Sartopore® Air Midisart®

Validation Guide

SARTORIUS

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1. Introduction

Pharmaceutical products, such as injectable and infusion solutions or those which come in contact with open wounds, must conform to exactly defined quality standards. The desired quality of the final product can only be obtained when the entire production process is adequately safeguarded against contamination. Final product quality meeting the standards of the respective pharmacopoeias 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.

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® Air Midisart®, filter with a hydrophobic polyethersulfone (PES) membrane, reliably fulfills the product-specific requirements which have to be imposed on a sterilizing grade filter for gas filtration.

Validation is indispensable for guaranteeing the safety of pharmaceuticals, being a logical supplement and significant part of the cGMP regulations which have been in force for quite some time.

Guidelines for validation are given in the US Code of Federal Regulations Title 21 and the current USP. In addition, guidelines have been established jointly by the Committee for Laboratories and Official Drug Product Inspection Services and the Department of Industrial Pharmacists of the Federation Internationale Pharmaceutique (F.I.P.), which is the European counterpart of the FDA. The term validation is defined by the F.I.P. guidelines as follows: "Validation, as used in these guidelines, comprises the systematic testing of essential production steps and equipment in the R & D and production departments, including testing and inspection of pharmaceutical products with the goal of ensuring that the finished products can be manufactured reliably and reproducibly and in the desired quality in keeping with the established production and quality control procedures."

We have compiled this validation guide so users of Sartopore® Air Midisart® filter can plan, implement and document their own validation procedures.

1.1 cGMP Quality from Sartorius

Consistent high quality of Sartorius Membrane Filters Disposables 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 batchto-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 years. Sartopore® Air Midisart® is completely manufactured under clean-room conditions in conformance with established cGMP standards.

1.2 Quality Assurance

For quality assurance, all materials are selected carefully in accordance with current regulations, to the extent to which they may be applicable, 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. Sartopore® Air Midisart® filters undergo final product quality control. This involves 100 % non-destructive testing, e.g. integrity testing, of each individual product. Other individual tests, e.g. Endotoxine Test, are carried out on a representative number of samples.

A lot is not released until all in-process and final quality control data are available.

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

1.3 Product Description

Sartopore® Air Midisart® readyto-connect filtration units consist of a hydrophobic PES membrane filter (0.2 µm) in a polypropylene housing.

1.4 Order Numbers

Order Code	Quantity
17805--------AIE	12
17805--------AIN	100
17805--------AIQ	500

2. Technical Details

2.1 Prevention of Contamination

Sartorius Sartopore® Air Midisart® are packed in protective plastic bags under clean room conditions in the production area.

2.2 Traceability

The pore size type and lot number are printed on the label of the protective plastic bag and on the label of the box in which the filter element is packed. In addition, these specifications are lasered on the top|upstream part of each Sartopore® Air Midisart® filter element. The traceable lot number allows convenient retrieval of all data compiled on the materials used, production steps and QC tests.

2.3 Product & Material Testing

The following tests are routinely carried out on each batch.

Raw materials (Random Sample Test)
Plastic housing parts
a) Visual appearance
b) Dimensions
c) Particle contamination

Membrane filters
a) Visual control
b) Thickness
c) Water Entry Point
d) Bubble Point with isopropanol 100 %
e) Air flow
f) Liquid BCT with Brev. dim.

Intermediate product
a) Membrane sealing (at the beginning of each lot – visual inspection)
b) Membrane integrity

Final product (100 % Integrity Test)
Each unit is automatically integrity tested by a diffusion test with IPA/Water (60/40)

Final product (Random Sample Test)
In-process control
a) Visual appearance
b) Housing leakage test
c) Bubble Point
d) Housing burst pressure

Final control, after irradiation with 50 kGy
a) Visual appearance
b) Housing burst pressure
c) Pressure hold test with ethanol
d) Bubble Point
e) Flow rate for air
f) Bacteria Challenge Test

2.4 Typical Air Flow Rates [L/min]

Prior gamma-irradiation

Differential Pressure [mbar]	[L/min]
20	1.37
50	3.12
100	5.48

Post gamma-irradiation (50 kGy)

Differential Pressure [mbar]	[L/min]
20	1.40
50	3.21
100	5.58

1 bar = 100 kPA = 14.5 psi

* Average values: 30 samples of 3 different lots

2.5 Materials and Dimensions

Membrane
Polyethersulfone (hydrophobic)

Housing material
Polypropylene

Filtration area
20 cm^2

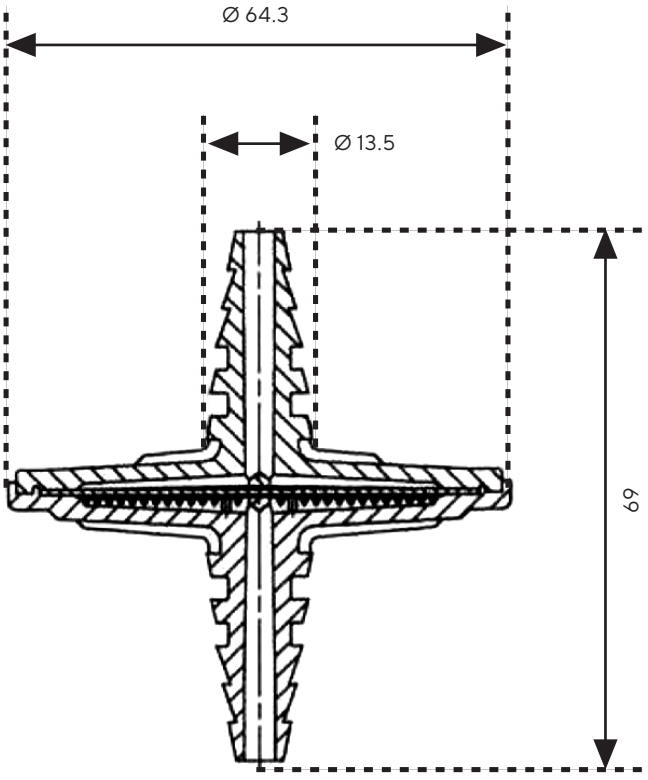
Housing diameter
643 mm

Weight
17 g

Priming volume
approx. 3 mL

Hold-up volume
approx. 1 mL before, 0.5 mL after bubble point test

Connector
Hose barb



2.6 Maximum Allowable Differential Pressure

In the direction of filtration:
Air: 2 bar
Liquid: 2 bar

In the reversed direction of filtration:
Air: 1 bar
Liquid: 1 bar

2.7 Biocompatibility

All materials used in the construction of Sartopore® Air Midisart® meet or exceed the requirements of the USP Class VI Plastics Tests.

Test method
Sartopore® Air Midisart® 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.

2.8 Shelf Life and Storage Conditions

Non-sterile Sartopore® Air Midisart® filters have a shelf life of 5 years.

Sterilized filters have a shelf life of 3 years.

For proper storage of filter elements the following conditions are required in order to guarantee the functionality of those products over a period of time.

- 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
- Products with damaged packaging should be discarded

2.9 Sterilization Method

Irradiation
25 kGy (recommended)
50 kGy (max.)

or

Autoclaving
max. temperature 134 °C for 30 min. (max. 20 cycles)

Note
Multiple sterilization cycles by gamma-irradiation are not allowed.

Once a Sartopore® Air Midisart® was irradiated, further autoclaving steps are prohibited.

3. Efficiency & Integrity Testing

Sartopore® Air Midisart® filtration units containing hydrophobic PES membrane filters of 0.2 micron pore size, taken from different production lots, were subjected to various tests to proof their removal efficiency. Integrity test limits are related to the test results of the liquid bacterial challenge test.

3.1 Liquid Bacterial Challenge

Sartopore® Air Midisart® were tested with liquid bacterial challenge tests in accordance with current ASTM F 838 Guideline. The test was carried out on units as supplied, on units subjected to gamma-irradiation (50 kGy) and on units that were autoclaved (5 ×). These tests demonstrated that Sartopore® Air Midisart® filters retain > 10^7 *Brevundimonas diminuta* per cm^2 in liquid.

Lot Number 58006113

Prior gamma-irradiation

Piece	**286**	**850**	**90**	**559**	**546**	**147**	**636**	**1688**	**1904**	**2137**
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After gamma-irradiation

Piece	**1721**	**1829**	**2248**	**1188**	**1175**	**1805**	**1812**	**2243**	**2280**	**1888**
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After 5 × Autoclaving

Piece	**558**	**1669**	**1835**	**119**	**204**	**832**	**594**	**577**	**62**	**849**
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

Lot Number 58008113

Prior gamma-irradiation

Piece	2045	411	2213	1304	649	1222	5747	5801	1119	2868
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After gamma-irradiation

Piece	1121	4710	5388	6071	2793	4685	1581	4904	5125	2705
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After 5 × Autoclaving

Piece	2635	4163	4240	4032	4477	2747	122	2853	991	4714
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

Lot Number 58008113

Prior gamma-irradiation

Piece	1055	1202	3576	1566	1710	1577	285	3096	3092	704
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After gamma-irradiation

Piece	1056	376	907	55	1266	1064	117	781	694	1086
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

After 5 × Autoclaving

Piece	2924	1533	2633	3173	2225	1178	2602	2943	2610	2309
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

3.2 Bi-directional Sterility

According to the liquid bacterial challenge test in forward direction (see 3.1), 10 filters each of three different batches (Lot. 58006113, Lot. 5008113 and Lot. 58009113) were tested in accordance with current ASTM F 838 Guideline in the reverse direction. All filters were subjected to gamma-irradiation (50 kGy). These tests demonstrated that Sartopore® Air Midisart® filter retain > 10^7 *Brevundimonas diminuta* per cm^2 in liquid bi-directionally.

Lot Number 58006113

After gamma-irradiation

Piece	560	574	760	886	554	780	710	712	768	575
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

Lot Number 58008113

After gamma-irradiation

Piece	3422	3204	3143	3119	3602	3328	3135	3156	3122	3155
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

Lot Number 58009113

After gamma-irradiation

Piece	2773	2551	2692	2704	2759	2568	2732	2758	2776	2944
Result	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

3.3 Aerosol Bacterial Challenge

The efficiencies of Sartopore® Air Midisart® filters from three different lots were determined using aerosolized *Brevundimonas diminuta* (ATCC 19146). The filters were challenged at 6 liters min^{-1} for 5 minutes at a relative humidity of approximately 95 %. The minimum required bacteria load to retain was set to 10^7 *Brevundimonas diminuta*/cm^2. All filters showed an efficiency of > 99.9999 %.

Filter	Titre Reduction	Efficiency [%]
Lot: 58006113 Piece: 909	> 2.475×10^8	> 99.9999995
Lot: 58008113 Piece: 3786	> 2.475×10^8	> 99.9999995
Lot: 58009113 Piece: 2077	> 2.475×10^8	> 99.9999995

3.4 Aerosol Phage Challenge

The efficiencies of Sartopore® Air Midisart® filters from three different lots were determined using aerosolized *MS-2 Coliphage* (NCIMB 10108). The filters were challenged at 6 liters min^{-1} for 5 minutes at a relative humidity of approximately 95 %. The minimum required bacteria load to retain was set to 10^7 *MS-2 Coliphage*. All filters showed an efficiency of > 99.9999 %.

Filter	Titre Reduction	Efficiency [%]
Lot: 58006113 Piece: 799	> 1.71×10^9	> 99.9999994
Lot: 58008113 Piece: 3730	> 1.71×10^9	> 99.9999994
Lot: 58009113 Piece: 2111	> 1.71×10^9	> 99.9999994

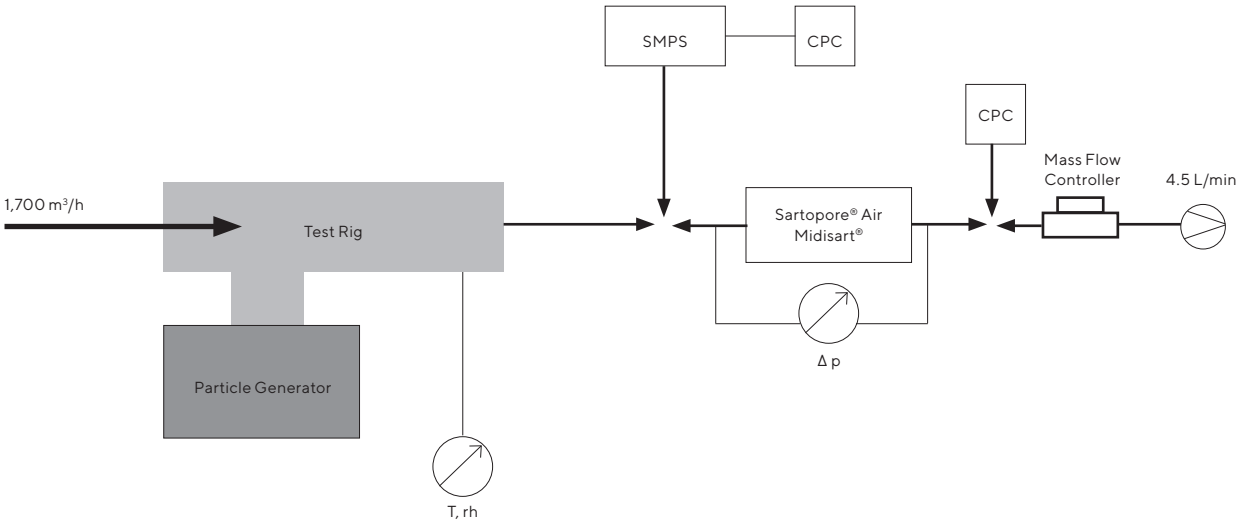
3.5 Aerosol Particle Challenge

The deposition efficiency for 5 and 300 nm NaCl particles, respectively, of Sartopore® Air Midisart® filters has been measured. In total six filters, belonging to three different batches (Lot. 58006113, Lot. 58008113 and Lot. 58009113) were tested.

Each filter was tested with 6 L/min and loaded with a minimum of 10^7 particles per cm^2. The test time was at least 75 min. From each batch one filter was used to determine the efficiency for 5 nm NaCl and one for 300 nm NaCl particles.

All filter showed an efficiency of > 99.9999 %.

Schematic test set-up



Test rig: EN 779 test rig
SMPS: Scanning Mobility Particle Sizer
CPC: Ultrafine Condensation Particle Counter

The particle size distribution in the raw gas was measured at the beginning and again at the end of the loading time. Also the pressure drop across the filter was monitored during the measurements.

3.6 Particle Release

Particle release can be a problem in critical applications. To demonstrate that Sartopore® Air Midisart® filters comply with "Grade A classification of cleanrooms under EU Annex1: Manufacture of Sterile Medicinal Products," particle release tests were performed (bi-directionally).

To comply with the Grade A specification, the particle count needs to be less than 3,520 particles in the 0.5 µm– 5 µm size range per cubic meter of air.

Test set-up
For counting released particles a "Hach MetOne 3425" was used. The test was performed under a clean bench to avoid external particles. To achieve an air flow of 50 L/min a pressure of 1.6 bar | 23 psi was applied in forward direction of filtration. In the opposite direction of filtration all filters were tested with 1.4 bar | 20 psi. One cycle of testing had a duration of one minute. Various cycles per filter were performed. A range of 0.5 µm – 5 µm particles were counted.

Prior and after testing the particle count under the clean bench was measured in five cycles (0 particles found). In addition to that the air in front of the clean bench was tested to verify that the test device worked correctly.

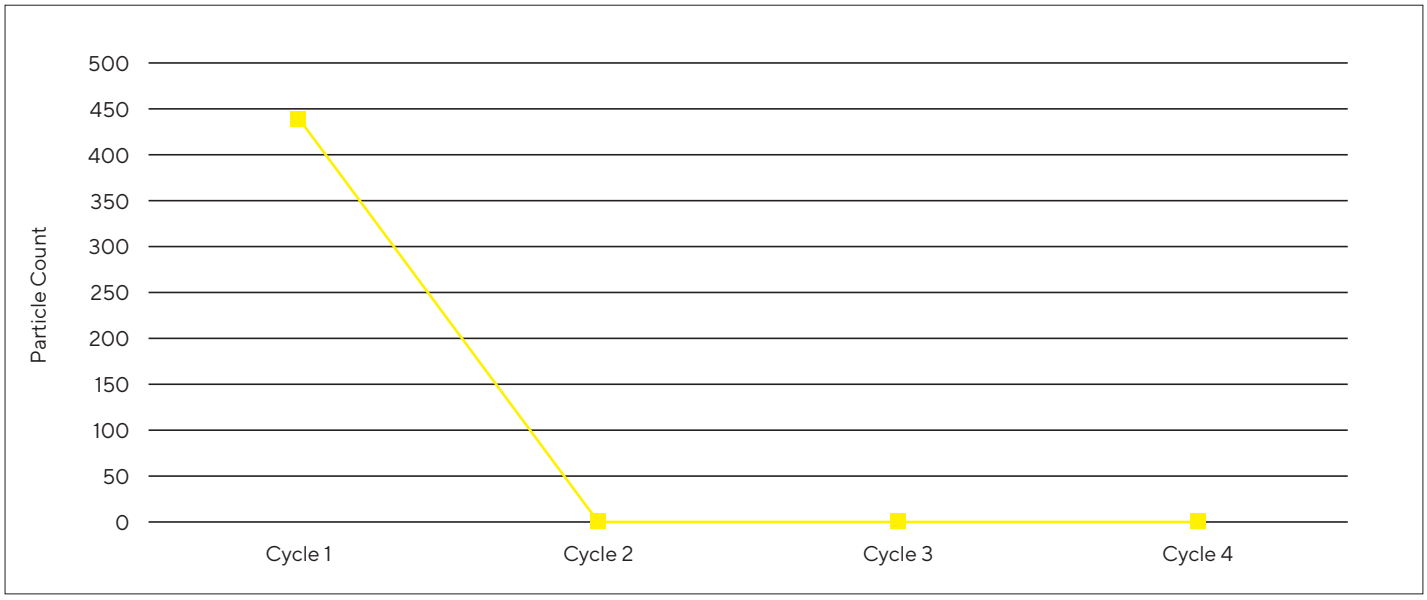
Sartopore® Air Midisart® from three different lots were tested bi-directional. In total 48 filters underwent the procedure.

- 15 filters unsterile in the forward direction of filtration
- 15 filters gamma-irradiated with 50 kGy in the forward direction of filtration
- 9 filters unsterile in the reverse direction of filtration
- 9 filters gamma-irradiated with 50 kGy in the reverse direction of filtration

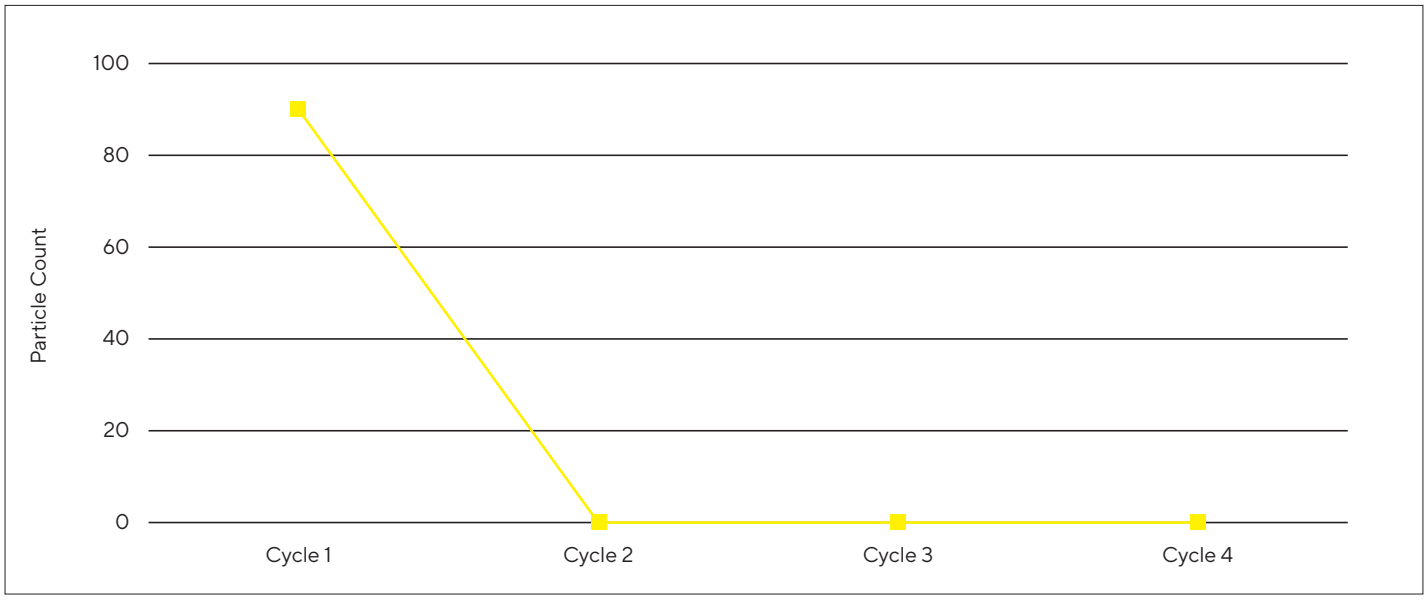
Test results

Average values were calculated for the first four cycles. The results are shown in the graphs below:

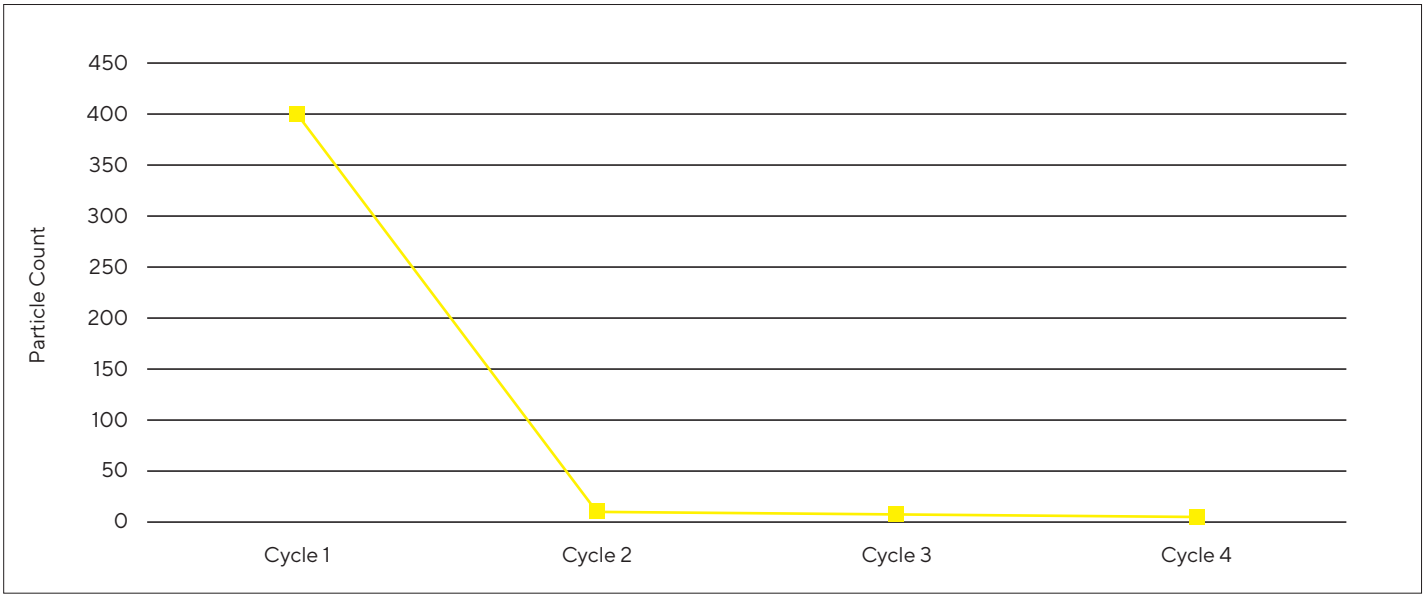
Sartopore® Air Midisart®, unsterile, forward



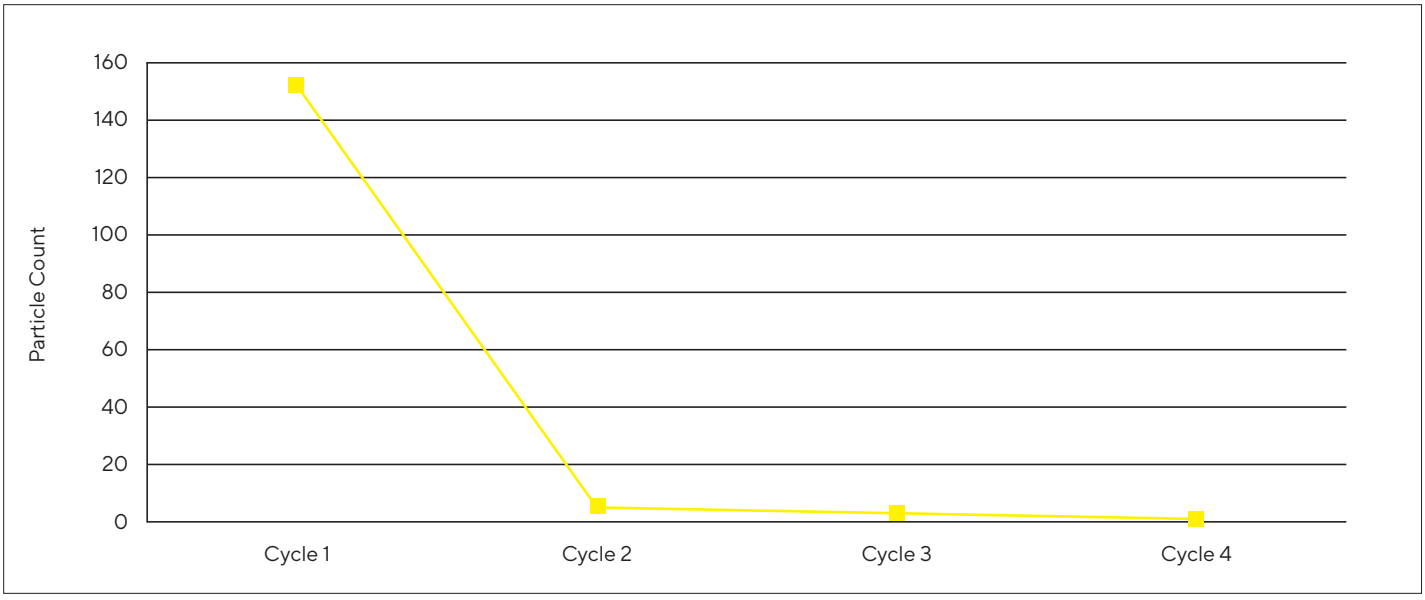
Sartopore® Air Midisart®, 50 kGy, forward



Sartopore® Air Midisart®, unsterile, reverse



Sartopore® Air Midisart®, 50 kGy, reverse



Conclusion

It can be observed that particles are only released during the first cycle of one minute. Already during the second cycle the particle count tend to be zero. The result shows that the test values are clearly within the limit of 3,520 particles (of 0.5 µm–5 µm) per cubic meter of air.

All tests showed that Sartopore® Air Midisart®, no matter if sterile, unsterile, IN or in opposite direction of filtration release particulate matter in quantities well below the requirements established for Grade A classification of cleanrooms under EU Annex1: Manufacture of Sterile Medicinal Products [corrected version]. European Commission. Brussels. 25 November 2008 [revised].

3.7 Oxidizable Substances

Sartopore® Air Midisart® were tested for oxidizable substances.

15 × ½ Filter were put in 1 liter purified water (RO) for 2.5 hours under constant shaking at room temperature. The extracts were analyzed in accordance to the current USP.

The results were negative. No oxidizable substances were found.

3.8 Gravimetrical Extractables

Sartopore® Air Midisart® were tested for gravimetrical extractables

15 × ½ Filter from three different lots were put in 1.5 liter IPA/water (60/40) for 24 hours under constant shaking at room temperature. Afterwards 200 mL of the IPA/water mixture was concentrated by evaporation.

All results showed that the total amount of extractables was less than 1 mg per unit after 24 hours in an IPA/water (60/40) mixture.

3.9 Integrity Testing

Before the challenge these units were integrity tested by the bubble point method in order to correlate the results of the challenge with those of a non-destructive integrity test. The given values are valid for Sartopore® Air Midisart® completely wetted with isopropanol 60 %.

The bubble point test is performed by two different methods:

- Utilizing a Sartocheck® automated integrity test unit
- Manual, visual determination

For determination of the bubble point, air pressure is slowly increased on the upstream-side of the Sartopore Air Midisart® filters.

The bubble point is the pressure at which a given liquid in the wetted pores of a membrane is forcibly removed. The removal of the liquid allows free flow of air through the membrane.

Sartocheck® units use algorithms for automatic detection of the BP. For the visual test, a tube is attached to the Midisart® outlet. This tube ends in a water filled vessel. When the first continuous stream of bubbles appears, the bubble point is detected.

Prior gamma-irradiation

Lot No.	Visual [bar]	Sartocheck® [mbar]
58006113	1.23	1089.5
58008113	1.19	1034
58009113	1.3	1034

Post gamma-irradiation (50 kGy)

Lot No.	Visual [bar]	Sartocheck® [mbar]
58006113	1.21	1078.2
58008113	1.21	1058.1
58009113	1.31	1136.9

These are average values of ten filters per lot.

All tested standard Sartopore® Air Midisart® filters (with | without gamma-irradiation) passed the Bacterial Challenge Test, i.e. the filtrate was sterile for all tested Midisart® filters.

The minimum Bubble Point (IPA 60 %) is set to **> 950 mbar | 13.8 psi** (prior and after gamma-irradiation).

3.10 Bubble Point

In order to get more reliable data for determining the required minimum Bubble Point limit, low BP Midisart® have been tested (after gamma-irradiation @ 50 kGy):

	Bubble Point	Liquid BCT Result
1	897	sterile
2	989	sterile
3	962	sterile
4	876	sterile
5	907	sterile
6	890	sterile
7	849	sterile
8	833	sterile
9	881	sterile
10	895	sterile
11	819	unsterile

These data show that even Midisart® filters with a BP down to (at least) 0.83 bar (Sartocheck®) result in a sterile filtrate.

Conclusion
All results showed that Sartopore® Air Midisart® units with a bubble point equal to, or larger than 0.83 bar retain the test organism *Brevundimonas diminuta* completely.

Taking a buffer margin into account, the minimum bubble point values for Sartopore® Air Midisart® completely wetted with isopropanol 60 % has been set to 950 mbar.

4. Certificate of Sartopore® Air Midisart®

eurofins

Certificate of compliance for USP tests

Test Item:	**Sartopore Air Midisart Type: 17805--------AIN Lot. no.: 60271113** **Sample after 50kGy Gamma irradiation and ageing (2,5 years at 20°C)**
Project:	**019-00176**
Batch No.:	**60271113**
Supplier:	**Sartorius Stedim Biotech GmbH** **August-Spindler-Straße 11, 37079 Göttingen, Germany**
Studies performed:	The following studies were performed in order to determine the biocompatiblity of the product Sartopore Air Midisart, Type: 17805--------AIN, Lot. no.: 60271113, Sample after 50kGy Gamma irradiation and ageing (2,5 years at 20°C) (Batch No.: 60271113) according to USP <87> and USP <88>: **CYTOTOXICITY (Eurofins Munich Study No. STUGC19AA1171-1)** No leachable substances were released in cytotoxic concentrations from the test item. **ACUTE SYSTEMIC TOXICITY (BSL Munich Study No.: STUGC19AA1171-2)** The saline, alcohol in saline, polyethylene glycol 400 and vegetable oil extracts of the test item injected into mice did not produce any significant systemic reaction. **INTRACUTANEOUS TOXICITY (BSL Munich Study No.: STUGC19AA1171-2)** The saline, alcohol in saline, polyethylene glycol 400 and vegetable oil extracts of the test item injected intracutaneously in rabbits did not produce a significantly greater tissue reaction than the blank extractant. **IMPLANTATION TEST (BSL Munich Study No.: STUGC19AA1171-2)** The macroscopic reaction of the test item was not significant as compared to the USP negative control plastic after aproximately 121 hours of implantation.
Results:	**The sample of the test item used directly (implantation tests) or extracted[1)] at a temperature of 121 ± 2 °C for 1 hour (37 ± 1 °C for 24 h for cytotoxicity test), met the requirements of a USP Class VI Plastic.** [1)] On the sponsor's request only the inner surface of the test item was extracted. The test item was completely filled with the corresponding extraction medium. The filling volume of one test item was 3.5 mL.

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signed by: Hana Hofman-Hüther
on: 2020-01-16
with: digiSeal® by secrypt

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Amtsgericht München, HRB 222 125
Erfüllung und Gerichtsstand München

USt-ID-Nr.: DE 305 239 234
Steuer-Nr.: 143/135/02385

5. Document History

Version Number	Description of Change	Version Date
00	Update to new Sartorius brand design. Renaming of document to include DIR number. Addition of certificates.	April 2022
01	Minor text adjustments for EPA compliant wording. Deletion of the Quality Assurance Certificate. Correction of maximum allowable differential pressure in the reversed direction of filtration for air (refer to Change Notification Letter of ECR 23729)	November 2022

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DIR No.: 2920913-000-01
Status 11|2022