sartorius stedim biotech

Validation Guide
Minisart®
Syringe Filters

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 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.

Therefore, a prior membrane filtration run is required by cGMP regulations (Current Good Manufacturing Practice of the US Food and Drug Administration) to ensure that particles and microbes are removed. Solutions containing heat-labile products, such as antibiotics, can be cold sterilized by membrane filtration immediately before aseptic filling. Microbe retentive filtration (bacteria retentive according to the European Pharmacopoeia) 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.

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

We have compiled this validation guide so users of Minisart® syringe filters can plan, implement and document their own validation procedures.

2. Quality and its Assurance

2.1 cGMP Quality Assurance from Sartorius

Consistent high quality of Sartorius Membrane Filters, Minisart® syringe filters 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.

2.2 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 Minisart® syringe filters 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 and within their specifications.

2.3 Prevention of Contamination

Minisart® syringe filters are individually sealed in PET blister packages with DuPont™ Tyvek® paper lid in a controlled production area. Following this step they are sterilized by gamma irradiation or EO gas to reliably prevent microbial growth, and thus rule out the possibility of pyrogen synthesis during shipping and storage.

2.4 Complete Traceability

The product name, product description, article code, pore size, sterilization method, expiration date, product lot number and the CE mark (for 16534 + 17597) is printed on each individual blister lid and on the label of the box in which the Minisart® syringe filters are packed. In addition, the pack size and the barcodes for article code and lot number are printed on the label of the box. The traceable lot number allows convenient retrieval of all data complied on the materials used, production steps and QC tests.

2.5 DIN ISO 9001 Certificates

The quality management system of Sartorius AG meets the requirements of DIN EN ISO 9001 and has been certified by DQS, the German Association for the Certification of Quality Systems.

Exemplary Quality Systems Certificates

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

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

2.6 Declaration as Medical Devices

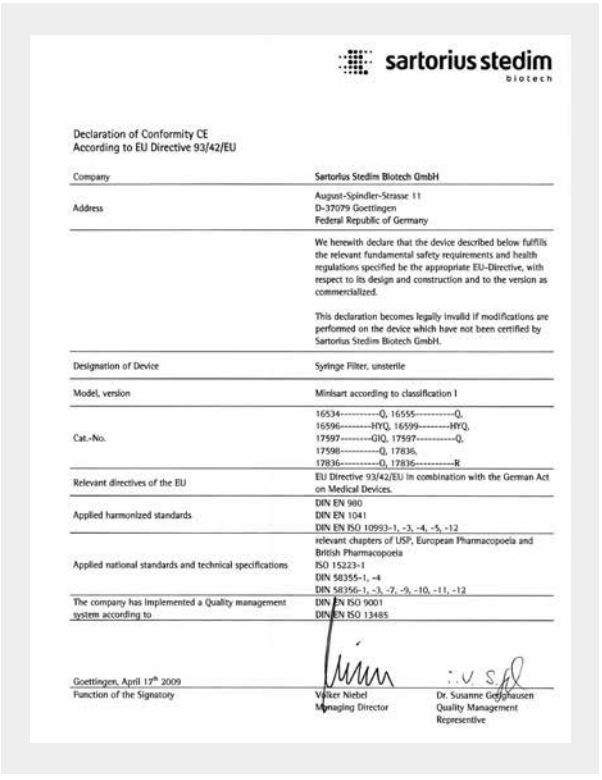
In addition the Sartorius Quality Management System fullfills the requirements of the DIN EN ISO 13485 the harmonized standard for Quality Systems for Medical Devices.

The certificate can be downloaded at

www.sartorius-stedim.com/qm-certificates

2.7 Declaration of Conformity CE

As part of the CE-marking procedure the Sartorius Quality Management system fullfills and is certified according to EU Guideline 93/42/EEC Annex II setting specific requirements for medical devices. On the basis of this certification as well as appropriate documentation the declaration of conformity for Sartorius Minisart® syringe filters was given.



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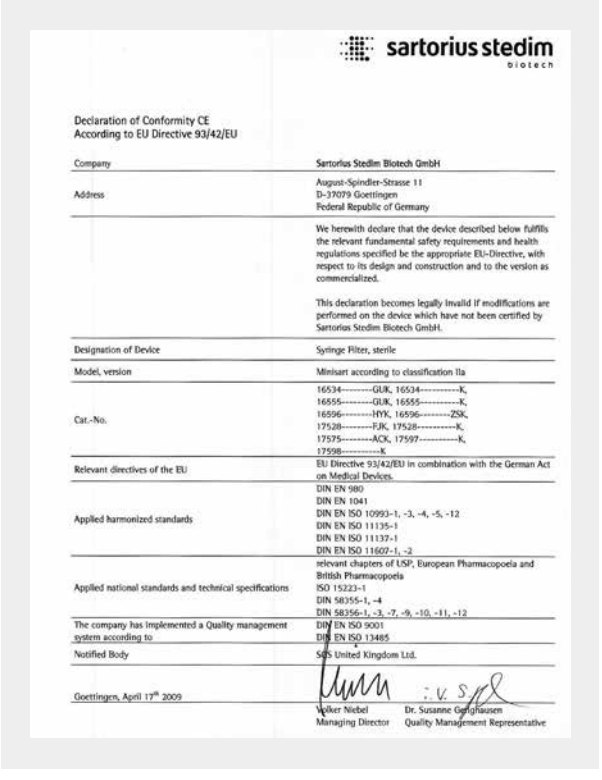
Declaration of Conformity CE
According to EU Directive 93/42/EU

Company	Sartorius Stedim Biotech GmbH
Address	August-Spindler-Strasse 11 D-37079 Goettingen Federal Republic of Germany
	We herewith declare that the device described below fulfills the relevant fundamental safety requirements and health regulations specified be the appropriate EU-Directive, with respect to its design and construction and to the version as commercialized. This declaration becomes legally invalid if modifications are performed on the device which have not been certified by Sartorius Stedim Biotech GmbH.
Designation of Device	Syringe Filter, unsterile
Model, version	Minisart according to classification I
Cat.-No.	16534----------Q, 16555----------Q, 16596---------HYQ, 16599---------HYQ, 17597---------GIQ, 17597----------Q, 17598----------Q, 17836, 17836----------Q, 17836----------R
Relevant directives of the EU	EU Directive 93/42/EU in combination with the German Act on Medical Devices.
Applied harmonized standards	DIN EN 980 DIN EN 1041 DIN EN ISO 10993-1, -3, -4, -5, -12
Applied national standards and technical specifications	relevant chapters of USP, European Pharmacopoeia and British Pharmacopoeia ISO 15223-1 DIN 58355-1, -4 DIN 58356-1, -3, -7, -9, -10, -11, -12
The company has implemented a Quality management system according to	DIN EN ISO 9001 DIN EN ISO 13485
Goettingen, April 17th 2009	i. V. S.
Function of the Signatory	Volker Niebel, Managing Director Dr. Susanne Geibhausen, Quality Management Representive



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Declaration of Conformity CE
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Designation of Device	Syringe Filter, sterile
Model, version	Minisart according to classification IIa
Cat.-No.	16534---------GUK, 16534----------K, 16555---------GUK, 16555----------K, 16596---------HYK, 16596---------ZSK, 17528---------FJK, 17528----------K, 17575---------ACK, 17597----------K, 17598----------K
Relevant directives of the EU	EU Directive 93/42/EU in combination with the German Act on Medical Devices.
Applied harmonized standards	DIN EN 980 DIN EN 1041 DIN EN ISO 10993-1, -3, -4, -5, -12 DIN EN ISO 11135-1 DIN EN ISO 11137-1 DIN EN ISO 11607-1, -2
Applied national standards and technical specifications	relevant chapters of USP, European Pharmacopoeia and British Pharmacopoeia ISO 15223-1 DIN 58355-1, -4 DIN 58356-1, -3, -7, -9, -10, -11, -12
The company has implemented a Quality management system according to	DIN EN ISO 9001 DIN EN ISO 13485
Notified Body	SGS United Kingdom Ltd.
Goettingen, April 17th 2009	i. V. S.
	Volker Niebel, Managing Director Dr. Susanne Geibhausen, Quality Management Representative

2.8 Biocompatibility

Minisart® syringe filters are free of cytotoxic and haemolytic effects, they pass the USP Biological Tests (classification VI|121 °C), Haemolysis Tests and the Cytotoxicity Tests.

BIOSERVICE

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Minisart High-Flow type, representing syringe filter with MBS housing and PES membrane**
Order No.: 16532 - GUK
Lot No.: 16532 050726

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

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

CYTOTOXICITY
HAEMOLYSIS TEST
USP BIOLOGICAL TESTS (CLASSIFICATION VI/121 °C)

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

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6
D-82152 Planegg

Dr. Daniela Brummer
Biological Safety Testing
Date: October 06, 2005

BSL BIOSERVICE Scientific Laboratories GmbH
GLP
ISO 17025

BIOSERVICE

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Minisart type, representing syringe filter with MBS housing and CA membrane**
Order No.: 16534 - K
Lot No.: 16534 050689

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

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

CYTOTOXICITY
HAEMOLYSIS TEST
USP BIOLOGICAL TESTS (CLASSIFICATION VI/121 °C)

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

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6
D-82152 Planegg

Dr. Daniela Brummer
Biological Safety Testing
Date: October 06, 2005

BSL BIOSERVICE Scientific Laboratories GmbH
GLP
ISO 17025

2.9 Test Methods for the Quality Assurance of Sartorius Minisart® Syringe Filters

Lot Related Tests
Non-destructive Tests
100 % Individual Testing

- Integrity Leakage Test

Lot Related Tests
Destructive Tests
Randomly Sampled
Minisart® Syringe Filters

- Bacteria Challenge Test
- Bubble Point Test
- Sterility
- Burst Pressure
- Pressure Hold Test
- Flow Rate Performance
- Endotoxin Test
- Visual Inspections

Testing Conducted for the Validation of Minisart® Syringe Filters

- Bacteria Challenge Test
- Bubble Point Test
- Correlation of Bubble Point Values with the HIMA|ASTM Bacteria Challenge Tests
- Validation of Gamma Irradiation
- Validation of Ethylene Oxide Gas Sterilization
- Burst Pressure
- Pressure Hold Test
- Flow Rate Performance
- Chemical Compatibility
- Endotoxin Test
- Cytotoxicity Test
- Haemolysis Test
- USP Biological Tests
- Visual Inspections

3. Technical Specifications

3.1 Product Description

The Minisart® NML and Minisart® high flow syringe filters remove microorganisms, particles, precipitates, undissolved powders larger than 0.2 µm from aqueous solutions or water. The single–use products consists a hydrophilic surfactant free Cellulose Acetate (SFCA) or Polyethersulfone (PES) membrane filter sealed in a MBS housing. They do not contain endotoxins and they are non-toxic. Minisarts® can be used bi-directional.

Typical application is the sterile filtration of protein solutions, tissue culture additives, buffer and water.

3.2 Order Number Overview

Article No.	Product Name	Membrane Filter	Pore Size [µm]	Sterilization	Pack Size	Connector Outlet
16534----------K	Minisart® NML	surfactant free Cellulose Acetate (SFCA)	0.2	EO	50 units individually, sterile packaged	Male Luer Lock
16534--------GUK	Minisart® NML	surfactant free Cellulose Acetate (SFCA)	0.2	Gamma irradiation	50 units individually, sterile packaged	Male Luer Lock
17597----------K	Minisart® NML	surfactant free Cellulose Acetate (SFCA)	0.2	EO	50 units individually, sterile packaged	Male Luer Slip
16532----------K	Minisart® high flow	Polyethersulfone (PES)	0.2	EO	50 units individually, sterile packaged	Male Luer Lock
16532--------GUK	Minisart® high flow	Polyethersulfone (PES)	0.2	Gamma irradiation	50 units individually, sterile packaged	Male Luer Lock
16541----------K	Minisart® high flow	Polyethersulfone (PES)	0.2	EO	50 units individually, sterile packaged	Male Luer Slip

3.3 Technical Specifications

Properties	Description
Burst pressure	min. 6 bar|87.0 psi
Color code	Top part: Clear transparent Base part: Royal blue for Minisart® NML 16534 and 17597 Dark blue for Minisart® high flow 16532 and 16541
Connections	Inlet: Female Luer Lock Outlet: Male Luer Lock: 16534 and 16532 Male Luer Slip: 17597 and 16541
Dimensions	Length (inlet to outlet): 26 mm Diameter: 33 mm
Filtration area	6.2 cm^2
Hold-up volume	0.1 mL before an air purge
Label indications	
Blister packaging	Product name, product description, article code, pore size, sterilization method, expiration date, product lot number and the CE mark (for 16534 + 17597)
Label on the outer box	Product name, product description, article code, pore size, sterilization method, expiration date, product lot number, the CE mark (for 16534 + 17597), pack size and the barcodes for article code and lot number. Expiration date is three years (36 months) from date of manufacture.
Materials	All materials meet the FDA requirements as defined in Title 21 Code of Federal Regulations. Biosafety testing, such as the Class VI Plastics Testing as described in the current USP, are also met and exceeded.
Housing	MBS
Membrane filter	16534 and 17597: Surfactant free Cellulose Acetate (SFCA) 16532 and 16541: Polyethersulfone (PES)
Operating instructions	A direction for use is placed in each box with Certificate of Quality
Operating pressure	max. 4.5 bar|65.3 psi
Operating temperature	max. 50 °C
Packaging	Units supplied individually, sterile packaged in PETG blisters with a DuPont™ Tyvek® or medicine paper cover sheet
Storage conditions	Storage in a closed, dry area, in the original packing Temperature: 5 °C – 40 °C, frost-free (for max. 7d at -10 °C–50 °C) 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
Warning	Do not use product if package is damaged. Do not re-sterilize or re-use the unit. It is a single-use product. Do not use this product to filter fluids at temperature above 50 °C. Take care when using syringes with a volume less than 10 mL since they can generate a pressure greater than the maximum operating pressure. Minisarts® are designed to filter bi-directional. However, once you start filtering in one direction, do not reverse it.

3.4 Lot Release Criteria

Sterility	Sterilisation process (EO or gamma irradiation) has been approved and certified
Endotoxin Test	≤ 0.06 EU/mL, meets current USP bacterial endotoxin test for devices
Integrity Leakage Test	100% tested during manufacture
Bacteria Challenge Test (Sterile Filtration Capability)	Retention of 10^7 bacteria/mL · cm^2 of Brevundimonas diminuta
Flow Rate Performance at 1.0 bar|14.5 psi	16534 and 17597, both with SFCA membrane: ≥ 60 mL/min 16532 and 16541, both with PES membrane: ≥ 140 mL/min
Bubble Point Test	16534 and 17597, both with SFCA membrane: ≥ 3.2 bar|46.4 psi 16532 and 16541, both with PES membrane: ≥ 3.2 bar|46.4 psi
Pressure Hold Test	16534 and 17597, both with SFCA membrane: no air passages at 2.0 bar|29.0 psi 16532 and 16541, both with PES membrane: no air passages at 2.5 bar|36.3 psi
Burst Pressure Testing of the Housing	≥ 6 bar|87.0 psi

4. Integrity Test Limits
Correlation of Bubble Point Values with the HIMA|ASTM Bacteria Challenge Tests

Background for the Determination of Integrity Test Values
Establishing a correlation between bacterial retention of a sterilizing grade filter such as a Minisart® syringe filter and a non-destructive integrity test is decisive for the reliability of a sterile filtration procedure.

According to the Health Industry Manufacturers Association (HIMA) Guidelines for "Microbiological Evaluation of filters for Sterilizing Liquids" Doc. No. 3, Vol. 4, 1982|ASTM F 838-83 Guideline, and the FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing", June 1987, a sterilizing grade filter 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 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.

Method
Several hundred Minisart® syringe filters from numerous production lots were tested according to a Bacteria Challenge Test in accordance with the HIMA Document No. 3, Vol. 4 (April 1982) "Microbiological Evaluation of Filters for Sterilizing Liquids"|ASTM F 838-83 Guideline, and DIN 58356, Part 1.

Through each Minisart® syringe filter a bacterial suspension is filtered at a constant pressure of 4 bar|58.0 psi. The suspension consists of Nutrient broth medium acc. to HIMA and Brevundimonas diminuta ATCC 19146.

For the validation studies of the Minisart® syringe filters a minimum concentration of 1×10^7 B. diminuta per cm^2 filtration area for each tested unit was used.

For the control and monitoring of the prevailing pressure during the Bacteria Challenge Test, pressure gauges and valves have been installed.

Each filtrate that passes through the Minisart® syringe filter is collected separately and incubated for 7 days at 30 ± 2 °C.

A quantitative determination was set up in parallel by filtering half of the filtrates through a microbiological gridded membrane filter, which was placed on agar and incubated under the same conditions.

Integrity Test
After the Bacteria Challenge Test the Minisart® syringe filters units were integrity tested by the bubble point test method in order to correlate the results of the destructive Bacteria Challenge Test with this non-destructive integrity test.

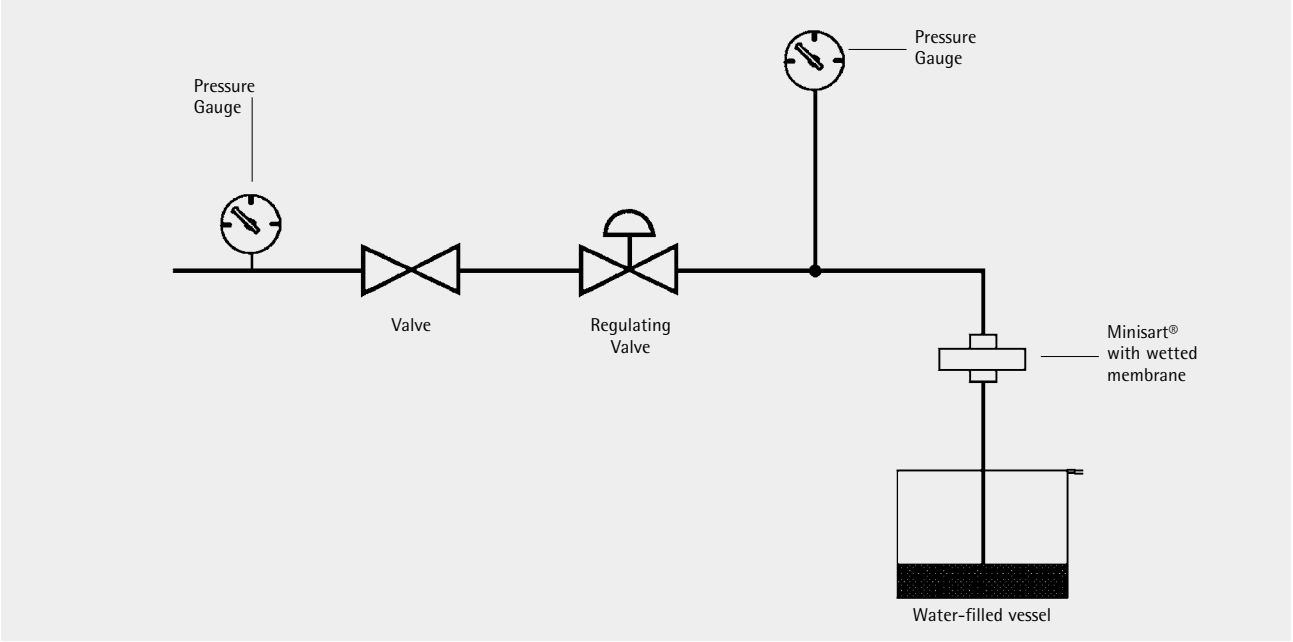
The Bubble Point Test is performed by two methods:
- utilizing a Sartocheck® automated integrity test unit
- manually, visually detection.

For the determination of the bubble point, air pressure is slowly increased on the upstream side of the Minisart® syringe filter housing.

The pressure point when a constant air flow pass the membrane filter is detected by measuring the pressure drop on the upstream-side of the Minisart® syringe filter.

For the visual test, a tube is attached to the Minisart® outlet. This tube ends in a water-filled vessel. When the first continuous stream of bubbles appears, the bubble point is detected.

Visual Bubble Point Test Set-up

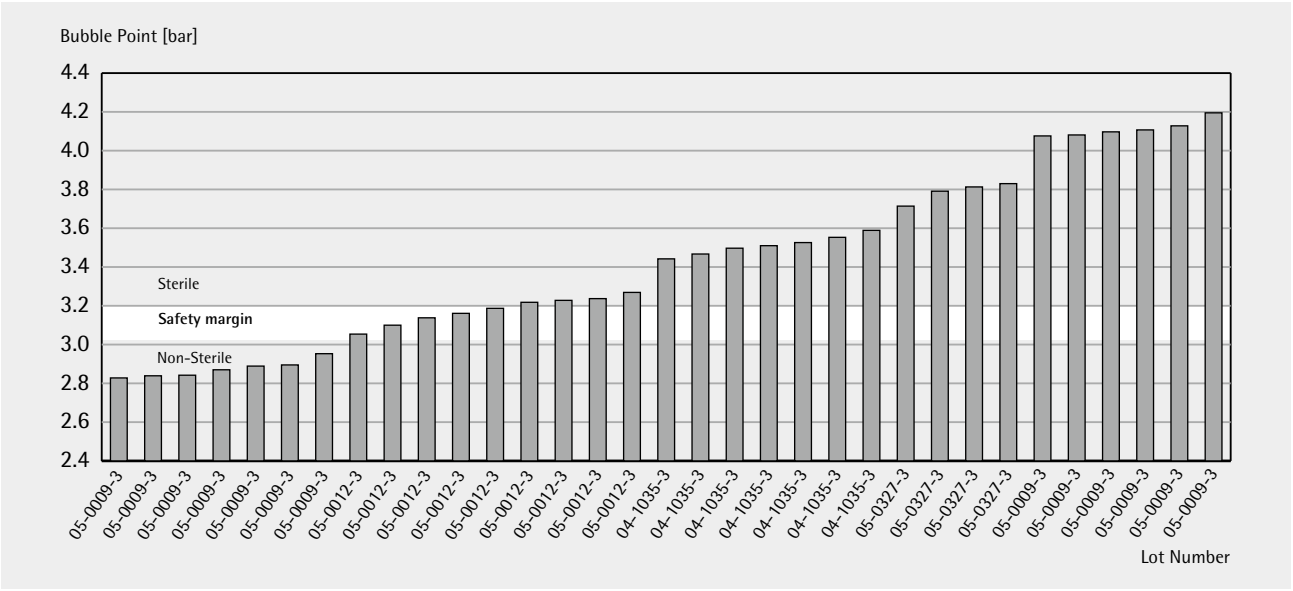


Results
Since most of the filters tested during the validation studies had high Bubble Point values and produced a sterile filtrate, the following data is a sampling from all filters tested during the validation testing indicating results near the Bubble Point|sterile filtrate limits.

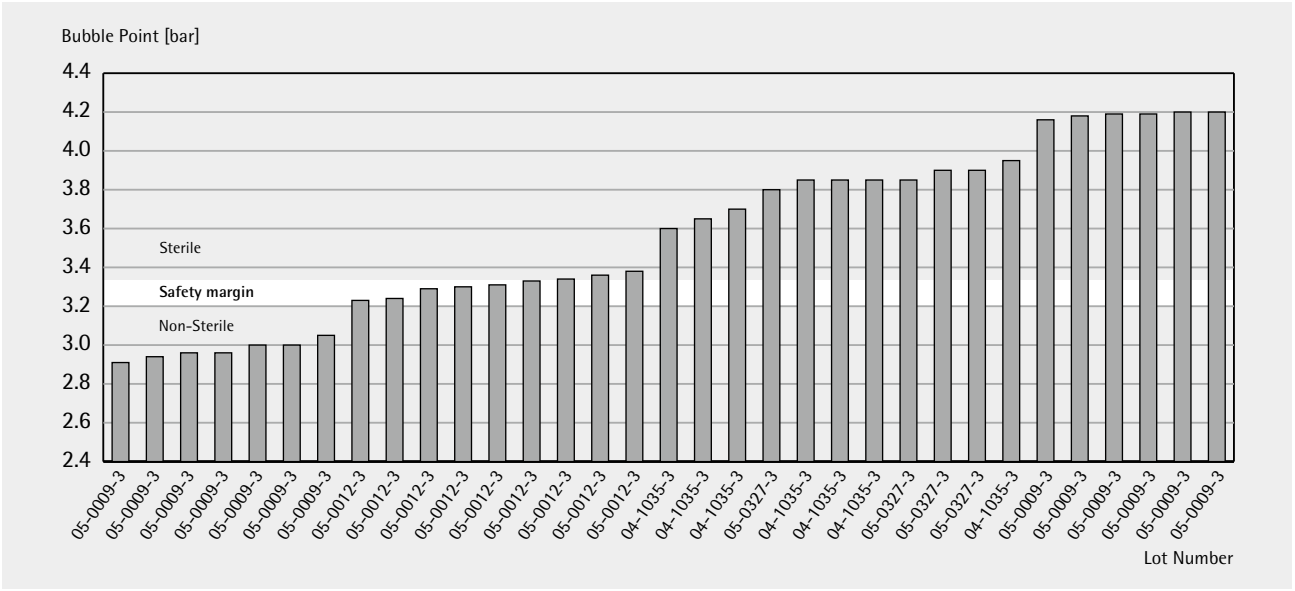
Results Minisart® NML 16534 and 17597

	Bubble Point Sartocheck® [bar]	Bubble Point visual [bar]	Results	Correlation Sartocheck® | visual
05-0009-3	2.828	2.94	non-sterile	1.040
05-0009-3	2.839	2.91	non-sterile	1.025
05-0009-3	2.842	2.96	non-sterile	1.042
05-0009-3	2.870	2.96	non-sterile	1.031
05-0009-3	2.889	3.00	non-sterile	1.038
05-0009-3	2.895	3.00	non-sterile	1.036
05-0009-3	2.953	3.05	non-sterile	1.033
05-0012-3	3.054	3.23	sterile	1.058
05-0012-3	3.100	3.24	sterile	1.045
05-0012-3	3.138	3.31	sterile	1.055
05-0012-3	3.161	3.29	sterile	1.041
05-0012-3	3.187	3.30	sterile	1.035
05-0012-3	3.218	3.38	sterile	1.050
05-0012-3	3.228	3.33	sterile	1.032
05-0012-3	3.237	3.36	sterile	1.038
05-0012-3	3.269	3.34	sterile	1.022
04-1035-3	3.442	3.65	sterile	1.060
04-1035-3	3.467	3.60	sterile	1.038
04-1035-3	3.497	3.85	sterile	1.101
04-1035-3	3.510	3.70	sterile	1.054
04-1035-3	3.526	3.85	sterile	1.092
04-1035-3	3.553	3.85	sterile	1.084
04-1035-3	3.589	3.95	sterile	1.101
05-0327-3	3.714	3.80	sterile	1.023
05-0327-3	3.791	3.85	sterile	1.016
05-0327-3	3.813	3.90	sterile	1.023
05-0327-3	3.830	3.90	sterile	1.018
05-0009-3	4.076	4.19	sterile	1.028
05-0009-3	4.081	4.16	sterile	1.019
05-0009-3	4.097	4.20	sterile	1.025
05-0009-3	4.107	4.19	sterile	1.020
05-0009-3	4.128	4.20	sterile	1.017
05-0009-3	4.195	4.18	sterile	0.996

Minisart® NML Bubble Point|BCT Correlation – Sartocheck®



Minisart® NML Bubble Point|BCT Correlation – Visual Determination



Conclusion
The data determined by the Sartocheck® automated device shows that Minisart® NML syringe filters that have Bubble Point values > 3.05 bar|44.2 psi always produced a sterile filtrate with 100% retention of the test organism, Brevundimonas diminuta. In order to have a high degree of safety when evaluating the test results, and considering that other filter integrity test units or other test methods may be used, a safety margin of 0.15|2.2 psi bar has been defined. For a thoroughly water wetted Minisart® NML 0.2 µm syringe filter (keeping in mind this safety factor) the minimum allowable Bubble Point value at 20 °C is:

≥ 3.2 bar|46.4 psi

Correction factors
The variations between the two test methods may be calculated by a correction factor:

Factor BP (Sartocheck®) to BP (visual): **1.041**

This is equivalent to a minimum BP of 3.2 bar|46.4 psi × 1.041 = **3.33 bar|48.3 psi for the visual BP determination**

Results Minisart® high flow 16532

Lot	060014 BCT	Sartocheck®	051075 BCT	Sartocheck®	050387 BCT	Sartocheck®
1	sterile	3.49	sterile	3.67	sterile	3.82
2	sterile	3.45	sterile	3.90	sterile	3.72
3	sterile	3.43	sterile	3.49	sterile	3.77
4	sterile	3.42	sterile	4.11	sterile	3.78
5	sterile	3.44	sterile	3.84	sterile	3.62
6	sterile	3.44	sterile	3.73	sterile	4.11
7	sterile	3.48	sterile	3.77	sterile	3.63
8	sterile	3.47	sterile	3.73	sterile	4.06
9	sterile	3.46	sterile	3.62	sterile	3.92
10	sterile	3.43	sterile	3.63	sterile	3.78

Results Minisart® high flow 16541

Lot	051053 BCT	Sartocheck®	051027 BCT	Sartocheck®	050684 BCT	Sartocheck®
1	sterile	3.71	sterile	3.52	sterile	3.62
2	sterile	3.73	sterile	3.53	sterile	3.72
3	sterile	3.65	sterile	3.50	sterile	3.73
4	sterile	3.73	sterile	3.48	sterile	3.67
5	sterile	3.79	sterile	3.51	sterile	3.83
6	sterile	3.78	sterile	3.50	sterile	3.73
7	sterile	3.69	sterile	3.53	sterile	3.68
8	sterile	3.72	sterile	3.51	sterile	3.62
9	sterile	3.73	sterile	3.48	sterile	3.73
10	sterile	3.58	sterile	3.45	sterile	3.68

Conclusion
The data determined by the Sartocheck® automated device do not fall below the minimum allowable Bubble Point value at 20 °C of:

≥ 3.2 bar|47.1 psi

for a thoroughly water wetted Minisart® high flow 0.2 µm syringe filter.

Note
The Bubble Point Test results are influenced by the nature of the wetting medium. The bubble point values listed in this validation guide are for Minisart® syringe 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.

5. Sterilization Validation

Background
A series of tests is needed to confirm that a sterilization procedure has been carried out successfully. Sterility testing of a system is used to prove that the entire contents of the inner packaging are sterile. The performance test ensures that the sterilization procedure does not damage any part of the product or lead to system malfunctions.

Sartorius uses two different methods for sterilization: The gamma-irradiation method is employed for 16534--------GUK and 16532--------GUK Minisart® types and the ethylene oxide gas method for 16534----------K, 17597------K, 16532------K and 16541----K Minisart® types.

Gamma-irradiation of products is carried out as required by DIN EN 552 and ISO 11137 and the ethylene oxide sterilization is in compliance with DIN EN 550 and ISO 11135.

5.1 Presterilization Bioburden

Background
The European Pharmacopoeia describes how the safety assurance level (SAL) of sterilization processes is calculated. The microbial load of a system is determined before sterilization to ensure that the burden is not too high for the sterilization process to be reliable.

Method
The bioburden was determined of all inner and outer Minisart® syringe filters surfaces by filling, shaking and rinsing the units in succession. The rinsing solution collected was filtered through a 0.45 µm gridded membrane filter made of cellulose nitrate (cellulose ester). The filter was transferred to nutrient agar (article no. 14144) and incubated for 7 days at 32.5 ± 2.5 °C. The resulting colonies were counted.

Results

Type	Lot No.	No. of units tested	Average bioburden outer surface Minisart® and inner surface packaging [cfu]	Average bioburden inner surface Minisart® [cfu]	Average bioburden total [cfu]
16534	050951	10	1.6	3.6	5.2
16532	050950	10	1.8	3.9	5.7

Conclusion
The bioburden of the Minisart® syringe filters proved are low enough to ensure that any standard sterilization procedure using gamma-irradiation or ethylene oxide gas will reduce the bioburden to zero.

5.2 Validation of Gamma Irradiation

Minisart® types:
16534--------GUK
16532--------GUK

5.2.1 Examination of the Validation and Sterility Test with Soybean-Casein Digest Broth (TSB) and Thioglycollate Broth after Irradiation at a Reduced Dose of 5 kGy

Background
The validation of gamma-irradiation was carried out by analogy with the VD_{Max}-method in which the average bioburden of 2 lots (total of 20 Minisart® syringe filter) is determined. For each Minisart® lot further 20 units are gamma-irradiated with a minimum-dose of 5 kGy. Afterwards a sterility test with these Minisart® units is performed.

Method
To ensure that the content of the Minisart® syringe filter packaging is sterile even at the minimum dose of 5 kGy, an applicable sterility test in accordance with USP and EP was carried out after the irradiation. After sterilization of numerous Minisart® units in their original packaging, the individually blister packaging was opened under sterile conditions and each Minisart® syringe filter was placed into 100 mL of sterile nutrient broth. 10 units were placed into TSB broth (tryptone soya broth, Oxoid code no. B00509M) and incubated together with a negative- and a positive control for 14 days at 22.5 ± 2.5 °C. 10 units were placed into thioglycollate medium (Oxoid code no. B00510M) and incubated together with a negative- and a positive control for 14 days at 32.5 ± 2.5 °C.

Results

Type	Lot No.	No. of units tested	Average bioburden outer surface Minisart® and inner surface packaging [cfu]	Average bioburden inner surface Minisart® [cfu]	Average bioburden total [cfu]
16534	050951	10	1.6	3.6	5.2
16532	050950	10	1.8	3.9	5.7

Sterility test after gamma-irradiation with 5kGy

Type	Lot No.	No. of systems tested	Sterility test with TSB broth	Sterility test with thioglycollate broth
16534	050951	20	10 sterile 0 failed	10 sterile 0 failed
16532	050950	20	10 sterile 0 failed	10 sterile 0 failed

Conclusion
The results demonstrate that even a minimum dose sterilizes all Minisart® syringe filters tested. The gamma-irradiation procedure with 25 kGy ensures that all surfaces of the Minisart® syringe filter units in contact with the sample are sterile.

In addition the results of the bioburden test and the sterility test demonstrate the fullfillment of ISO 11137 by an Safety Assurance Level (SAL) of 10^{-6}.

5.2.2 Dose Mapping

Method
During dose mapping, the dosimeters are placed on the packed palette at various depths on two parallel levels according to a predefined raster pattern, once on the surface and once in the middle of the palette. The density and the specific weight of the load was determined to establish a dose mapping guide value for the sterilizer.

After sterilization, all dosimeters were subjected to photometric analysis.

Dosimeter manufacturer:
FWT Far West Technology, USA
Dosimeter type:
Nylon dosimeter FWT 60-00

Photometer type:
Radiachromic reader
Photometer manufacturer:
Aérial Genesys 5, Type 3V1B354005

Calibrated with:
NPL (National Physical Laboratory, England) – Dichromat Dosimeter

Level I

Width	5 cm	26 cm	52 cm
Dosimeter on the surface: Height 150 cm	40.5 kGy	41.5 kGy	40.8 kGy
Dosimeter in the geometric middle: Height 55 cm	39.0 kGy	39.3 kGy	39.1 kGy
Dosimeter in the geometric middle: Height 15 cm	36.0 kGy	36.2 kGy	36.2 kGy

Level II

Width	5 cm	26 cm	52 cm
Dosimeter on the surface: Height 150 cm	33.5 kGy	33.9 kGy	34.5 kGy
Dosimeter in the geometric middle: Height 55 cm	31.1 kGy	32.9 kGy	32.9 kGy
Dosimeter in the geometric middle: Height 15 cm	29.3 kGy	30.3 kGy	30.0 kGy

Conclusion
When the validation procedure is followed, Minisart® syringe filter units are gamma-irradiated as required, with a minimum dose of 25 kGy reaching all areas.

5.2.3 Performance Test after Irradiation with 25 kGy

Method
Ready-manufactured, non-sterile Minisart® syringe filters were gamma-irradiated at doses not less than 25 kGy and not more than 50 kGy. After sterilization, the units were visually inspected for cracks or discoloration and the microbiological and physical performance of the systems was tested.

Results
The color of the Minisart® syringe filters and the packaging doesn't change. Damage such as cracks was not observed.

Type	Lot No.	Bacteria Challenge Test (Section 4)	Bubble Point Test (Section 4)	Burst Pressure Test (Section 6.1)	Pressure Hold Test (Section 6.2)
16534	050951	10 passed 0 failed	10 passed 0 failed	10 passed 0 failed	10 passed 0 failed
16532	050950	10 passed 0 failed	10 passed 0 failed	10 passed 0 failed	10 passed 0 failed

Conclusion
A 25-kGy dose of gamma-irradiation does not influence the performance of Minisart® syringe filter units.

5.3 Validation of Ethylene Oxide Gas Sterilization

5.3.1 Parameters of the Ethylene Oxide Gas Sterilization

5.3.1.1 Sterilization Method
Ethylene Oxide Gas Sterilization

5.3.1.2 Sterilization Assurance Level (SAL)
10^{-6}, demonstrated by half-cycle validation

5.3.1.3 Sterilization Conditions

Before Sterilization	Time	≥ 24 hours
	Temperature	≥ 15 °C
Pre-Conditioning	Time	7–48 hours
	Temperature	40–50 °C
	Humidity	≥ 50% RH
Sterilization	Initial vacuum	85–95 mbar abs. (1.2–1.4 psi)
	Ethylene oxide gas concentration	820 mg/L
	Time	4 hours
	Humidity	≥ 50% RH
	Degassing time	≥ 60 minutes
	Desorption steps	3 to 5 times
Aeration	Time	20–48 hours
	Temperature	37–47 °C

5.3.1.4 Quantitative Assay of Residual Ethylene Oxide Gas

Method
Head Space Method according to DIN EN ISO 10993 – 7

Maximum allowance level:
20 mg/product

The process of sterilization with ethylene oxide gas is validated according to DIN EN 550; all documents and data of this validation may be consulted within the scope of an audit.
The compliance with the specified parameters of the sterilization process is certified for each sterilization batch.

5.3.2 Sterility Test with Bioindicators

Method
The Minisart® syringe filters were prepared with Bacillus subtilis endospore strips with a concentration of 10^6 spores per strip. Some units were gassed with ethylene oxide for a minimum of 2 hours (concentration 820 mg/L). The remaining units were gassed with ethylene oxide for an average of 4 hours (concentration 820 mg/L). The gassing was repeated three times. After sterilization, the spore strips were removed under aseptic conditions and poured into liquid Soybean Casein Digest broth medium and incubated for 7 days at 30 ± 2 °C. Sterility was demonstrated if no microbial growth was observed.

Results
After the ethylene oxide gas sterilization all bioindicators (Bacillus subtilis spore strips) were sterile.

Number and distribution of bioindicators

Cycle	No.	Number of bioindicators used
half-cycle	11040411	120
half-cycle	25040411	130
half-cycle	29040411	260
full-cycle	11050411	20
half-cycle (minimum load)	19050412	34

Results of bioindicator tests

Type	Lot	Gassing time	Result of bioindicator test
16534	040019	4 hours	all bioindicators sterile

Conclusion
The results demonstrate that even a half-cycle of the ethylene oxide sterilization sterilizes all bioindicators tested.

The standard procedure of gassing the Minisart® syringe filters for 4 hours with a concentration of 820 mg/L ethylene oxide gas always produces sterile products.

5.3.3 Sterility Test with Soybean-Casein Digest Broth (TSB) and Thioglycollate Broth

Method
To ensure that the content of the Minisart® syringe filter packaging is sterile after the EO sterilization, an applicable sterility test in accordance with USP and EP was carried out.

After sterilization of numerous Minisart® units in their original packaging, the individually blister packaging was opened under sterile conditions and each Minisart® syringe filter was placed into 100 mL of sterile nutrient broth. 10 units were placed into TSB broth (tryptone soya broth, Oxoid code no. B00509M) and incubated together with a negative- and a positive control for 14 days at 22.5 ± 2.5 °C. 10 units were placed into thioglycollate medium (Oxoid code no. B00510M) and incubated together with a negative- and a positive control for 14 days at 32.5 ± 2.5 °C.

Results

Sterility Test|1. Half-Cycle

Type	Lot no.	No. of systems tested	Sterility test with TSB broth; no. of containers	Sterility test with thioglycollate broth; no. of containers
16534	040019	20	10 sterile 0 failed	10 sterile 0 failed

Sterility Test|2. Half-Cycle

Type	Lot no.	No. of systems tested	Sterility test with TSB broth; no. of containers	Sterility test with thioglycollate broth; no. of containers
16534	040019	20	10 sterile 0 failed	10 sterile 0 failed

Sterility Test|3. Half-Cycle

Type	Lot no.	No. of systems tested	Sterility test with TSB broth; no. of containers	Sterility test with thioglycollate broth; no. of containers
16534	040019	20	10 sterile 0 failed	10 sterile 0 failed

Conclusion
Ethylene oxide sterilization with a concentration of 820 mg/L ensures that all surfaces of the Minisart® syringe filters in contact with the sample are sterile.

6. Physical Tests

6.1 Burst Pressure

Background
The use of syringes are capable of building up high pressure within a system. A high burst pressure assures that the system maintains its integrity and does not leak during usage or sample may bypass the membrane.

Method
Positive pressure was applied from the top of the Minisart® syringe filter and gradually increased (about 1 bar|14.5 psi per second).

The outlet connector of the Minisart® syringe filter is closed, either by melting or it is plugged with a closure. The pressure was increased to the burst pressure of the Minisart® syringe filter or to a maximum of 9 bar|130.5 psi. The burst pressure is indicated by a maximum pointer.

Results

Minisart® NML [bar]

Type Lot	16534 060031	16534 051157	16534 050980	17597 050989	17597 050947	17597 050847
1	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
2	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
3	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
4	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
5	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
6	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
7	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
8	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
9	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
10	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0

Minisart® high flow [bar]

Type Lot	16532 060014	16532 51075	16532 050387	16541 051053	16541 051027	16541 050684
1	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
2	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
3	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
4	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
5	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
6	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
7	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
8	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
9	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0
10	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0	> 9.0

Conclusion
The minimum burst pressure is 6 bar|130.5 psi. The recommended maximum operation pressure is set at 4.5 bar|65.3 psi to allow for a safety margin.

6.2 Pressure Hold Test

Background
This test assures that the Minisart® syringe filters maintain their integrity and do not leak during usage when the system is stressed with constant pressure.

Method
A sufficient amount of Minisart® syringe filters from numerous production lots were sampled. Positive pressure was applied from the top of the Minisart® syringe filter containing a water-wetted membrane filter.

The pressure is set to a constant pressure to 2.0 bar|29.0 psi for Minisart® NML and to 2.5 bar|36.3 psi for Minisart® high flow. During the 1 minute test period, no air pressure may pass the membrane, which would be indicated by air bubbles at the outlet of the Minisart® syringe filter.

Results Minisart® NML

	16534 Result at 2.0 bar|29.0 psi			17597 Result at 2.0 bar|29.0 psi		
Lot	**060031**	**051157**	**050980**	**050989**	**050947**	**050847**
1	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
2	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
3	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
4	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
5	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
6	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
7	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
8	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
9	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
10	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed

Results Minisart® high flow

	16532 Result at 2.5 bar|36.3 psi			16541 Result at 2.5 bar|36.3 psi		
Lot	**060014**	**51075**	**050387**	**051053**	**051027**	**050684**
1	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
2	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
3	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
4	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
5	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
6	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
7	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
8	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
9	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed
10	no air passed	no air passed	no air passed	no air passed	no air passed	no air passed

Conclusion
All Minisart® syringe filters hold the positive pressure on the upstream side and no air passed the membrane.

6.3 Flow Rate Performance Test

Method
A sufficient amount of Minisart® syringe filters from numerous production lots were sampled. Each of the units were connected to a pressure vessel containing water. With a constant pressure of 1 bar|14.5 psi water is filtered through the Minisart® syringe filter.

The values are determined in filtered volume of water within 1 min. 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.

Results

Minisart® NML 16534 and 17597 [mL/min · Minisart®]

Type Lot	16534 060031	16534 051157	16534 050980	17597 050989	17597 050947	17597 050847
1	88.9	74.3	72.1	70.0	80.3	83.1
2	85.8	76.1	76.5	75.5	78.6	80.3
3	86.0	72.3	76.4	81.0	82.1	81.5
4	80.8	70.2	77.8	65.6	84.2	85.8
5	83.9	72.6	74.6	78.2	78.4	81.0
6	82.4	74.2	78.8	82.1	83.2	82.4
7	83.6	72.6	77.8	65.8	76.0	85.9
8	83.3	73.4	75.4	69.6	82.4	80.6
9	81.8	75.1	76.6	69.3	76.6	84.4
10	86.2	74.3	76.3	67.8	82.3	85.1
∅	**84.3**	**73.51**	**76.2**	**72.5**	**80.4**	**83.0**

Conclusion
The values of the flow rates for Minisart® syringe filters with surfactant-free Cellulose Acetate membranes vary between 65.6 mL/min and 88.9 mL/min.

The minimum flow rate per Minisart® with SFCA membrane is set to 60 mL/min.

Results

Minisart® high flow 16532 and 16541 [mL/min · Minisart®]

Type Lot	16532 060014	16532 51075	16532 050387	16541 051053	16541 051027	16541 050684
1	226.8	168.8	194.1	228.7	229.8	246.8
2	219.7	184.7	185.9	212.5	231.4	220.9
3	217.4	184.9	191.2	210.9	226.2	208.1
4	221.5	180.7	194.9	218.3	229.1	214.2
5	224.7	179.6	185.7	213.2	228.2	227.8
6	214.2	183.1	201.5	194.2	238.6	188.8
7	213.5	183.5	187.5	210.2	227.0	216.7
8	210.4	184.7	187.5	211.1	229.0	196.1
9	223.8	179.2	198.8	199.7	229.4	214.4
10	221.8	194.2	200.0	225.9	224.8	196.8
Ø	**219.4**	**182.3**	**192.7**	**212.5**	**229.4**	**213.1**

Conclusion

The values of the flow rates for Minisart® syringe filters with Polyethersulfone membranes vary between 168.8 mL/min and 246.8 mL/min. The minimum flow rate per Minisart® with PES membrane is set to 140 mL/min.

7. Chemical Compatibility – Minisart® Syringe Filters

Solvents	
Acetone	– –
Acetonitrile	– –
Gasoline	■
Benzene	– –
Benzyl alcohol	?
n-Butyl acetate	– –
n-Butanol	▭
Cellosolve	– –
Chloroform	– –
Cyclohexane	– –
Cyclohexanone	– –
Diethylacetamide	– –
Diethyl ether	?
Dimethyl formamide	– –
Dimethylsulfoxide	– –
Dioxane	– –
Ethanol, 98 %	– –
Ethyl acetate	▭
Ethylene glycol	?
Formamide	?
Glycerin	■
n-Heptane	■
n-Hexane	■
Isobutanol	▭
Isopropanol	▭
Isopropyl acetate	▭
Methanol, 98 %	– –
Methyl acetate	– –
Methylene chloride	– –
Methyl ethyl ketone	– –
Methyl isobutyl ketone	?
Monochlorobenzene	?
Nitrobenzene	?
n-Pentane	■
Perchloroethylene	▭
Pyridine	– –
Carbon tetrachloride	▭
Tetrahydrofuran	– –
Toluene	– –
Trichloroethane	▭
Trichloroethylene	?
Xylene	– –

Acids	
Acetic acid, 25 %	▭
Acetic acid, 96 %	– –
Hydrofluoric acid, 25 %	▭
Hydrofluoric acid, 50 %	▭
Perchloric acid, 25 %	?
Phosphoric acid, 25 %	■
Phosphoric acid, 85 %	?
Nitric acid, 25 %	– –
Nitric acid, 65 %	– –
Hydrochloric acid, 25 %	– –
Hydrochloric acid, 37 %	– –
Sulfuric acid, 25 %	– –
Sulfuric acid, 98 %	– –
Trichloroacetic acid, 25 %	■

Bases	
Ammonium, 1N	■
Ammonium hydroxide, 25 %	▭
Potassium hydroxide, 32 %	– –
Sodium hydroxide, 32 %	– –
Sodium, 1N	▭

Aqueous solutions	
Formalin, 30%	– –
Sodium hypochlorite, 5 %	■
Hydrogen peroxide, 35 %	■

Legend:
■ = Compatible
▭ = Limited compatibility
– – = Not compatible
? = not tested

Contact time: 24 hours at 20 °C

Chemical compatibilities can be influenced by various factors. Therefore, we recommend that you confirm compatibility with the liquid you wish to filter by performing a trial filtration run before you begin with actual filtration.

8. Analytical Tests

8.1 Endotoxin Test

Background
The goal of these tests is to determine that the amount of endotoxins released in the effluent of 10 Minisart® syringe filters is acc. to the USP Bacterial Endotoxin Test Chapter <85> less than 0.06 EU/mL.

Method
Minisart® syringe filters from a variety of production lots were tested under the following conditions for endotoxins utilizing a kinetic turbidimetric method based on the LAL test. 20 mL of endotoxin-free water is filtered through ten Minisart® syringe 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 determine the actual concentration of endotoxins.

Results Minisart® NML [EU/mL]

Type Lot	16534 060031	16534 051157	16534 050980	17597 050989	17597 050947	17597 050847
1	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
2	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
3	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
4	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
5	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
6	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
7	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
8	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
9	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
10	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025

Results Minisart® high flow [EU/mL]

Type Lot	16532 060014	16532 51075	16532 050387	16541 051053	16541 051027	16541 050684
1	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
2	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
3	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
4	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
5	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
6	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
7	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
8	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
9	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
10	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025

Conclusion
All Minisart® syringe filters tested, under the conditions of the elution test described above, gave results below 0.025 EU/mL bacterial endotoxin.

8.2 Biocompatibility Test

Background

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

Method

Minisart® syringe filters 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 Minisart® syringe filters units. All material used in the construction of the Minisart® syringe filter units meet or exceed the requirements of the USP Class VI–121 °C Plastics Tests.

BIOSERVICE

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Minisart type, representing syringe filter with MBS housing and CA membrane**
Order No.: 16534 - K
Lot No.: 16534 050689

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

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

CYTOTOXICITY
HAEMOLYSIS TEST
USP BIOLOGICAL TESTS (CLASSIFICATION VI/121 °C)

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

BSL BIOSERVICE Scientific Laboratories GmbH
Behringstraße 6
D-82152 Planegg

Dr. Daniela Brummer
Biological Safety Testing
Date: October 06, 2005

BSL BIOSERVICE Scientific Laboratories GmbH GLP ISO 17025

BIOSERVICE

BIOCOMPATIBILITY

CERTIFICATE

Testmaterial: **Minisart High-Flow type, representing syringe filter with MBS housing and PES membrane**
Order No.: 16532 - GUK
Lot No.: 16532 050726

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

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

CYTOTOXICITY
HAEMOLYSIS TEST
USP BIOLOGICAL TESTS (CLASSIFICATION VI/121 °C)

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

BSL BIOSERVICE Scientific Laboratories GmbH
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Dr. Daniela Brummer
Biological Safety Testing
Date: October 06, 2005

BSL BIOSERVICE Scientific Laboratories GmbH GLP ISO 17025

8.3 Extractables Analysis

Background

These tests are to determine that all components used in the manufacture of Minisart® syringe filters are biosafe. The Extractable Analysis informs specifically about the release of heavy metal- and ammonium-ions.

Method

Minisart® syringe filters were supplied to an independent testing facility for extraction and evaluation. 120 g Ultrapure water (arium®) was filtered through 10 Minisarts® and in addition un-sealed membrane material was shaked in Ultrapure water. The water extracts were analysed.

Conclusion

It can be summarized, that only few compounds are eluated from the Minisart® syringe filter. The Minisart® syringe filters are usually rinsed prior utilization (for e. g. integrity testing, etc.) and during this flush procedure the extractables are reduced to insignificant amounts.

Results

Minisarts® NML
(DIN EN ISO 11732; DIN EN ISO 17294-2|DIN EN ISO 11885)

		Minisart® 16534 Lot 11134103	Minisart® 16534 Lot 11135103	Blind Value	Detection Limit
NH_4^+	µg/L	20	20	< 20	20
Pb	µg/L	< 5	< 5	< 5	5
Cd	µg/L	< 0.5	< 0.5	< 0.5	0.5
Ca	µg/L	< 50	< 50	< 50	50
Cr	µg/L	< 5	< 5	< 5	5
Fe	µg/L	< 10	< 10	< 10	10
K	µg/L	< 50	< 50	< 50	50
Cu	µg/L	< 5	< 5	< 5	5
Mg	µg/L	< 50	< 50	< 50	50
Na	µg/L	< 50	< 50	< 50	50
Ni	µg/L	< 5	< 5	< 5	5
P	µg/L	< 50	< 50	< 50	50
Hg	µg/L	< 0.1	< 0.1	< 0.1	0.1
Zn	µg/L	22	< 10	< 10	10
Sn	µg/L	< 10	< 10	< 10	10

Minisarts® high flow NML

		Minisart® 16532 Lot 90554103	Minisart® 16532 Lot 90452103	Blind Value	Detection Limit
NH_4^+	µg/L	70	20	< 20	20
Pb	µg/L	< 5	< 5	< 5	5
Cd	µg/L	0.7	< 0.5	< 0.5	0.5
Ca	µg/L	< 50	< 50	< 50	50
Cr	µg/L	< 5	< 5	< 5	5
Fe	µg/L	< 10	< 10	< 10	10
K	µg/L	< 50	< 50	< 50	50
Cu	µg/L	< 5	< 5	< 5	5
Mg	µg/L	< 50	< 50	< 50	50
Na	µg/L	< 50	< 50	< 50	50
Ni	µg/L	< 5	< 5	< 5	5
P	µg/L	< 50	< 50	< 50	50
Hg	µg/L	< 0.1	< 0.1	< 0.1	0.1
Zn	µg/L	210	30	< 10	10
Sn	µg/L	< 10	< 10	< 10	10

9. Visual Inspections

Background
Minisart® syringe filters are manufactured under clean room conditions. The plastic parts are treated with care, their dimensions should be within the specifications and they should have no structural damages, which might affect the manufacture or the usage.

Method
The Minisart® syringe filters components were inspected visually acc. to DIN EN 1707 for:

- measuring the dimensions of the in- and outlet connectors by using a DIN steel reference cone
- a leakage rate test
- a tensile stress test

In addition the parts were inspected visually for:

- injection molded particles > 0.1 mm
- loose particles or fibers > 0.1 mm
- membrane sealing
- molding faults
- residues of the molding process
- air inclusions
- discolor
- cracks or other damages

Results
Minisart® NML

Type Lot	16534 060031	16534 051157	16534 050980	17597 050989	17597 050947	17597 050847
1	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
2	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
3	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
4	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
5	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
6	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
7	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
8	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
9	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
10	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.

Minisart® high flow

Type Lot	16532 060014	16532 51075	16532 050387	16541 051053	16541 051027	16541 050684
1	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
2	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
3	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
4	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
5	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
6	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
7	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
8	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
9	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.
10	o.k.	o.k.	o.k.	o.k.	o.k.	o.k.

Conclusion
When Minisart® syringe filters are manufactured under defined parameters the percentage of rejected devices is less than 0.1%.

10. Test Parameters for Quality Assurance of Minisart® Syringe Filters

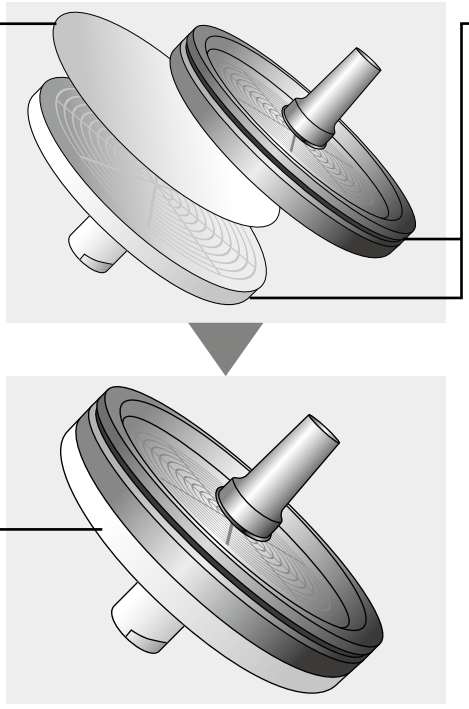
10.1 Test scheme for the Quality Assurance of Minisart® Syringe Filters

Membrane Filter

- Bacteria Challenge Test with Brevundimonas diminuta 10^7 microorganisms per cm^2 filtration area
- Bubble point
- Burst pressure
- Flow rate for water
- Filtration rate for water
- Thickness
- Extractables for water (only 16534 and 17597)
- UV absorption of extractables at 190-400 nm (only 16534 and 17597)
  Wetting time for water (only 16534 and 17597)

Final Product

- Bacteria Challenge Test
- Bubble Point Test
- Integrity Leakage Test
- Sterility Test
- Burst Pressure
- Pressure Hold Test
- Flow Rate Performance
- Endotoxin Test
- Visual Inspections



Plastic Housing

- **Visual inspection acc. to DIN EN 1707 of:**
  - dimensions
  - leakage rate test
  - tensile stress test
- **Additional visual inspection:**
  - injection molded particles
  - loose particles or fibers
  - membrane sealing
  - molding faults and residues
  - air inclusions
  - discolor
  - cracks or other damages

10.2 Final Product Testing

Test Type	Reference and Test Method Equipment	Method Description in this Validation Guide	Measuring Unit
Bacteria challenge test	acc. to DIN 58355, suspension of Brev. diminuta	Chapter 4.	number of filtrates sterile|non-sterile
Bubble point test	acc. to DIN 58355, compressed air, Sartocheck® Integrity Tester, pressure gauge	Chapter 4.	bar
Sterility test	TSB and Thioglycollate broth	Chapter 5.2.1, 5.3.2 and 5.3.3	number of samples sterile|non-sterile
Burst pressure	compressed air, maximum pointer (pressure gauge)	Chapter 6.1	bar
Pressure hold test	compressed air, pressure gauge	Chapter 6.2	bar
Flow Rate Performance	acc. to DIN 58355, water, pressure gauge, stop watch, balance	Chapter 6.3	mL/(cm² × min² × bar)
Endotoxin Test	acc. to USP by the kinetic turbidimetric method	Chapter 8.1	EU/mL
Visual Inspections	acc. to DIN EN 1707, steel reference cone, optical devices	Chapter 9.	percentage of rejected devices

10.3 In-Process Control

Test Type	Reference and Test Method Equipment	Method Description in this Validation Guide	Measuring Unit
Membrane Filter			
Bacteria challenge test	acc. to DIN 58355, suspension of Brev. diminuta	acc. to Chapter 4., but adjusted to disc filters	number of filtrates sterile|non-sterile
Bubble point test	acc. to DIN 58355, compressed air, Sartocheck® Integrity Tester, pressure gauge	acc. to Chapter 4., but adjusted to disc filters	bar
Burst pressure	compressed air, maximum pointer (pressure gauge)	acc. to Chapter 6.1, but adjusted to disc filters	bar
Flow Rate Performance	acc. to DIN 58355, water, pressure gauge, stop watch, balance	Chapter 6.3	mL/(cm² × min² × bar)
Filtration rate for water	acc. to DIN 58355, water, pressure gauge, stop watch, balance	the value is calculated from the result of the test described in Chapter 6.3	s/(100 mL × 12.5 cm² × 0.93 bar)
Thickness	acc. to DIN 53105	Chapter 10.3.1.1	µm
Extractables for water	boiled water, moisture analyzer (balance)	Chapter 10.3.1.2	%
UV absorption	methanol|water, UV spectrometer	Chapter 10.3.1.3	ppm
Wetting time for water	water, stop watch	Chapter 10.3.1.4	sec
Plastic parts of the housing			
Visual Inspections	acc. to DIN EN 1707, steel reference cone, optical devices	Chapter 9.	percentage of rejected devices

10.3.1 Additional Descriptions of In-Process Control Tests

10.3.1.1 Thickness

The thickness of membranes are determined by using a special thickness gauge The thickness must be within the specifications.

10.3.1.2 Extractables for Water

A defined number of membranes is extracted in a defined volume of boiled water. The difference in weight before and after the extraction is measured.
The loss of weight in percentage is calculated.

10.3.1.3 UV Absorption of Extractables

A defined volume of a methanol | water mixture is filtered through the tested membrane filter. The filtrate of each membrane is analyzed by an UV spectrometer at 190–400 nm. The resulted spectrum is compared with a reference spectrum.

10.3.1.4 Wetting Time for Water

A membrane is placed on the surface of deionized water. The time is measured at this point until the membrane is wetted with water completely by a stop watch.

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