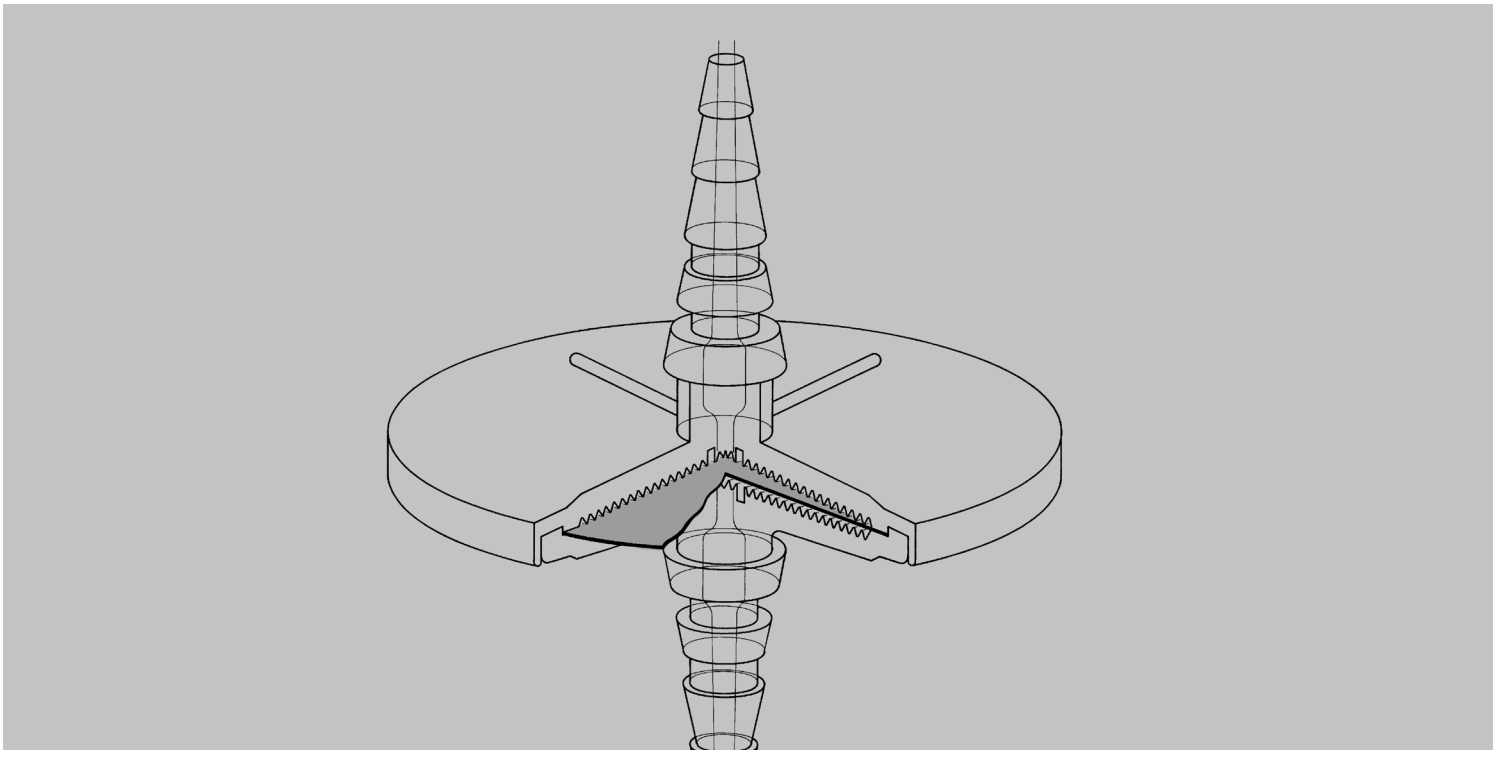
sartorius stedim biotech

Validation Guide
Midisart® 2000



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1. Introduction

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

Therefore, a prior membrane filtration run is required by cGMP regulations (Current Good Manufacturing Practice of the US Food and Drug Administration) to ensure that particles and microbes are removed. Solutions containing heat-labile products, such as antibiotics, can be cold sterilized by membrane filtration immediately before aseptic filing. Microbe retentive filtration (bacteria retentive according to the European Pharmacopeia 2 and DAB 10) or sterile 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. Midisart®, filter with a hydrophobic PTFE membrane, reliably fulfills the product-specific requirements which have to be imposed on a sterilizing grade filter both for gas and liquid 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 equipement 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 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, wellplaned and validated production technologies and an excepionally 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 years.

Midisart® filters are completely manufactured under clean-room conditions.

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. Finished Sartorius Disposables Capsules and Filter Cartridges 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.

1.3 Prevention of Contamination

Sartorius sterile Midisart® are sealed in gas-permeable protective plastic bags under clean room conditions in the production area. Following this step, they are sterilized with Ethylene Oxide.

1.4 Complete Traceability

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

1.5 Sartorius Drug Master File – DMF 5967

In compliance with Title 21 Code of Federal Regulations (CFR) 314.420, the required information has been filed in the Sartorius Drug Master File – DMF 5967 under the heading "Sartoflour Mini Cartridge and Capsule Validation Guide" at the US Food and Drug Administration (FDA).

1.6 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

1.7 Test Methods for the Quality Assurance of Midisart® 2000 Filter Elements

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) Flow rates for isopropanol 100 %, air
d) Bubble Point with isopropanol 100 %

Intermediate product (random sample test):

a) Membrane sealing (membrane, sealing edge, housing)
b) Membrane integrity

Final product (100% Integrity Test):

Each unit is tested during manufacture for membrane and housing integrity by an air pressure drop test.

Final product (random sample test):

Final control

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
g) Housing leakage test

For sterilized Midisart® types (additional):

Endotoxine test
Sterility = Check for sterilization certificate

2. Technical Specifications

2.1 Product Description and Application

Midisart® 2000 ready-to-connect filtration units consist of a hydrophobic (PTFE) membrane filter in a polypropylene housing. They are available with 0.2 µm and 0.45 µm pore size membranes, and are ideally suitable for all small scale air|gas sterilizing purposes, such as:

- the sterile venting of filling vessels and fermentation carboys including culture vessels
- the venting of holding tanks for sterile, distilled water and liquid culture media
- autoclave venting
- the in-line sterilization of and particulate removal from air and gases.

The excellent chemical stability of these practical units also makes them useful for particle removal from chemicals and organic solvents.

Midisart® units can also be used for the filtration of aqueous liquids, but the hydrophobic PTFE membrane filter must first be wetted with a watermiscible solvent such as ethanol. It may be necessary to repeat this wetting, e.g. if the filtration is interrupted.

A further application is as a pump protector in vacuum lines. Please note, when using the unit as a protective barrier in a vacuum line (positioned between a suction flask and an electrical pump, to stop and overflow of filtrate from an overfilled suction flask) or connected to a water jet pump (to stop a water backflash) the flat side with the lot number must face away from the vacuum source. On longer use, water can condense in the pores, so increasing the air flow resistance, with a consequent drop in the speed of filtration.

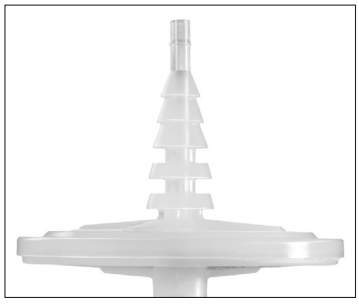
This can be remedied by either blowing the Midisart® dry (1.9 bar for 5 min) or by drying it at 80 °C for 8 hours.

2.2 Order Information

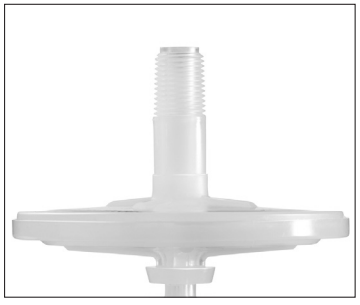
Order Numbers	Pore Size [µm]	Membrane	Connectors E|A	Pieces/Case	Sterile
17804 E	0.45	PTFE	Hose Barb|Hose Barb	12	Yes
17804 G	0.45	PTFE	Hose Barb|Hose Barb	25	Yes
17804 NPE	0.45	PTFE	1/8"|1/8" NPT	12	Yes
17804 NPG	0.45	PTFE	1/8"|1/8" NPT	25	Yes
17805 E	0.2	PTFE	Hose Barb|Hose Barb	12	Yes
17805 G	0.2	PTFE	Hose Barb|Hose Barb	25	Yes
17805 NPE	0.2	PTFE	1/8"|1/8" NPT	12	Yes
17805 NPG	0.2	PTFE	1/8"|1/8" NPT	25	Yes
17805 UPN	0.2	PTFE	Hose Barb|Hose Barb	100	No
17805 UPQ	0.2	PTFE	Hose Barb|Hose Barb	500	No
17809 UNN	0.2	PTFE	1/8"|1/8" NPT	100	No
17812 UNN	0.2	PTFE	1/8"|Hose Barb	100	No
17805 TCN	0.2	PTFE	TriClamp|TriClamp	100	No
17877 UPN	0.2	PTFE	Small Hose Barb|Small Hose Barb	100	No
17805 UQN	0.2	PTFE	Hose Barb|Hose Barb	100 (plastic bucket)	No

In the interest of further development of Sartorius Stedim biotech products, we reserve the right to make changes without notice.

Standard Hose Barb



Small Hose Barb



1/8" NPT Thread

TriClamp

2.3 Specifications

Filter Material:
PTFE reinforced with polypropylene gauze

Housing Material:
Polypropylene

Filtration Area:
20 cm^2

Housing Diameter:
64 mm

Max. Differential|Operating Pressure:
3 bar (2 bar in reverse direction)

Water Penetration Point:
4 bar (0.2 µm)

Max. Temperature (autoclave):
134 °C

Biosafety:
Materials pass current USP Plastics, class VI

Weight:
20 g

Lot Number and Individual Unit Number:
Lasered on the top part of each Midisart®-housing

Inlet and Outlet:
Inlet cleary indicated on Midisart® housing

Box of 100-with:
Memory disc included

Priming Volume:
approx. 3 mL

Hold-up Volume:
approx. 1 mL

Sterile Types Pre-sterilized with:
Ethylene oxide

Sterilization Method:
1) 20 autoclaving cycles recommended
2) Ethylene Oxide (see pre-sterilized types)
3) Gamma irradiation: If required, please use Midisart® BV instead!

Typical Air Flow Rates per Pore Size

Differential Pressure	0.2 µm [L/min]	0.45 µm [L/min]
Δ p = 0.02 bar	1.1	1.8
Δ p = 0.05 bar	2.9	4.6
Δ p = 0.1 bar	5.0	8.5

1 bar = 100 kPa = 14.5 psi

3. Chemical Compatibility – Midisart®

Media:
Acetic acid (concentrated)
Acetone
Acelonitrile
n-Butanol
Cellosolve (ethyl)
Chloroform
Diethyl acetamide
Dimethylformamide
Dimethylsulfoxide
Dioxane
Ethyl acetate
Ethanol
Ethylene glycol
Freon TF
Gasoline
1 N Hydrochloric acid
Hexane
Isobutanol
Methanol
Methylene chloride
Methyl ethyl ether
Methyl ethyl ketone
Pentone
Sodium hydroxide (5 %)
Tetrahydrofuron
Toluene
Trichloracelic acid
Trichlorethane
Water
Xylene

The materials (PP and PTFE) used in Midisart® give it excellent compatibility with the products listed below. However, its compatibility can be affected by various factors, such as temperature, concentration, composition, etc. We therefore recommend that you test whether Midisart® is compatible with the particular medium you wish to filter.

4. Determination of Integrity Test Data

4.1 Basis for the Determination of Integrity Test Values

Objective:
To correlate the microbial retention efficiency of Midisart® 2000 filtration units to a practical, non-destructive integrity test.

According to the International Standard ISO 13408-2, Part 2: Filtration (2003) and the FDA "Guideline on sterile drug products produced by aseptic processing, September 2004", a filter for sterilizing filtration, when challenged with a minimum concentration of 10^7 Brevundimonas diminuta organisms/cm^2 of filter surface, must yield a sterile filtrate.

For more information about this process see PDA Technical Report No. 26.

Since the Bacteria Challenge Test is a destructive method, it must be correlated with a non-destructive test by forming a test series.

The FDA "Guideline on sterile drug products produced by aseptic processing, September 2004", states:

"After a filtration process is properly validated for a given product, process and filter, it is important to assure that identical filter replacement (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 of perforations that may have occurred during the filtration."

4.2 Bacterial Challenge Test

Method:
Midisart® 2000 ready-to-connect filtration units containing PTFE membrane filters of 0.2 micron pore size (order no. 17805), taken from different production lots, were subjected to a Bacterial Challenge Test in accordance with ASTM F 838-05 Guideline, but at the higher test pressure of 3.0 bar, corresponding to the maximum recommended operating pressure of these units. The set was carried out on units as supplied and on units subjected to various numbers of autoclavings.

Test organism:
Brevundimonas diminuta (ATCC 19146)

Challenge:
$> 2 \times 10^8$ organisms per Midisart® 2000 (effective filter area 20 cm^2).

Integrity Test:
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 Midisart® 2000 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 Midisart® 2000 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.

The 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 waterfilled vessel. When the first continuous stream of bubbles appears, the bubble point is detected.

4.3 Bubble Point Test Limits Typical Results

"Midisart® 2000" 17805 Lot Number	Number of Autoclaving cycles (121 °C)	Bubble Point in bar (20 °C) with Isopropanol 60 %	Results Bacteria Challenge Test
003|9	0	1.6	sterile
	5	1.4	sterile
	10	1.4	sterile
	15	1.4	sterile
004|9	0	1.5	sterile
	5	1.3	sterile
	10	1.3	sterile
	15	1.3	sterile
006|9	0	1.4	sterile
	5	1.2	sterile
	10	1.2	sterile
	15	1.1	sterile
008|9	0	1.6	sterile
	5	1.4	sterile
	10	1.4	sterile
	15	1.4	sterile
011|9	0	1.3	sterile
	5	1.1	sterile
	10	1.0	sterile
	15	0.7	sterile

Conclusion
All results showed that Midisart® 2000 units with a bubble point equal to, or larger than 0.7 bar retain the test organism Brevundimonas diminuta completely, i.e., the filtrate is sterile. The actual bubble point will be reduced after the first autoclaving cycle. However, this does not affect the integrity of the filter.

Taking a safety factor into account, the minimum bubble point values for Midisart® 2000 completely wetted with isopropanol 60 % have been set to 1.1 bar. Please note that this limit value has to be readjusted as soon as a different wetting liquid is used.

Midisart® 0.2 µm ref 17805

Requirement
A comparison between the Bubble Point of 3 different lots is to be made for Midisart® 17805 (0.2 µm PTFE) using 2 wetting liquids (IPA 99.9 % + IPA 60 %).

Another 3 lots were additionally tested with Ethanol.

Result (wetting with 60 % IPA)

Batch 990508 Piece	BP Sartocheck® [bar]
1567	1.679
1409	1.653
1280	1.649
1201	1.668
1683	1.629
1389	1.691
1405	1.653
1241	1.689

Batch 990559 Piece	BP Sartocheck® [bar]
0292	1.578
0075	1.594
0342	1.626
0362	1.608
0182	1.581
0067	1.594
0064	1.640
0461	1.595

Batch 990571 Piece	BP Sartocheck® [bar]
3986	1.642
4128	1.610
4125	1.616
4117	1.609
4003	1.626
4038	1.636
4182	1.644

Result (wetting with 99.9 % IPA)

Batch 990508 Piece	BP Sartocheck® [bar]
1581	1.530
1257	1.528
1644	1.526
1127	1.526
1130	1.522
1387	1.544
1206	1.541

Batch 990559 Piece	BP Sartocheck® [bar]
0299	1.485
0219	1.478
0039	1.505
0271	1.473
0106	1.457
0031	1.455
0005	1.462

Batch 990571 Piece	BP Sartocheck® [bar]
3608	1.523
3960	1.514
4161	1.526
3817	1.495
4108	1.508
3995	1.500
4147	1.517

Batch	Piece	Ethanol visually	Ethanol Sartocheck®	IPA 100% visually	IPA 100% Sartocheck®	IPA 60% visually	IPA 60% Sartocheck®
4005113	3581	1.88	1.553	1.8	1.638	1.99	1.821
	12839	1.77	1.616	1.71	1.536	1.88	1.703
	19628	1.77	1.601	1.72	1.553	1.88	1.686
40010113	1309	1.75	1.599	1.7	1.529	1.86	1.688
	9366	1.75	1.605	1.7	1.54	1.86	1.692
	20509	1.81	1.639	1.78	1.59	1.95	1.755
4014113	2434	1.72	1.555	1.66	1.5	1.83	1.64
	6494	1.75	1.593	1.7	1.538	1.85	1.691
	12166	1.75	1.588	1.7	1.539	1.86	1.69

4.4 Validation of Drying Procedure after Integrity Test IPA 60 %

Purpose of the validation
A customer who uses Midisart® 2000 units for sterile venting intends to subject each unit to an integrity test (BP measurement). An integrity test can only be carried out on a wetted Midisart® unit. However, to recover its hydrophobicity, the unit must be completely dried subsequent to a succesful integrity test.

Procedure
10 Midisart® 2000 (17805) units were taken from each of 3 different batches, numbered and weighed to an accuracy of 1 mg.

Each of the units was wetted with 10 mL of an isopropanol|water mixture (60|40 by volume) and then subjected to a bubble point determination to simulate the measurement carried out by the customer.

A) The units were dried at 80 °C. This temperature of 80 °C was selected because many years of experience have shown that is does not cause any adverse effect to Midisart® 2000 units.

B) The units were dried for 5 minutes with compressed air free from oil and particles at 1900 mbar. The Midisart® 2000 units were weighed at hourly, 10 seconds, 20 seconds and 5 min. intervals during the drying process.

For the 2 methods, the drying procedure was confirmed by a water pressure hold test to check the filter hydrophobicity.

A blank test was performed on 10 new Midisart® without any wetting: new Midisart® were dried for 8 hours/80 °C to measure their loss in weight (Annex).

Results (see attached tables)

Conclusion
The 2 methods described below are efficient for drying Midisart® 2000 units after a bubble point integrity test with IPA 60|40.

Method for rinsing and drying of Midisart® after B.P. Test

1. Wet the Midisart® from side "IN" with 20 mL IPA. Use a 20 mL disposable syringe.
2. Make the Bubble Point Test by visual method or by Sartocheck®.
3. After Bubble Point the Midisart® contains 0.6–1.3 g of IPA.
4. Dry the Midisart® in an ventilate drying oven by 80 °C for ≥ 8 hours or with air 5 min. at 1900 mbar.
5. Midisart® is now reusable.

Test A) Drying at 80 °C

Type: 17805 PTFE 0.2 µm **Incubator: Heraeus Typ VT 5050 EK**

Charge: 000859

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
1	17.866	18.204	18.12	18.046	17.947	17.869	17.864
2	17.61	17.975	17.892	17.812	17.707	17.651	17.608
3	17.752	18.038	17.961	17.893	17.812	17.751	17.745
4	17.745	18.061	17.988	17.907	17.822	17.743	17.74
5	17.953	18.276	18.197	18.133	18.031	17.952	17.949
6	17.862	18.175	18.08	18.017	17.924	17.862	17.856
7	17.701	18.015	17.948	17.877	17.782	17.718	17.713
8	17.645	17.981	17.913	17.836	17.735	17.649	17.642
9	17.821	18.21	18.12	18.035	17.915	17.818	17.817
10	17.956	18.322	18.261	18.181	18.064	17.971	17.965

Charge: 980190

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
11	17.706	18.027	17.948	17.866	17.748	17.71	17.717
12	17.735	18.055	17.982	17.898	17.808	17.733	17.733
13	17.927	18.267	18.182	18.113	18.023	17.933	17.926
14	17.944	18.234	18.159	18.091	18.004	17.946	17.945
15	17.954	18.257	18.185	18.114	18.022	17.953	17.949
16	17.832	18.205	18.107	18.035	17.938	17.842	17.84
17	17.758	18.085	18.004	17.94	17.832	17.756	17.752
18	17.893	18.234	18.153	18.082	17.975	17.896	17.893
19	17.701	17.99	17.91	17.838	17.758	17.709	17.708
20	17.821	18.167	18.082	18.014	17.918	17.829	17.826

Charge: 980165

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
21	17.708	18.048	17.975	17.904	17.817	17.708	17.705
22	17.72	18.081	17.992	17.914	17.828	17.721	17.718
23	17.896	18.198	18.129	18.066	17.973	17.893	17.891
24	17.676	18.001	17.929	17.868	17.776	17.678	17.677
25	17.766	18.08	18.013	17.934	17.848	17.761	17.763
26	17.923	18.237	18.177	18.091	18.003	17.926	17.923
27	17.781	18.168	18.056	17.943	17.867	17.785	17.78
28	17.833	18.172	18.087	17.995	17.924	17.831	17.829
29	17.879	18.208	18.154	18.085	17.999	17.894	17.881
30	17.76	18.076	17.995	17.922	17.838	17.762	17.756

Test B) Drying with air 5 min./1.9 bar

Type: 17805 PTFE 0.2 µm
Wet with IPA|Water (60|40)

Charge: 000814

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
1	17.582	17.996	17.831	17.759	17.673	17.591
2	17.878	18.288	18.101	18.066	17.975	17.894
3	17.437	17.75	17.632	17.601	17.517	17.446
4	17.576	17.967	17.801	17.74	17.664	17.585
5	17.795	18.142	18.053	18.004	17.873	17.798
6	17.868	18.227	18.108	18.029	17.938	17.879
7	17.522	17.884	17.747	17.676	17.615	17.523
8	17.756	18.174	18.013	17.976	17.852	17.767
9	17.599	17.983	17.787	17.747	17.681	17.601
10	17.735	18.15	17.987	17.876	17.843	17.739

Charge: 000859

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
11	17.963	18.239	18.123	18.09	18.019	17.965
12	17.949	18.271	18.165	18.116	18.034	17.953
13	17.842	18.211	18.07	18.038	17.952	17.845
14	17.976	18.317	18.176	18.115	18.026	17.978
15	17.977	18.34	18.23	18.19	18.096	17.981
16	17.946	18.309	18.188	18.121	18.052	17.948
17	17.618	17.957	17.779	17.742	17.685	17.621
18	17.643	17.976	17.871	17.787	17.732	17.649
19	17.645	18.006	17.866	17.784	17.709	17.652
20	17.648	17.983	17.858	17.802	17.723	17.654

Charge: 010108

No	Dry Weight [g]	Wet with IPA|Water 60|40 and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
21	18.018	18.298	18.212	18.147	18.072	18.018
22	17.814	18.128	18.03	17.971	17.907	17.818
23	17.667	18.02	17.85	17.806	17.743	17.67
24	17.911	18.205	18.066	18.024	17.969	17.913
25	17.2	18.46	18.382	18.327	18.242	17.204
26	17.913	18.322	18.089	18.036	17.974	17.914
27	17.776	18.004	17.932	17.879	17.819	17.777
28	17.917	18.189	18.057	18.005	17.949	17.921
29	18.163	18.436	18.32	18.265	18.21	18.165
30	18.238	18.527	18.408	18.367	18.303	18.241

Verification of Hydrophobicity
Each unit is tested after drying [A) 8 hours 80 °C, B) 5 min./1.9 bar with air] by water pressure hold test with colored water for 2 minutes by 1 bar.

Result
All pieces passed the water pressure hold test.

Additional water pressure hold tests were performed at 3.5 bar for 2 min. after air drying on 10 units.

Result
All pieces passed the water pressure hold test.

Note
For method B) it is important to dry the Midisart® units single with a leakproof connection between Midisart® and air pressure source.

Blank Test

Drying of Midisart® 2000 (17805)

Lot 000859
Pore Size 0.2 µm

No	Dry Weight New Midisart® [g]	Midisart® Weight after Drying 80 °C/8 h [g]	Loss of Weight on a New Midisart®|Blank value [g]
1	17.784	17.777	0.007
2	18.109	18.1	0.009
3	18.235	18.227	0.008
4	17.587	17.578	0.009
5	18.074	18.066	0.008
6	17.99	17.983	0.007
7	17.886	17.877	0.009
8	18.03	18.024	0.006
9	17.662	17.65	0.012
10	17.899	17.891	0.008

10 Midisart® units were taken out from the original packaging and the dry weight was measured. Then, the Midisart® were dried by 80 °C over 8 h.

Conclusion
We can observe a loss in weight (blank value) after drying a new Midisart® 8 h at 80 °C.

4.5 Validation of Drying Procedure after Integrity Test IPA 99.99 %

Purpose of the Validation
A customer who uses Midisart® 2000 units for sterile venting intends to subject each unit to an integrity test (BP measurement). An integrity test can only be carried out on a wetted Midisart® unit. However, to recover its hydrophobicity, the unit must be completely dried subsequent after a successful integrity test.

Procedure
10 Midisart® 2000 (17805) units were taken from each of 3 different batches, numbered and weighed to an accuracy of 1 mg. Each of the units was wetted with 10 mL of isopropanol 99.9 % and then subjected to a bubble point determination to simulate the measurement carried out by the customer.

A) The units were dried at 80 °C. This temperature of 80 °C was selected because many years of experience have shown that it does not cause any adverse effect to Midisart® 2000 units.

B) The units were dried for 5 minutes with compressed air free from oil and particles at 1900 mbar. The Midisart® 2000 units were weighed at hourly, 10 seconds, 20 seconds and 5 min. intervals during the drying process.

For the 2 methods, the drying procedure was confirmed by a water pressure hold test to check the filter hydrophobicity. A blank test was performed on 10 new Midisart® without any wetting: new Midisart® were dried for 8 hours/80 °C to measure their loss in weight (Annex).

Results (see attached tables)

Conclusion
The 2 methods described below are efficient for drying Midisart® 2000 units after a Bubble Point Integrity Test with IPA 99.9 %.

Method for rinsing and drying of Midisart® after B.P. Test

1. Wet the Midisart® from side "IN" with 20 mL IPA. Use a 20 mL disposable syringe.
2. Make the Bubble Point Test by visual method or by Sartocheck®.
3. After Bubble Point the Midisart® contains 0.6–1.3 g of IPA.
4. Dry the Midisart® in a ventile drying oven by 80 °C for ≥ 8 hours or with air 5 min. at 1900 mbar.
5. Midisart® is now reusable.

Test A) Drying at 80 °C

Type: 17805 PTFE 0.2 µm Incubator: Heraeus Typ VT 5050 EK
Wet with IPA 99.9 %

Charge: 010082

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	6 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
1	18.155	18.734	18.641	18.578	18.393	18.254	18.162	18.151
2	17.986	18.454	18.395	18.333	18.177	18.025	17.997	17.988
3	18.076	18.628	18.552	18.489	18.372	18.227	18.087	18.074
4	18.004	18.57	18.484	18.418	18.298	18.162	18.011	18.001
5	18.109	18.602	18.526	18.466	18.306	18.177	18.115	18.11
6	17.968	18.49	18.413	18.34	18.187	18.054	17.976	17.967
7	17.974	18.508	18.421	18.348	18.178	18.017	17.979	17.974
8	18.006	18.528	18.456	18.384	18.243	18.131	18.012	18.004
9	17.485	17.989	17.923	17.849	17.7	17.544	17.492	17.484
10	18.226	18.76	18.694	18.638	18.501	18.402	18.234	18.221

Charge: 010116

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	6 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
11	17.993	18.588	18.51	18.442	18.277	18.119	18.002	17.99
12	17.932	18.437	18.375	18.304	18.116	17.971	17.938	17.932
13	17.947	18.556	18.48	18.42	18.256	18.12	17.951	17.948
14	18.107	18.603	18.528	18.474	18.304	18.163	18.114	18.108
15	18.044	18.538	18.475	18.402	18.24	18.074	18.05	18.042
16	17.986	18.498	18.419	18.358	18.194	18.037	17.988	17.984
17	17.939	18.476	18.399	18.33	18.205	18.083	17.94	17.937
18	18.161	18.731	18.666	18.606	18.451	18.322	18.17	18.162
19	18.183	18.677	18.599	18.532	18.415	18.292	18.186	18.181
20	18.116	18.587	18.512	18.453	18.307	18.193	18.119	18.113

Charge: 010108

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	1 h/80 °C [g]	2 h/80 °C [g]	4 h/80 °C [g]	6 h/80 °C [g]	8 h/80 °C [g]	20 h/80 °C [g]
21	18.143	18.649	18.574	18.501	18.334	18.197	18.151	18.142
22	17.982	18.441	18.376	18.306	18.173	18.032	17.989	17.983
23	18.187	18.741	18.673	18.604	18.46	18.298	18.199	18.183
24	17.953	18.39	18.302	18.234	18.075	17.972	17.953	17.948
25	17.761	18.218	18.195	18.137	18.013	17.843	17.768	17.762
26	18.209	18.848	18.746	18.678	18.536	18.355	18.214	18.202
27	18.017	18.655	18.593	18.529	18.361	18.197	18.024	18.016
28	17.918	18.577	18.484	18.427	18.272	18.16	17.934	17.917
29	17.725	18.129	18.046	17.983	17.846	17.751	17.729	17.724
30	17.518	18.166	18.089	18.024	17.909	17.748	17.519	17.514

Test B) Drying with air 5 min./1.9 bar

Type: 17805 PTFE 0.2 µm
Wet with IPA 99.9 %

Charge: 000814

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
1	17.58	17.994	17.724	17.639	17.605	17.582
2	17.875	18.37	18.033	17.936	17.916	17.876
3	17.435	18.002	17.616	17.524	17.468	17.436
4	17.577	17.955	17.726	17.602	17.59	17.581
5	17.788	18.241	17.953	17.875	17.811	17.791
6	17.864	18.347	18.04	17.94	17.881	17.864
7	17.52	17.93	17.709	17.586	17.545	17.498
8	17.755	18.198	17.897	17.809	17.769	17.756
9	17.595	17.984	17.77	17.665	17.621	17.597
10	17.736	18.162	17.934	17.807	17.753	17.738

Charge: 000859

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
11	17.962	18.413	18.105	18.023	17.975	17.965
12	17.945	18.39	18.105	18.013	17.971	17.943
13	17.841	18.257	18.031	17.927	17.874	17.845
14	17.966	18.345	18.15	18.066	17.992	17.968
15	17.974	18.44	18.16	18.062	18.01	17.977
16	17.946	18.403	18.111	18.046	17.981	17.951
17	17.619	18.085	17.805	17.688	17.642	17.623
18	17.642	18.112	17.826	17.704	17.67	17.646
19	17.634	18.092	17.826	17.714	17.658	17.635
20	17.648	18.075	17.803	17.696	17.668	17.651

Charge: 010108

No	Dry Weight [g]	Wet with IPA 99.9 % and Bubble Point [g]	10 sec/ 1.9 bar [g]	20 sec/ 1.9 bar [g]	40 sec/ 1.9 bar [g]	5 min./ 1.9 bar [g]
21	18.019	18.399	18.093	18.031	18.024	18.021
22	17.813	18.218	17.944	17.852	17.825	17.816
23	17.668	18.033	17.794	17.71	17.68	17.671
24	17.909	18.272	18.01	17.931	17.912	17.910
25	18.198	18.562	18.307	18.231	18.209	18.2
26	17.91	18.298	18.005	17.932	17.925	17.914
27	17.773	18.122	17.893	17.810	17.781	17.775
28	17.915	18.252	18.056	17.954	17.919	17.915
29	18.16	18.536	18.276	18.193	18.171	18.163
30	18.237	18.591	18.348	18.263	18.249	18.24

Verification of Hydrophobicity
Each unit is tested after drying [A) 8 hours 80 °C, B) 5 min./1.9 bar with air] by water pressure hold test with colored water for 2 minutes by 1 bar.

Result
All pieces passed the water pressure hold test.

Additional water pressure hold tests were performed at 3.5 bar for 2 min. after air drying on 10 units.

Result
All pieces passed the water pressure hold test.

Note
For method B) it is important to dry the Midisart® units only with a leakproof connection between Midisart® and the air pressure source.

Blank Test

Drying of Midisart® 2000 (17805)

Lot 000859
Pore Size 0.2 µm

No	Dry Weight New Midisart® [g]	Midisart® Weight after drying 80 °C/8 h [g]	Loss of weight on a New Midisart®/Blank value [g]
1	17.784	17.777	0.007
2	18.109	18.1	0.009
3	18.235	18.227	0.008
4	17.587	17.578	0.009
5	18.074	18.066	0.008
6	17.99	17.983	0.007
7	17.886	17.877	0.009
8	18.03	18.024	0.006
9	17.662	17.65	0.012
10	17.899	17.891	0.008

10 Midisart® units were taken out from the original packaging and the dry weight was measured. Then, the Midisart® were dried by 80 °C over 8 h.

Conclusion
We can observe a loss in weight (blank value) after drying a new Midisart® 8 h at 80 °C.

5. Validation of Resistance to Repeated Autoclaving Cycles 134 °C/30 min.

Method

- Midisart® 17805 (0.2 µm PTFE)
- 60 sterilization cycles at 134 °C 30 minutes. Units are cooled down to room temperature after each autoclaving cycle
- After 20, 30, 40, 50 and 60 cycles integrity test of bubble point with IPA 99.99 % (visual method) and pressure hold test by 1 bar
- Recognition of B.P. continuous stream of bubbles
- BP Min IPA 99.9 % before autoclaving: 1.3 bar
- BP Min IPA 99.9 % after autoclaving: 1 bar
- After bubble point each unit will be dried with compressed air
- 3 lots each 5 Midisart®

BC-Test Method

- Each unit after 60 cycles was autoclaved again
- Test organism: Brevundimonas diminuta (ATCC 19146)
- Challenge 10^7 organisms/cm^2 in accordance to ASTM
- Test pressure 3.0 bar: Test volume 50 mL

Conclusion

All filters passed Bubble Point Test and BC Test.

Pressure Hold Test 1.0 bar/Bubble Point (IPA) [bar]
Lot 000814

Midisart®	Before 1 ×	After 20 ×	After 30 ×	After 40 ×	After 50 ×	After 60 ×	BCT
00578	Ok/1.6	Ok/1.4	Ok/1.35	Ok/1.4	Ok/1.4	Ok/1.35	Passed
00675	Ok/1.55	Ok/1.45	Ok/1.35	Ok/1.35	Ok/1.4	Ok/1.3	Passed
00790	Ok/1.6	Ok/1.5	Ok/1.4	Ok/1.35	Ok/1.35	Ok/1.25	Passed
01057	Ok/1.6	Ok/1.4	Ok/1.4	Ok/1.4	Ok/1.35	Ok/1.3	Passed
01198	Ok/1.6	Ok/1.45	Ok/1.35	Ok/1.35	Ok/1.35	Ok/1.3	Passed

Lot 010285

Midisart®	Before 1 ×	After 20 ×	After 30 ×	After 40 ×	After 50 ×	After 60 ×	BCT
00160	Ok/1.6	Ok/1.4	Ok/1.35	Ok/1.4	Ok/1.4	Ok/1,35	Passed
00415	Ok/1.6	Ok/1.45	Ok/1.35	Ok/1.4	Ok/1.4	Ok/1.3	Passed
00489	Ok/1.65	Ok/1.45	Ok/1.4	Ok/1.4	Ok/1.4	Ok/1.35	Passed
00498	Ok/1.6	Ok/1.45	Ok/1.4	Ok/1.4	Ok/1.35	Ok/1.3	Passed
00776	Ok/1.65	Ok/1.45	Ok/1.4	Ok/1.4	Ok/1.4	Ok/1.35	Passed

Lot 010215

Midisart®	Before 1 ×	After 20 ×	After 30 ×	After 40 ×	After 50 ×	After 60 ×	BCT
03171	Ok/1.65	Ok/1.45	Ok/1.4	Ok/1.35	Ok/1.35	Ok/1.3	Passed
03232	Ok/1.65	Ok/1.45	Ok/1.4	Ok/1.4	Ok/1.4	Ok/1.3	Passed
03285	Ok/1.6	Ok/1.35	Ok/1.3	Ok/1.3	Ok/1.3	Ok/1.25	Passed
03304	Ok/1.65	Ok/1.4	Ok/1.35	Ok/1.35	Ok/1,35	Ok/1.35	Passed
03334	Ok/1.7	Ok/1.35	Ok/1.35	Ok/1.35	Ok/1.35	Ok/1.3	Passed

Extractables

Problem
Extractables in Midisart® analog to Sartofluor® with decreased volume. Tested filter: Midisart® Type 17805 (1/2 housing with PTFE-Membran).

Method
15 × 1/2 Midisart® in 1 L VE-water by 80 °C and 15 × 1/2 Midisart® in 1 L ethanol by 50 °C 24 h. The extracts were analysed in accordance to the current USP.

Results

No 1–15	Conductivity [µS/cm]	pH	NVR [g/200 mL]	Oxidiz Subst.	Chloride	Sulfate	Ammonia	Heavy Metal
BLW H_2O	0.670	6.09	0.00010	neg.	neg.	neg.	neg.	neg.
EX H_2O	2.500	6.78	0.00250	neg.	neg.	neg.	neg.	neg.
BLW EtOH	n.b.	n.b.	0.00040	neg.	neg.	neg.	neg.	neg.
EX EtOH	n.b.	n.b.	0.00150	neg.	neg.	neg.	neg.	neg.

Conclusion
Adherence of the current USP.

5.1 Biocompatibility

Purpose
These tests are to determine that all components used in the manufacture of Midisart® 2000 are biosafe and meet and exceed the requirements for the current USP Class VI – 121 °C Plastics Tests.

Test Method and Results
Midisart® 2000 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 certificates were released as a result of the testing of Midisart® 2000 filter elements. All materials used in the construction of Midisart® 2000 meet or exceed the requirements of the USP Class VI – 121 °C Plastics Tests.

5.2 Storage Conditions

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 which corresponds to the herewith recommended shelf lives.

- 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

6. Endotoxin Test

Background
The goal of these tests is to determine that the amount of endotoxins released in the effluent of 3 Midisart® 2000 filters is acc. to the USP Bacterial Endotoxin Test Chapter <85> less than 0.25 EU/mL.

Method
Each lot of sterile Midisarts® was tested for endotoxins utilizing a kinetic turbidimetric method based on the LAL test. After wetting the filters with ethanol, 20 mL of endotoxin-free water is filtered through three Midisart® 2000 filters. The filtrates are collected in a test tube. The endotoxin test is performed with the filtrates together with a positive and negative control according to the kinetic turbidimetric method with an automatical reader, which determines the actual concentration of endotoxins.

Conclusion
All Midisart® 2000 filters tested, under the conditions of the elution test described above, gave results below 0.25 EU/mL bacterial endotoxin.

Sales and Service Contacts

For further contacts, visit www.sartorius-stedim.com

Europe

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen

Phone +49.551.308.0
Fax +49.551.308.3289

Sartorius Stedim Systems GmbH
Robert-Bosch-Strasse 5–7
34302 Guxhagen

Phone +49.5665.407.0
Fax +49.5665.407.2200

France
Sartorius Stedim FMT S.A.S.
ZI des Paluds
Avenue de Jouques – CS 91051
13781 Aubagne Cedex

Phone +33.442.845600
Fax +33.442.845619

Sartorius Stedim France SAS
ZI des Paluds
Avenue de Jouques – CS 71058
13781 Aubagne Cedex

Phone +33.442.845600
Fax +33.442.846545

Austria
Sartorius Stedim Austria GmbH
Franzosengraben 12
1030 Vienna

Phone +43.1.7965763.18
Fax +43.1.796576344

Belgium
Sartorius Stedim Belgium N.V.
Leuvensesteenweg, 248/B
1800 Vilvoorde

Phone +32.2.756.06.80
Fax +32.2.756.06.81

Hungary
Sartorius Stedim Hungária Kft.
Kagyló u. 5
2092 Budakeszi

Phone +36.23.457.227
Fax +36.23.457.147

Italy
Sartorius Stedim Italy S.p.A.
Via dell'Antella, 76/A
50012 Antella-Bagno a Ripoli (FI)

Phone +39.055.63.40.41
Fax +39.055.63.40.526

Netherlands
Sartorius Stedim Netherlands B.V.

Phone +31.30.60.25.080
Fax +31.30.60.25.099

filtratie.nederland@sartorius-stedim.com

Poland
Sartorius Stedim Poland Sp. z o.o.
ul. Wrzesinska 70
62-025 Kostrzyn

Phone +48.61.647.38.40
Fax +48.61.879.25.04

Russian Federation
LLC "Sartorius ICR"
Uralskaya str. 4, Lit. B
199155, Saint-Petersburg

Phone +7.812.327.5.327
Fax +7.812.327.5.323

Spain
Sartorius Stedim Spain, S.A.U.
Avda. de la Industria, 32
Edificio PAYMA
28108 Alcobendas (Madrid)

Phone +34.902.110.935
Fax +34.91.358.96.23

Switzerland
Sartorius Stedim Switzerland AG
Ringstrasse 24 a
8317 Tagelswangen

Phone +41.52.354.36.36
Fax +41.52.354.36.46

U.K.
Sartorius Stedim UK Ltd.
Longmead Business Centre
Blenheim Road, Epsom
Surrey KT19 9 QQ

Phone +44.1372.737159
Fax +44.1372.726171

America

USA
Sartorius Stedim North America Inc.
5 Orville Drive, Suite 200
Bohemia, NY 11716

Toll-Free +1.800.368.7178
Fax +1.631.254.4253

Argentina
Sartorius Argentina S.A.
Int. A. Ávalos 4251
B1605ECS Munro
Buenos Aires

Phone +54.11.4721.0505
Fax +54.11.4762.2333

Brazil
Sartorius do Brasil Ltda
Avenida Senador Vergueiro 2962
São Bernardo do Campo
CEP 09600-000 - SP - Brasil

Phone +55.11.4362.8900
Fax +55.11.4362.8901

Mexico
Sartorius de México S.A. de C.V.
Circuito Circunvalación Poniente
No. 149
Ciudad Satélite
53100, Estado de México
México

Phone +52.5555.62.1102
Fax +52.5555.62.2942

Asia|Pacific

Australia
Sartorius Stedim Australia Pty. Ltd.
Unit 5, 7–11 Rodeo Drive
Dandenong South Vic 3175

Phone +61.3.8762.1800
Fax +61.3.8762.1828

China
Sartorius Stedim Biotech (Beijing) Co. Ltd.
No. 33 Yu'an Road
Airport Industrial Zone B
Shunyi District, Beijing 101300

Phone +86.10.80426516
Fax +86.10.80426580

Sartorius Stedim Biotech (Beijing) Co. Ltd.
Shanghai Branch Office
3rd Floor, North Wing, Tower 1
No. 4560 Jin ke Road
Pudong District, Shanghai, 201210

Phone +86.21.68782300
Fax +86.21.68782332|68782882

Sartorius Stedim Biotech (Beijing) Co. Ltd.
Guangzhou Representative Office
Unit K, Building 23
Huihua Commerce & Trade Building
No. 80 Xianlie Middle Road
Room 704, Broadway Plaza,
Guangzhou 510070

Phone +86.20.37618687|37618651
Fax +86.20.37619051

India
Sartorius Stedim India Pvt. Ltd.
#69/2-69/3, NH 48, Jakkasandra
Nelamangala Tq
562 123 Bangalore, India

Phone +91.80.4350.5250
Fax +91.80.4350.5253

Japan
Sartorius Stedim Japan K.K.
4th Fl., Daiwa Shinagawa North Bldg.
8-11, Kita-Shinagawa 1-chome
Shinagawa-ku, Tokyo, 140-0001 Japan

Phone +81.3.4331.4300
Fax +81.3.4331.4301

Malaysia
Sartorius Stedim Malaysia Sdn. Bhd.
Lot L3-E-3B, Enterprise 4
Technology Park Malaysia
Bukit Jalil
57000 Kuala Lumpur, Malaysia

Phone +60.3.8996.0622
Fax +60.3.8996.0755

Singapore
Sartorius Stedim Singapore Pte. Ltd.
1 Science Park Road,
The Capricorn, #05-08A,
Singapore Science Park II
Singapore 117528

Phone +65.6872.3966
Fax +65.6778.2494

South Korea
Sartorius Korea Biotech Co., Ltd.
8th Floor, Solid Space B/D,
PanGyoYeok-Ro 220, BunDang-Gu
SeongNam-Si, GyeongGi-Do, 463-400

Phone +82.31.622.5700
Fax +82.31.622.5799

◀▶ www.sartorius-stedim.com

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