	passed	passed
11024683	passed	passed	passed
11025283			

HB Version

Blank	passed		
Lot Number	**Test Results After 0.5 L Flush**	**Test Results After 1 L Flush**	**Test Results After 1.5 L Flush**
10018383	passed	passed	passed

Conclusion

Sartopore® Platinum family products 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".

7.5 Biological Reactivity

Purpose
These tests are to determine that all components used for the manufacturing of Sartopore® Platinum family filter elements meet or exceed the requirements for the current USP Class VI–121 °C Plastics Tests.

Test method and results
Sartopore® Platinum family filter elements 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
- Systemic injection test
- Implantation test (7 days)

The complete test report is available upon request.

Result
The following certificate was released as a result of the testing of Sartopore® Platinum family filter elements. All material used in the construction of the Sartopore® Platinum filter elements meet or exceed the requirements of the USP Class VI–121 °C Plastics Tests.

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Name:** **Sartopore PLATINUM**
Order No.: **5492507H1**
Lot No.: **0017283**

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. 104317)

USP BIOLOGICAL TEST (CLASSIFICATION VI/121 °C) (BSL Project No. 104318)

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

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

Dr. Daniela Stelter
Biological Safety Testing
Date: 04 November 2010
Re-issue Date: 18 May 2012

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial:

Name:	**Sartopore PLATINUM T-Style MaxiCaps**
Order no.:	**5498307H1G-SS**
Lot no.:	**111021583**
Pore size:	**0.45 + 0.2 µm**

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. 120931)

USP BIOLOGICAL TEST (CLASSIFICATION VI/121 °C) (BSL Project No. 120932)

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

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

Dr. Katharina Lütkenhaus
Biological Safety Testing
Date: 27 March 2012
Re-issue Date: 18 May 2012

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial:
Name: Inline MaxiCaps Housing (Redesign)
Lot No.: 130050583
Manufacturing date: 11/2013

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

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. 140194)

USP BIOLOGICAL TEST (CLASSIFICATION VI/121 °C) (BSL Project No. 140195)

Results: **The test item did not show any effect in the USP Class VI / 121 °C 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: 10 April 2014

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

BIOSERVICE
SCIENTIFIC LABORATORIES GmbH

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial:
Name: **Sartopore PLATINUM (MidiCap)**
Order No. **5495307H9--SS**
Lot No. **11024783**
Pore Size **0.45 + 0.2 µm**

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. 116099)

USP BIOLOGICAL TEST (CLASSIFICATION VI/121 °C) (BSL Project No. 116100)

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

BSL BIOSERVICE Scientific Laboratories GmbH ISO 17025

Dr. Daniela Stelter
Biological Safety Testing
Date: 30 January 2012
Re-issue Date: 18 May 2012

7.6 Total Organic Carbon (TOC)

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. The test for TOC acc. to USP monograph (643) is performed in dynamic extraction mode, the best representative methodology for determining levels of extractable substances and particles present in varying filtrate volumes for filtration applications. The samples for all tests are taken after 5 and 10 liters flush volume for each element.

The analytical method completely oxidizes the organic molecules in an aliquot of sample water to carbon dioxide, measures the resultant carbon dioxide level and expresses the response as carbon concentration. It discriminates between inorganic carbon and the carbon dioxide generated from the oxidization of organic molecules in the sample.

A calibrated instrument is used and its suitability is periodically tested as described in USP (643).

7.6.1 Standard Cartridges

Blank	**≤ 50**	
Lot Number	**Test Results After 5 L Flush [ppb]**	**Test Results After 10 L Flush [ppb]**
11019083	126	59
11020583	87	61
11022083	100	63

7.6.2 T-Style Maxicaps®

Autoclaved

Blank	**≤ 50**	
Lot Number	**Test Results After 5 L Flush [ppb]**	**Test Results After 10 L Flush [ppb]**
111022183	173	113
111021583	234	118

γ-irradiated

Blank	**≤ 50**	
Lot Number	**Test Results After 5 L Flush [ppb]**	**Test Results After 10 L Flush [ppb]**
111021583	284	189
111022183	336	190
111021583	258	191

7.6.3 Maxicaps®

Autoclaved

Blank	≤ 50	
Lot Number	Test Results After 5 L Flush [ppb]	Test Results After 10 L Flush [ppb]
140018483	381	240
140018583	812	351

γ-irradiated

Blank	≤ 50	
Lot Number	Test Results After 5 L Flush [ppb]	Test Results After 10 L Flush [ppb]
140018483	381	240
140018583	812	351

7.6.4 Midicaps® | Gamma Midicaps®

Autoclaved

Blank	≤ 50	
Lot Number	Test Results After 5 L Flush [ppb]	Test Results After 10 L Flush [ppb]
11024983	65.7	55.5
11024683	47.9	44.9
11025283	150.2	100.0

γ-irradiated

Blank	≤ 50	
Lot Number	Test Results After 5 L Flush [ppb]	Test Results After 10 L Flush [ppb]
11027583	170	133
11027783	208	156
11027583	174	128

7.6.5 Capsules | Gamma Capsules Size 4

Autoclaved

Blank	≤ 50	
Lot Number	Test Results After 5 L Flush [ppb]	Test Results After 10 L Flush [ppb]
10018483	65.41	–
10018383	114.0	–
10018583	63.8	–

8. Endotoxin Testing

Purpose
The goal of these tests is to determine whether the amount of endotoxins released in the effluent of a Sartopore® Platinum family filter element meets the requirements of EP and USP monographs for "Sterile Water for Injection" (0.25 EU/mL).

Test method
The filter cartridges are shaken in a defined, smallest possible volume of endotoxin free water. Sartopore® Platinum filter c artridges from a variety of production lots are placed into glass vessels and filled with the required amount of endotoxin free water. In contrast to filter cartridges, capsule filters are filled from both sides of the plastic housing with the required amount of endotoxin free water.

Then the vessels or capsule filtersare placed on a shaker in order to free any endotoxins that may be present. They are shaken for 60 minutes with 100 rpm. Samples are then taken and evaluated with the LAL gel clot test with a sensitivity of 0.06 EU/mL.

Along with these samples a positive control containing 0.06 EU of endotoxin per mL is incubated as well as the endotoxin free water itself as a negative control. A clot indicates the presence of endotoxins. No clot indicates absence of endotoxins (i.e. < 0.06 EU/mL).

Results

Standard cartridges

Lot Number	LAL Test Results
11022083	passed
11019083	passed
11020583	passed

Midicaps®

Lot Number	LAL Test Results
11025083	passed
11024983	passed
11024483	passed

Gamma Midicaps®

Lot Number	LAL Test Results
11027283	passed
11027883	passed
11026983	passed

Maxicaps®

Lot Number	LAL Test Results
140018483	passed
140018583	passed

T-Style Maxicaps®

Lot Number	LAL Test Results
111021583	passed

Conclusion
All Sartopore® Platinum family standard cartridges, T-Style Maxicaps®, Maxicaps®, Midicaps® and camma Midicaps® tested, under the conditions of the extraction test described above, gave results below 0.18 EU/mL bacterial endotoxin.

9. Shelf Life

The shelf life of non sterile filters is at least 5 years after manufacturing.

Sterile Maxicaps®, Midicaps®, capsules size 4 and T-Style Maxicaps® have been determined to have a shelf life of 3 years after manufacturing with regard to sterility.

The shelf life of Sartopore® Platinum (HB) T-Style Maxicaps®, Maxicaps®, gamma capsules size 4 and camma Midicaps® after gamma irradiation (50 kGy) has been determined to be at least 3 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

10. Document History

Version Number	Description of Change	Version Date
00	Update to new Sartorius brand design. Renaming of document to include DIR number.	October 2021
01	Minor text and document structure adjustments. Addition of rinsing volumes and integrity test values (bubble point values) for IPA|water mixtures. Harmonization of dimension data across filter families.	January 2023

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia NY 11716
Phone +1 800 368 7178

For further contacts, visit
www.sartorius.com

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