
# Sartocube® and Sartocon® Slice Self Contained Assemblies and Devices

Validation Guide

SARTORIUS

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# 1. Introduction

This validation information has been compiled to assist Sartocon® Slice and Sartocube® self contained filter as stand alone and assembly users in the planning, implementation and documentation of their own validation procedures.

Pharmaceutical products must conform to well-defined quality standards. The production of infusion and injectable solutions, or those which come into contact with open wounds, are regulated by such standards. Quality results can only be achieved by adequately safe guarding an entire process against contamination.

Membrane technology is critically reviewed in various international pharmacopeias, with a concentration on sterilizinggrade filters. However, most of the points are also applicable to tangential flow filtration (TFF). Systems used for the preparation of pharma ceuticals should not add substances to a pharmaceutical product.

TFF technology is commonly used during downstream pro cessing of proteins. Various applications such as product clarification and concentration are best achieved by the use of TFF systems. For many processes, crossflow technology is often the last processing step before final formulation of heat-labile products. Enzymes, antibiotics, antibodies and proteins are usually sensitive to the stress of some processing techniques. Therefore TFF systems have a wide application spectrum.

Downstream processes should be validated in terms of reproducibility and safety. This is especially true for products of mammalian cell fermentation where virus clearance is necessary.

Validation is an indispensable process step to ensure the safety of pharmaceuticals. It is an essential part of long-standing cGMP regulations.

Guidelines for validation are found in both the FDA Title 21 Code of Federal Regulations 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 Fédération Internationale Pharmaceutique (F.I.P.), the European counterpart of the FDA. All the above-mentioned bodies focus on sterile processing. However, many principles are also applicable to TFF filtration.

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 pharma ceutical products with the goal that the finished products can be manufactured reliably and reproducibly and in the desired quality in keeping with established production and quality control procedures.”

# 2. Operating Instructions

## 2.1 Read This Important Information First!

- The Sartocube® self contained filter assembly is designed to be used as part of the Sartoflow® Expert SU and Flexact® UD system. The Sartocon® Slice self contained bag loop assembly is designed to be used as part of the Sartoflow® Expert SU and Sartoflow® Alpha Plus SU system.
- A hydraulic holder is required to compress the self contained filtration device before usage.
- The maximum inlet pressure must not be exceeded (see "Technical Specifications" on page 25). Higher pressures will damage the self contained unit.
- Do not allow the self contained unit to dry out to avoid loss of filtration properties.
- Make sure that the self contained unit you plan to use, has the required chemical compatibility before beginning a filtration run in order to avoid damaging the membranes. If you are not sure about the compatibility of the filtration device with a certain chemical, please consult our application specialist.

- Observe the following when setting up the system and during operation:
- Avoid abrupt changes in pressures (approx. > 1 bar/sec.), like those that can occur when the pump is switched on or the valve settings are changed.
- As far as possible, operate hydraulic clamping elements in such a way that the effective clamping force is kept constant during operation.
- Ensure that crystallization does not occur during operation or storage due to temperature or concentration changes.
- Ensure that the tubing lines used are able to withstand the operating pressure.
- Do not forget the upper stay bars | connecting rods when using hydraulic holding devices.

**The back pressure on the filtrate side is defined as:**
Back pressure on the filtrate side ($P_{back}$) occurs when the permeate pressure is higher than the retentate pressure.

$p_{per} > p_{ret}$

$p_{back} = p_{per} - p_{ret}$

This should especially be taken into consideration if hydrostatic conditions (e.g., tank height and pipe diameter) are influencing the back pressure.

Ensure that these pressure values are not exceeded.

Note that there is a difference between the transmembrane pressure (TMP).

$TMP = ((P_{feed} + P_{ret}) : 2) - P_{per}$

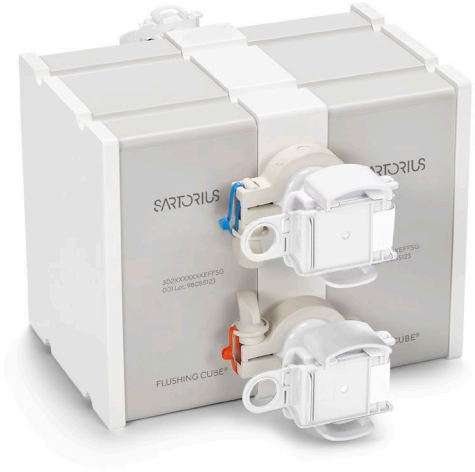
and the differential pressure:

$P_{diff} = P_{feed} - P_{per}$

**The back pressure on the permeate side must not exceed 0.5 bar for Hydrosart®.**

# 2.2 General Information

- The Sartocon® Slice and Sartocube® SCU with AseptiQuik® connectors are designed to be used with the Sartoflow® Expert SU system. The filter assembly is designed to be used with the Flexact® UD system. The bag loop assembly is designed to be used with the Sartoflow® Alpha Plus SU system. All other filter assemblies can be used with individual systems. The self contained filtration devices themselves are not available as standalone units.
- A hydraulic holding device is required to compress the self contained TFF filter before usage.
- If these safety instructions are not followed, damage to the self contained or to other equipment and material can be caused.
- Every time before using the equipment, check that all components are in perfect working order.
- The temperature of the retentate must not exceed that given for continuous operation, which is listed in the “Technical Specifications” on page 25. During TFF filtration, the temperature will increase over time because the kinetic energy of the pump is transferred to the liquid undergoing filtration. If the temperature increases beyond that indicated in the “Technical Specifications” on page 25, the pressure resistance of the TFF system will decrease.
- If you would like to use a holding device from other manufacturers, please consult our application specialist.
- Monitor TFF conditions during filtration. When filtering under static conditions (dead-end filtration), the filtration performance of the cassettes is rapidly reduced (see also “Filtration” on page 13).
- Use only original accessories from Sartorius. If other components are used, reliable operation and performance of the devices cannot be guaranteed.

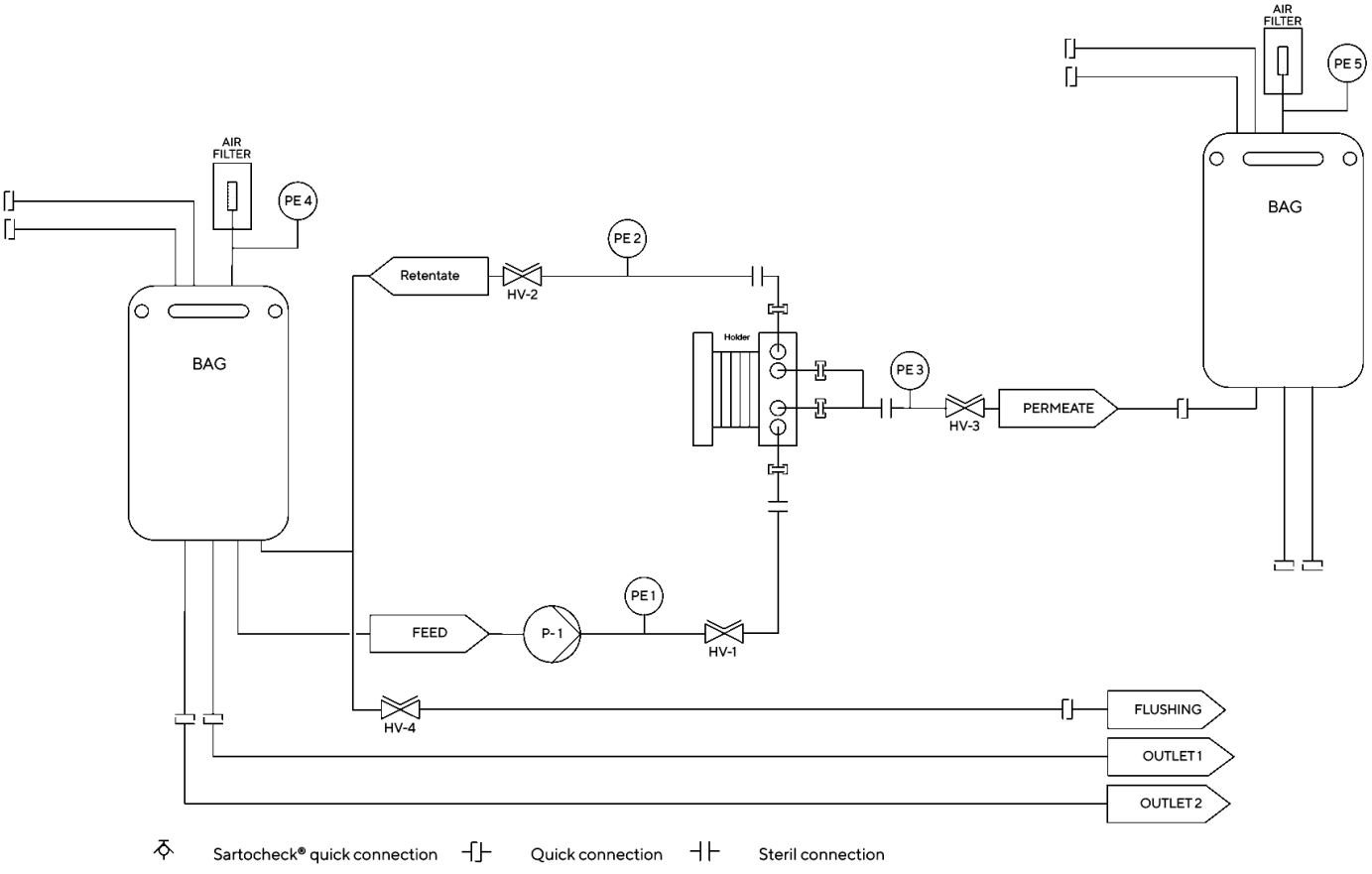



Sartocube® self contained


Sartocon® Slice self contained

# 2.3 Components of a Basic TFF System

- Diagram



# 2.4 Installing the Self Contained in a Holding Device

To install the self contained in a Sartorius holding device, proceed as follows:

1. Remove the self contained from its packaging.
2. Check and record self contained labeling.
3. When installing the self contained into the holder, ensure that the direction of the filtration device is correct.
4. Clamp the self contained device according to the specification of the holder.
5. When installing the filtration device, ensure that the direction the slots are facing (for the upper and lower connecting rods) is correct.
6. Do not forget the upper stay bars | connecting rods when using a hydraulic holder.

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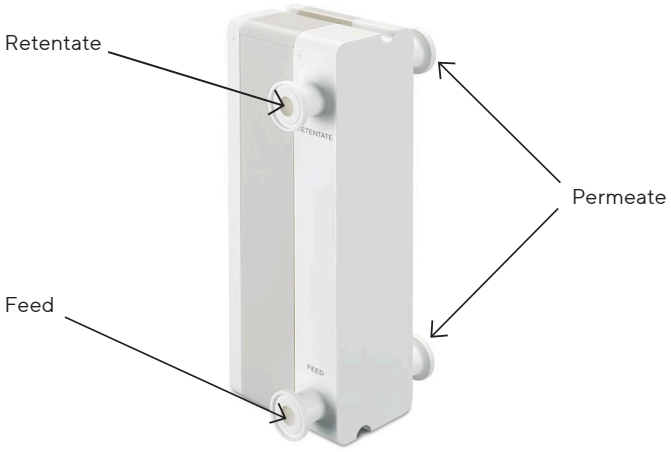
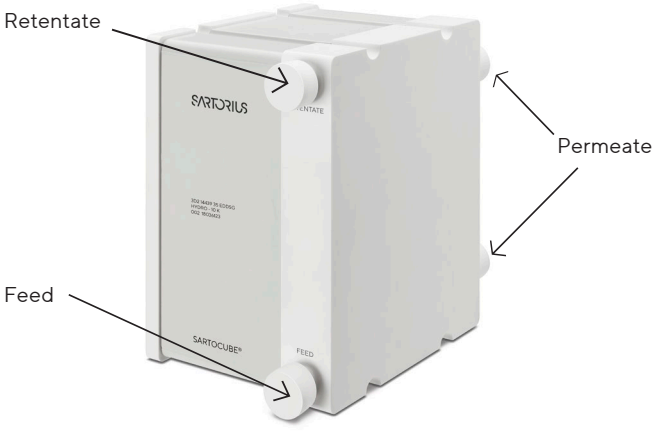
Do not increase the compression pressure beyond the pressure specified.




Sartocon® Slice self contained




Sartocube® self contained

# 2.5 Clamping Forces

## 2.5.1 Sartocon® Slice Self Contained

| Membrane | Sartocon® Slice Filter Holder | | Sartocon® Slice Filter Holder With Trapezoidal Thread, PEEK Washers and Bronze Clamping Nuts |
|---|---|---|---|
| | Required Clamping Force | Required Torque | Required Torque |
| Hydrosart® | 10 – 14 kN | 20 Nm | 17 Nm |
| PES | 14 – 17 kN | 25 Nm | 17 Nm |

### Sartocon® Slice Self Contained Holder With Hydraulic Piston (12.5 cm²)

| Membrane | Required Clamping Force, Operating Conditions | Hydraulic Pressure, Operating Conditions |
|---|---|---|
| Hydrosart® | 10 – 14 kN | 80 – 115 bar (1,200 – 1,650 psi) |
| PES | 14 – 17 kN | 115 – 140 bar (1,650 – 2,000 psi) |

## 2.5.2 Sartocube® Self Contained

### Sartocube® Self Contained Holder, Hydraulic

| Membrane | Required Compression Operating Parameters | Hydraulic Pressure Operating Parameters for Hydraulic Holder With 12.5 cm² Piston |
|---|---|---|
| Hydrosart® | 18 – 22 kN | 150 – 170 bar (2,175 – 2,465 psi) |
| PES | 22 – 25 kN | 170 – 200 bar (2,465 – 2,900 psi) |

### Sartocube® Self Contained Holder, Manual With Ball Bearing

| Membrane | Required Compression Operating Parameters | Torque Applied With a Torque Wrench Operating Parameters |
|---|---|---|
| Hydrosart® | 18 – 22 kN | 60 Nm |
| PES | 22 – 25 kN | 80 Nm |

*After every tenth time of use, the peek washers should be replaced. The bronze nut or the trapezoidal thread should be replaced as soon as abrasion is visible. It is essential that the bronze nut and the trapezoidal thread are kept clean.

## Component overview

| Membrane Material | Molecular Weight Cut-Off | Order Number | Effective Filtration Area [$m^2$] | Frame | Mesh | Mounting Plates | Sealing Material |
|---|---|---|---|---|---|---|---|
| Hydrosart® | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFM-AQ-144... | 0.14, 0.28, 0.42, 1.4, 3.5, 7, 14 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 10 kDa, 30 kDa, 100 kDa, 300 kDa... | SFM-AQ-146... | 0.14, 0.28, 0.42, 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFA-SUM144... | 0.14, 0.28, 0.42 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFA-SUM146... | 0.14, 0.28, 0.42 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 10 kDa, 30 kDa | SFA-SU-146... | 0.1, 0.2, 0.3 | PVDF | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 0.1 µm | SFA-SU-15458... | 0.1, 0.2, 0.3 | PVDF | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 10 kDa, 30 kDa | 3D5146... | 0.1, 0.2, 0.3 | PVDF | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 5 kDa | 4XC48 | 1.2 | PVDF | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 10 kDa | 4XC27; 4XC31 | 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 30 kDa | 4XC28; 4XC32 | 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 100 kDa | 4XC29; 4XC33 | 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 10 kDa | 4XC40; 4XC41 | 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 30 kDa | 4XC34; 4XC37 | 1.4; 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 100 kDa | 4XC35; 4XC38 | 1.4; 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 300 kDa | 4XC36; 4XC39 | 1.4; 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |
| PES | 100 kDa | SFB-LY-146... | 1.4 | PVDF | PP | Stabilized Polypropylene | Silicone Grey |
| Hydrosart® | 30 kDa | SFM-OP-144... | 0.14, 0.28, 0.42, 0.7, 1.4, 3.5 | PP | PP | Stabilized Polypropylene | Silicone Grey |

## List of materials

| Component | Material |
|---|---|
| Membrane | Hydrosart® or PES |
| Frame | PP or PVDF |
| Mesh | PP |
| Sealing material | Silicone Grey |
| Mounting plates | Stabilized Polypropylene |

## 2.6 Flushing

All self contained filter devices have been pre-rinsed at the factory with purified water to reach a TOC of less than 500 ppb (according to USP <887>). Thereafter sterilization is achieved by gamma irradiation. The self contained assemblies contain no preservatives.

In order to fulfil the USP and EP requirements for WFI it is required to perform a pre flush. The following procedure has proven to be effective.

| Loop Assembly Type | Ratio of Retentate to Permeate | Recommended Flush Volume [L] |
|---|---|---|
| All slice self contained assemblies | Approx. 1 : 1 | 10 |
| Sartocube® assemblies 0.7 to 3.5 m² | Approx. 1 : 1 | 50 |
| Sartocube® assemblies 7 m² | Approx. 1 : 1 | 100 |
| Sartocube® assemblies 14 m² | Approx. 1 : 1 | 200 |

Set inlet pressure to 1 bar. After approx. ⅓ of the rinsing solution has been used, stop pump and let soak for 15 minutes, then start pump again. The permeate and the retentate must be disposed of.

## 2.7 Integrity Test

Each Sartocon® Slice and Sartocube® self contained has been 100 % tested in-house for integrity.

The air diffusion test is performed for each completed filter cassette. The results have passed our internal specification and can be traced for each membrane lot as well as for each cassette device.

### Diffusion release criteria

| Configuration | Filtration Area [m²] | Maximum Diffusion at 1 bar Test Pressure [mL/min] |
|---|---|---|
| Hydrosart® Sartocon® Slice self contained | 0.1 – 0.42 | ≤ 5 |
| PES Sartocon® Slice self contained | 0.1 – 0.42 | ≤ 15 |
| Hydrosart® and PES Sartocube® self contained | 0.7 – 3.5 | ≤ 50 |
| Hydrosart® and PES Sartocube® self contained | 7 | ≤ 75 |
| Hydrosart® and PES Sartocube® self contained | 14 | ≤ 100 |

## 2.8 Filtration

A critical moment for TFF filtration is at start-up. The medium to be filtered reaches a clean membrane surface. It has not yet formed a gel layer (secondary layer), and the speed at which the retentate flow passes the membrane is still not constant or sufficient for TFF conditions.

To start the filtration process, always proceed as follows:

- Make sure that the permeate area is filled with one of the liquids listed below:
  - The final rinse water
  - Suitable buffer
  - Isotonic saline solution

To prime the system, the flushing procedure given in "**Flushing**" has proven to be effective.

- At the beginning of the filtration process, close the permeate outlets by about 90 %.
- Introduce the process fluid into the system. Generate the desired TFF rate.
- Open the permeate outlet valve until the desired TMP is reached.
- Make sure that the desired TFF rate for the process is maintained.
  - Ensure that the TFF rate is sufficient.
  - If the transmembrane pressure (TMP) is low, ensure that a high TFF rate is set.
- For information about the reference values for your solution, ask our applications specialists.

**The pressure of the feed inlet ($P_{feed}$) must not exceed 3 bar. The filtration device may be damaged if the pressure is higher.**

**SFM-AQ-144... up to 1.4m² are qualified to withstand a pressure of 4 bar.**

**The back pressure on the permeate side must not exceed 0.5 bar for Hydrosart®.**

# 3. Trouble Shooting

## 3.1 No Permeate

- Are the permeate valves open?
- Check that the pump is primed and operating.
- Are feed and retentate valves open?
- Check the inlet pressure.
- Check for membrane blockage.
  A blocked membrane will cause an increase in retentate flux and a decrease of permeate flux.

## 3.2 Product Loss to the Permeate or Cloudy Permeate

- Inspect the compression of the self contained holder.
  It is important that the applied compression force is within the specification stated in the instruction manual for the holding device. Overturning torque will damage the self contained.

- Before you start a filtration run, check the chemical compatibility of the self contained. The filtration device may be damaged by an incompatible chemical. If you are not sure about the compatibility of a specific chemical with the filter cassette, please contact our application specialist.

## 3.3 Low or Absent Retentate Flux

- Make sure the rotation direction of the pump is set correctly.
- Make sure all feed and retentate valves are open.
- Check that the pump is primed and operating.
- Check the inlet pressure.
- Monitor compression. It is important that the applied compression is within the specification stated in the instruction manual for the holding device. Overturning torque will reduce the retentate channel flux.

# 4. Sartocon® Slice and Sartocube® Self Contained

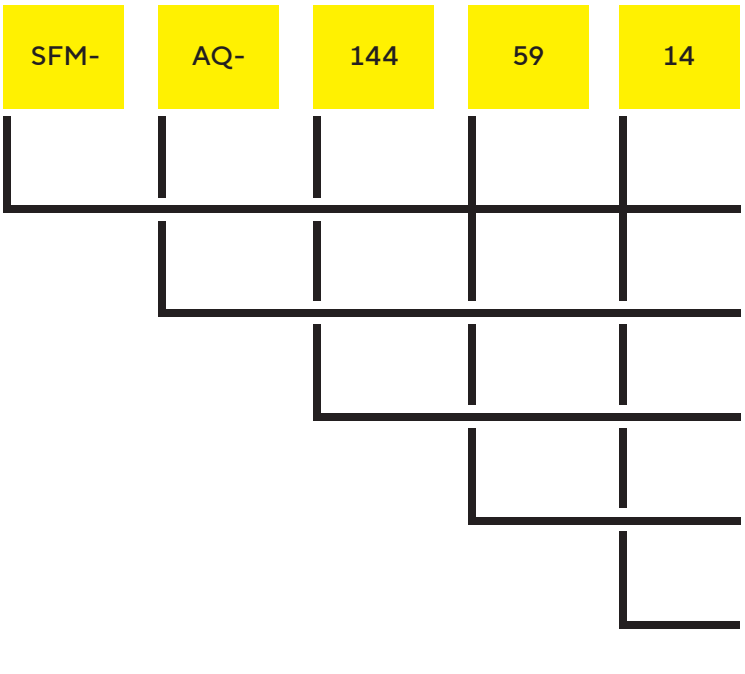
## 4.1 Product Pictures

## 4.2 Product Overview

| Order No. Screen | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) [kDa] | Effective Filtration Area [m²] | Connector |
|---|---|---|---|---|---|
| SFM-AQ-1443901 | ECO | Hydrosart® | 10 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1443921 | ECO | Hydrosart® | 10 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1443931 | ECO | Hydrosart® | 10 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1443914 | ECO | Hydrosart® | 10 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1443935 | ECO | Hydrosart® | 10 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1443970 | ECO | Hydrosart® | 10 | 7 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-14439A4 | ECO | Hydrosart® | 10 | 14 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-1445901 | ECO | Hydrosart® | 30 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1445921 | ECO | Hydrosart® | 30 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1445931 | ECO | Hydrosart® | 30 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1445914 | ECO | Hydrosart® | 30 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |

| Order No. Screen | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) [kDa] | Effective Filtration Area [$m^2$] | Connector |
|---|---|---|---|---|---|
| SFM-AQ-1445935 | ECO | Hydrosart® | 30 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1445970 | ECO | Hydrosart® | 30 | 7 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-14459A4 | ECO | Hydrosart® | 30 | 14 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-1446801 | ECO | Hydrosart® | 100 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1446821 | ECO | Hydrosart® | 100 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1446831 | ECO | Hydrosart® | 100 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1446814 | ECO | Hydrosart® | 100 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1446835 | ECO | Hydrosart® | 100 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1446870 | ECO | Hydrosart® | 100 | 7 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-14468A4 | ECO | Hydrosart® | 100 | 14 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-1447901 | ECO | Hydrosart® | 300 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1447921 | ECO | Hydrosart® | 300 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1447931 | ECO | Hydrosart® | 300 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1447914 | ECO | Hydrosart® | 300 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1447935 | ECO | Hydrosart® | 300 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1447970 | ECO | Hydrosart® | 300 | 7 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-14479A4 | ECO | Hydrosart® | 300 | 14 | AseptiQuik® L 1" Feed \| Ret.; G ¾" Permeate |
| SFM-AQ-1463901 | ECO | PES | 10 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1463921 | ECO | PES | 10 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1463931 | ECO | PES | 10 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1463914 | ECO | PES | 10 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1463935 | ECO | PES | 10 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1465901 | ECO | PES | 30 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1465921 | ECO | PES | 30 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1465931 | ECO | PES | 30 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1465914 | ECO | PES | 30 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1465935 | ECO | PES | 30 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1466801 | ECO | PES | 100 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1466821 | ECO | PES | 100 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1466831 | ECO | PES | 100 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1466814 | ECO | PES | 100 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1466835 | ECO | PES | 100 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1467901 | ECO | PES | 300 | 0.14 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1467921 | ECO | PES | 300 | 0.28 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1467931 | ECO | PES | 300 | 0.42 | AseptiQuik® G ⅜" Feed, Retentate, Permeate |
| SFM-AQ-1467914 | ECO | PES | 300 | 1.4 | AseptiQuik® G ¾" Feed, Retentate, Permeate |
| SFM-AQ-1467935 | ECO | PES | 300 | 3.5 | AseptiQuik® G ¾" Feed, Retentate, Permeate |

# 4.3 Type and Part Number Overview




**Explanation**

**Cassette type**
**SFM-** Sartocube® self contained with ECO screen

**Connector**
**AQ-** AseptiQuik®

**Membrane**
**144** Hydrosart®
**146** PES

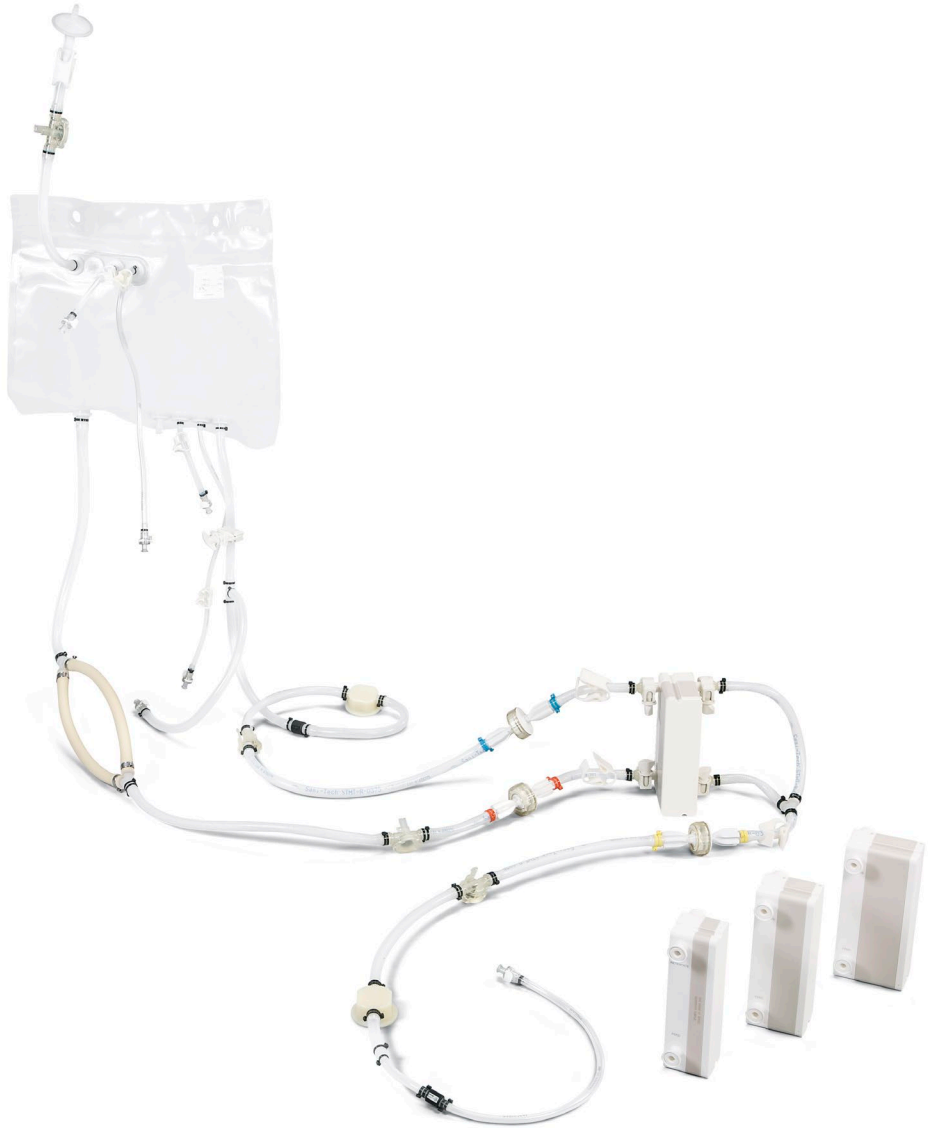
**Cut-off**
**39** 10 kDa
**59** 30 kDa
**68** 100 kDa
**79** 300 kDa

**Filtration area**
**01** 0.14 $m^2$
**21** 0.28 $m^2$
**31** 0.42 $m^2$
**14** 1.4 $m^2$
**35** 3.5 $m^2$
**07** 7 $m^2$
**A4** 14 $m^2$

**Example for a part number:**
SFM-AQ-1445914, Sartocube® Self Contained Hydrosart® 30 kDa MWCO ECO configuration with AseptiQuik® connectors 1.4 $m^2$ filtration area.

# 5. Sartocon® Slice Bag Loop Assembly (for Sartoflow® Alpha Plus SU Systems)

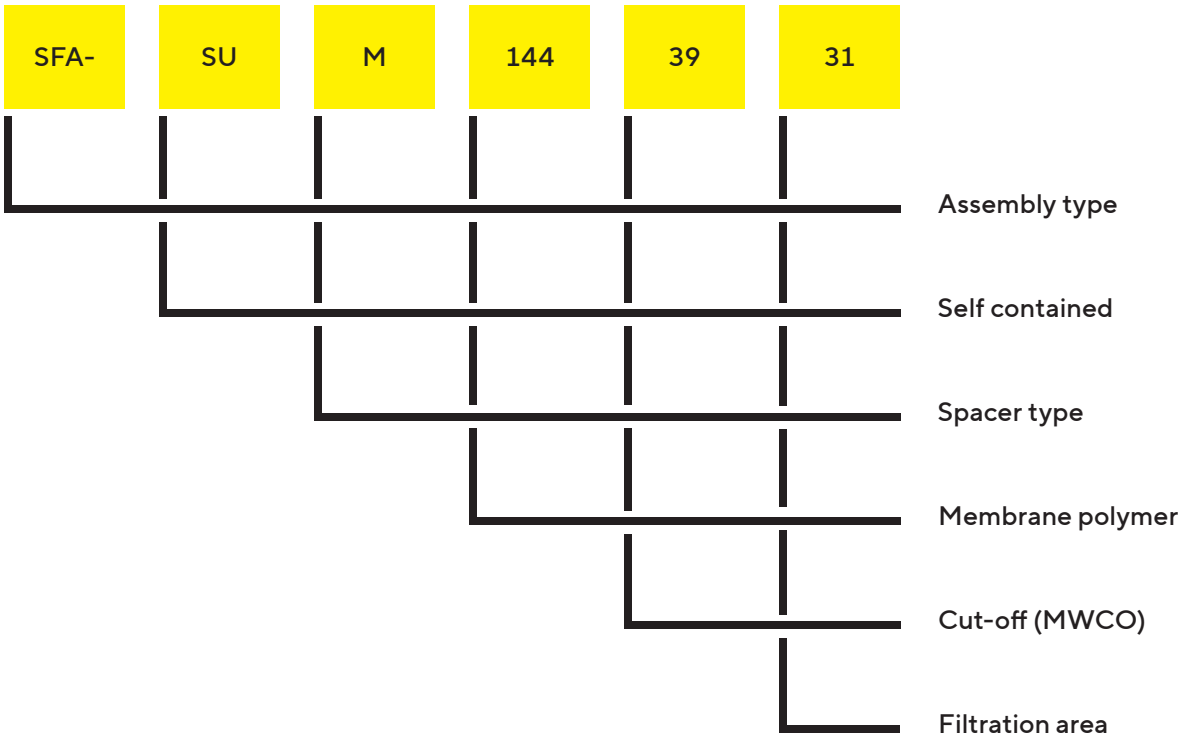
## 5.1 Product Pictures



# 5.2 Product Overview

| Order No. | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) | Effective Filtration Area [$m^2$] | Connector |
|---|---|---|---|---|---|
| SFA-SU-1463901 | E-screen | PES | 10 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SU-1463921 | E-screen | PES | 10 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SU-1463931 | E-screen | PES | 10 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SU-1465901 | E-screen | PES | 30 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SU-1465921 | E-screen | PES | 30 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SU-1465931 | E-screen | PES | 30 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SU-1545801 | W-screen | PES | 0.1 µm | 0.14 | Opta® male small size ⅜" HB |
| SFA-SU-1545821 | W-screen | PES | 0.1 µm | 0.28 | Opta® male small size ⅜" HB |
| SFA-SU-1545831 | W-screen | PES | 0.1 µm | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1443901 | ECO | Hydrosart® | 10 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1443921 | ECO | Hydrosart® | 10 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1443931 | ECO | Hydrosart® | 10 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1445901 | ECO | Hydrosart® | 30 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1445921 | ECO | Hydrosart® | 30 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1445931 | ECO | Hydrosart® | 30 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1446801 | ECO | Hydrosart® | 100 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1446821 | ECO | Hydrosart® | 100 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1446831 | ECO | Hydrosart® | 100 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1463901 | ECO | PES | 10 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1463921 | ECO | PES | 10 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1463931 | ECO | PES | 10 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1465901 | ECO | PES | 30 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1465921 | ECO | PES | 30 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1465931 | ECO | PES | 30 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1466801 | ECO | PES | 100 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1466821 | ECO | PES | 100 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1466831 | ECO | PES | 100 kDa | 0.42 | Opta® male small size ⅜" HB |
| SFA-SUM1467901 | ECO | PES | 300 kDa | 0.14 | Opta® male small size ⅜" HB |
| SFA-SUM1467921 | ECO | PES | 300 kDa | 0.28 | Opta® male small size ⅜" HB |
| SFA-SUM1467931 | ECO | PES | 300 kDa | 0.42 | Opta® male small size ⅜" HB |

# 5.3 Type and Part Number Overview




Explanation

**Assembly type**
**SFA-** Sartocon® Slice bag loop assembly

**Self contained**
**SU** Single-use

**Spacer type**
**M** ECO screen
**-** E-screen

**Membrane polymer**
**144** Hydrosart® UF
**146** PES UF
**154** PES MF

**Cut-off (MWCO)**
**39** 10 kDa
**59** 30 kDa
**68** 100 kDa
**79** 300 kDa
**58** 0.1 µm

**Filtration area**
**01** 0.1 m² E-screen and W-screen
0.14 m² ECO screen
**21** 0.2 m² E-screen and W-screen
0.28 m² ECO screen
**31** 0.3 m² E-screen and W-screen
0.42 m² ECO screen
**14** 1.4 m² ECO screen
**35** 3.5 m² ECO screen

**Example for a part number:**
SFA-SUM1443931, Sartocon® Slice bag loop assembly. The gamma sterilized bag loop assembly consists of a Hydrosart® 10 kDa ECO screen configuration with 0.42 m² filtration area, tubing, four pressure domes, retentate and permeate flow meters, two valve bodies for back pressure control in the retentate and permeate line, perestaltic pump tubing and a 10 L recirculation bag including a thermowell and a vent filter.

# 6. Sartocon® Filter Assembly (for Flexact® UD Systems)

## 6.1 Product Picture

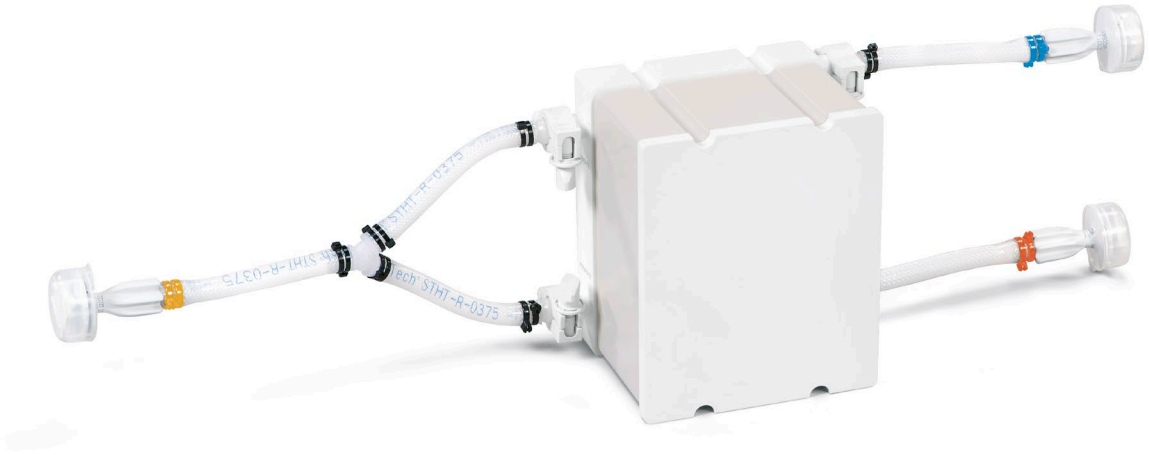
## 6.2 Product Overview

**Filter loop assemblies for Flexact®**

| Order No. | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) [kDa] | Effective Filtration Area [$m^2$] | Connector |
|---|---|---|---|---|---|
| 4XC48 | E | Hydrosart® | 5 | 1.2 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC31 | ECO | Hydrosart® | 10 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC27 | ECO | Hydrosart® | 10 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC40 | ECO | PES | 10 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC41 | ECO | PES | 10 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC32 | ECO | Hydrosart® | 30 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC28 | ECO | Hydrosart® | 30 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC34 | ECO | PES | 30 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC37 | ECO | PES | 30 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC29 | ECO | Hydrosart® | 100 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC33 | ECO | Hydrosart® | 100 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC35 | ECO | PES | 100 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC38 | ECO | PES | 100 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC36 | ECO | PES | 300 | 1.4 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |
| 4XC39 | ECO | PES | 300 | 3.5 | Feed, Retentate Opta®male ½" HB; Permeate MPX ½" male coupling body |

# 7. Opta® Filter Assembly

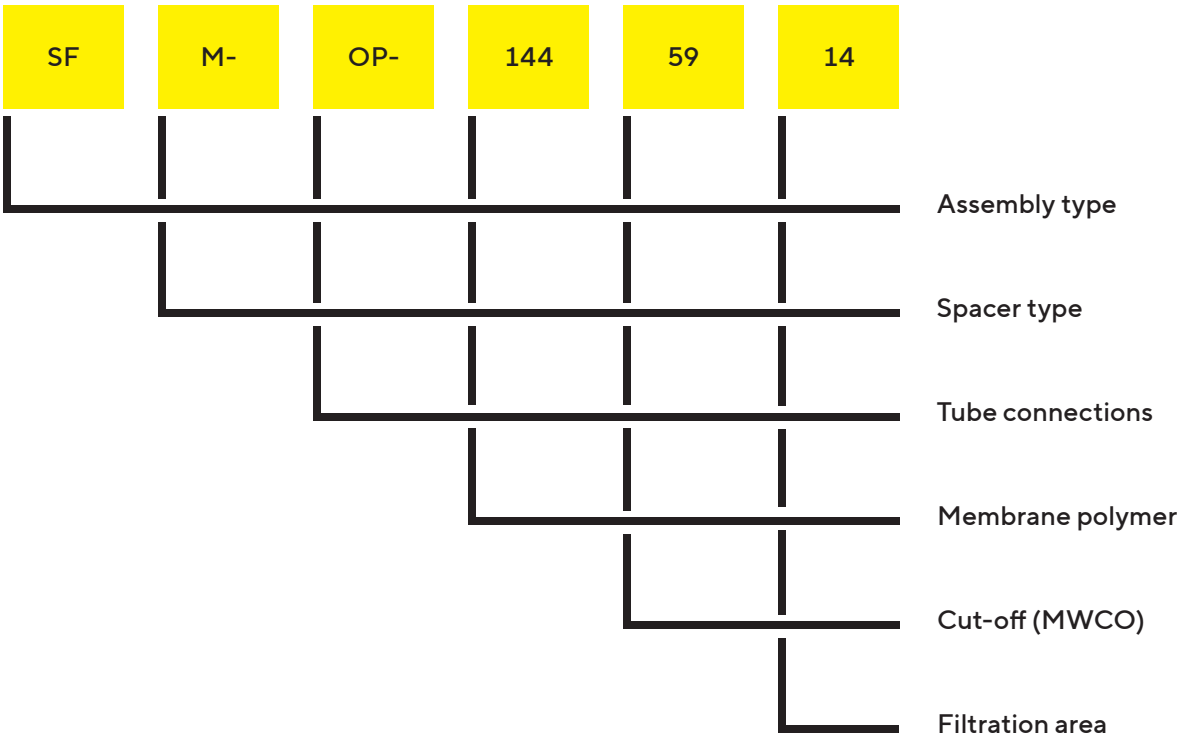
## 7.1 Product Picture



## 7.2 Product Overview

| Part Number Filter Assembly | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) [kDa] | Filtration Area [m²] | Connector |
|---|---|---|---|---|---|
| SFM-OP-1445901 | ECO channel | Hydrosart® | 30 | 0.14 | Feed Opta®female ⅜" HB; Retentate Permeate Opta®male ⅜" HB |
| SFM-OP-1445921 | ECO channel | Hydrosart® | 30 | 0.28 | Feed Opta®female ⅜" HB; Retentate Permeate Opta®male ⅜" HB |
| SFM-OP-1445931 | ECO channel | Hydrosart® | 30 | 0.42 | Feed Opta®female ⅜" HB; Retentate Permeate Opta®male ⅜" HB |
| SFM-OP-1445907 | ECO channel | Hydrosart® | 30 | 0.7 | Feed Opta®female ½" HB; Retentate Permeate Opta®male ½" HB |
| SFM-OP-1445914 | ECO channel | Hydrosart® | 30 | 1.4 | Feed Opta®female ½" HB; Retentate Permeate Opta®male ½" HB |
| SFM-OP-1445935 | ECO channel | Hydrosart® | 30 | 3.5 | Feed Opta®female ½" HB; Retentate Permeate Opta®male ½" HB |

# 7.3 Type and Part Number Overview




Explanation

**Assembly type**
**SF** Self contained filter assembly

**Spacer type**
**M-** ECO screen

**Tube connections**
**OP-** Tubing with Opta® ⅜" or ½"

**Membrane polymer**
**144** Hydrosart®

**Cut-off (MWCO)**
**59** 30 kDa

**Filtration area**
**01** 0.14 m² ECO screen
**21** 0.28 m² ECO screen
**31** 0.42 m² ECO screen
**07** 0.7 m² ECO screen
**14** 1.4 m² ECO screen
**35** 3.5 m² ECO screen

**Example for a part number:**
SFM-OP-1445914, filter assembly with 1.4 m² filtration area Hydrosart® membrane 30 kDa ECO configuration ½" Opta® tubing assembly. Silicone grey, connecting plates polypropylene, sterilized by gamma ray treatment.

# 8. Custom Filter Assembly

## 8.1 Product Overview

| Order No. | Channel Configuration | Membrane Material | Molecular Weight Cut-Off (MWCO) [kDa] | Effective Filtration Area [$m^2$] | Connector |
|---|---|---|---|---|---|
| SFB-LY-1466814 | E-screen | PES | 100 | 1.4 | Lynx® |
| 3D51463901EFFSG | E-screen | PES | 10 | 0.1 | ½" TC |
| 3D51463921EFFSG | E-screen | PES | 10 | 0.2 | ½" TC |
| 3D51463931EFFSG | E-screen | PES | 10 | 0.3 | ½" TC |
| 3D51465901EFFSG | E-screen | PES | 30 | 0.1 | ½" TC |
| 3D51465921EFFSG | E-screen | PES | 30 | 0.2 | ½" TC |
| 3D51465931EFFSG | E-screen | PES | 30 | 0.3 | ½" TC |

# 9. Technical Specifications

## 9.1 Stability

| Membrane Material | Molecular Weight Cut-Off (MWCO) | Order Number | Effective Filtration Area [m²] | pH Stability | Maximum Inlet Pressure Filter Assembly [bar] | Temperature Range During Continuous Operation [°C] | Maximum Diffusion at 1 bar [mL/min] |
|---|---|---|---|---|---|---|---|
| Hydrosart® | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFM-AQ-144... | 0.14, 0.28, 0.42, 1.4, 3.5, 7, 14 | 2 – 14 | 4<br>4<br>3 | 2 – 40 | 0.14, 0.28, 0.42 ≤ 5,<br>1.4, 3.5 m² ≤ 50<br>7 m² ≤ 75<br>14 m² ≤ 100 |
| PES | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFM-AQ-146... | 0.14, 0.28, 0.42, 1.4, 3.5 | 1 – 4 | 3 | 2 – 40 | ≤ 15<br>≤ 50 |
| Hydrosart® | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFA-SUM144... | 0.14, 0.28, 0.42 | 2 – 10 | 3 | 2 – 40 | ≤ 5 |
| PES | 10 kDa, 30 kDa, 100 kDa, 300 kDa | SFA-SUM146... | 0.14, 0.28, 0.42 | 1 – 10 | 3 | 2 – 40 | ≤ 15 |
| PES | 10 kDa, 30 kDa | SFA-SU-146... | 0.1, 0.2, 0.3 | 1 – 10 | 3 | 2 – 40 | ≤ 15 |
| PES | 0.1 µm | SFA-SU-15458 | 0.1, 0.2, 0.3 | 1 – 10 | 3 | 2 – 40 | ≤ 15 |
| PES | 10 kDa, 30 kDa | 3D5146... | 0.1, 0.2, 0.3 | 1 – 14 | 3 | 2 – 40 | ≤ 15 |
| Hydrosart® | 30 kDa | SFM-OP-144... | 0.14, 0.28, 0.42, 0.7, 1.4, 3.5 | 2 – 10 | 3 | 2 – 40 | ≤ 5<br>≤ 50 |
| Hydrosart® | 5 kDa | 4XC48 | 1.2 | 2 – 10 | 3 | 2 – 40 | ≤ 50 |
| Hydrosart® | 10 kDa | 4XC27, 4XC31 | 1.4, 3.5 | 2 – 10 | 3 | 2 – 40 | ≤ 50 |
| Hydrosart® | 30 kDa | 4XC28, 4XC32 | 1.4, 3.5 | 2 – 10 | 3 | 2 – 40 | ≤ 50 |
| Hydrosart® | 100 kDa | 4XC29, 4XC33 | 1.4, 3.5 | 2 – 10 | 3 | 2 – 40 | ≤ 50 |
| PES | 10 kDa | 4XC40, 4XC41 | 1.4, 3.5 | 1 – 10 | 3 | 2 – 40 | ≤ 50 |
| PES | 30 kDa | 4XC34, 4XC37 | 1.4, 3.5 | 1 – 10 | 3 | 2 – 40 | ≤ 50 |
| PES | 100 kDa | 4XC35, 4XC38 | 1.4, 3.5 | 1 – 10 | 3 | 2 – 40 | ≤ 50 |
| PES | 300 kDa | 4XC36, 4XC39 | 1.4, 3.5 | 1 – 10 | 3 | 2 – 40 | ≤ 50 |
| PES | 100 kDa | SFB-LY-146... | 1.4 | 1 – 10 | 3 | 2 – 40 | ≤ 50 |

# 9.2 Chemical Compatibility

| Medium | Concentration | Contact Time [h] | Temperature [°C] | Hydrosart® UF E-Screen | PES UF E-Screen | Hydrosart® UF ECO Screen | PES UF ECO Screen | PES MF |
|---|---|---|---|---|---|---|---|---|
| Acetic acid | < 6 %<br>< 20 % | 50<br>24 | RT<br>20 | E<br>G | E<br>N | E<br>G | E<br>N | E<br>- |
| Aceton | < 5 % | 24 | RT | P | P | G | P | - |
| Acetonitrile | < 10 %<br>< 45 % | 4<br>72 | RT<br>RT | E<br>G | E<br>N | E<br>E | E<br>N | E<br>N |
| Butanol | < 5 % | 24 | 20 | E | - | E | - | - |
| Caprylic acid | < 0.05 % | 24 | RT | P | G | P | G | - |
| Chloroform | < 1.5 % | 24 | RT | E | N | E | N | N |
| Dimethyl acetamid (DMAc) | < 15 %<br>< 50 % | 48<br>24 | RT<br>RT | E<br>N | P<br>N | E<br>P | P<br>N | -<br>- |
| Dimethyl-formamide | < 30 %<br>> 50 % | 24<br>24 | RT<br>RT | E<br>N | N<br>N | E<br>N | N<br>N | N<br>N |
| Dimethyl-sulfoxide | < 50 % | 24 | RT | E | N | E | N | N |
| Ethanol | < 10 %<br>> 10-95 % | | RT<br>RT | E<br>E | E<br>P | E<br>E | E<br>P | E |
| Ethanol denatured with isopropanol | 30 % | | RT | N | N | N | N | N |
| Formaldehyde | < 0.5 % | | RT | N | E | N | E | E |
| Glycerin | Pure | | RT | E | E | E | E | E |
| Guanidine hydrochloride | 6 mol | 8 | RT | E | E | E | E | E |
| Hydrogen peroxide | < 3 % | | RT | N | N | N | N | N |
| Sodium hypochlorite | < 0.5 % @ pH 10<br>< 0.5 % @ pH 11 | 8<br>8 | 20<br>4 | N<br>N | G<br>G | N<br>N | G<br>G | -<br>- |
| Isopropanol | < 50 % | 24 | RT | N | N | N | N | N |
| Methanol | < 20 % | 24 | RT | E | N | E | P | P |
| PEG 200 | > 80 % | 24 | RT | N | N | N | N | - |
| Polypropylene glycol | < 40 %<br>< 60 % | 2–4<br>24 | 4<br>20 | G<br>E | N<br>N | G<br>E | N<br>N | N<br>- |
| Phenol | < 10 % | 24 | RT | G | N | G | N | N |
| Phosphoric acid | < 10 % | 24 | RT | P | G | P | G | G |
| Sodium hydroxide | 1 n | | 45 | G | G | G | G | G |
| TFA Trifluoracedic acid | < 0.1 % @ pH 2.1 | 24 | RT | G | N | G | N | N |
| THF | < 4 % | 12 | N | N | N | N | N | - |
| Tween 80 (Polysorbate 80) in 0.5 M Imidazole | 0.20 % | 24 | RT | N | G | N | G | - |
| Urea | < 30 % | | RT | G | G | G | G | G |

PES = Polyethersulfone

A cassette can be considered fully chemically compatible only if all components (membranes, spacers, gaskets and sealing compound) used in its construction are chemically compatible as well. The table shows the compatibility of the filter only.

E = Excellent compatibility. No change in physical properties was observed.
G = Good compatibility. Minor changes in physical properties have been observed.
P = Poor compatibility. Measurable' changes in physical properties. Short-term exposure at low temperatures and pressure may be suitable.
N = Not compatible. Severe attack on one or multiple construction components.
- = Insufficient data available.

# 9.3 Rejection Coefficient (Characterization of Membranes)

**Hydrosart® Ultrafiltration**

| Substance | Approx. Mol. Wt. | 10 kDa [%] | 30 kDa [%] | 100 kDa [%] | 300 kDa [%] |
|---|---|---|---|---|---|
| Cytochrome C | 12,400 | > 97.5 | – | – | – |
| Albumin | 67,000 | – | ≥ 97.5 | ≤ 60 | – |
| γ-Globulin | 169,000 | – | – | ≥ 96 | – |
| Blue Dextran | 500,000 | – | – | – | < 90 |

– = not measured

**Polyethersulfone (PES) Ultrafiltration**

| Substance | Approx. Mol. Wt. | 10 kDa [%] | 30 kDa [%] | 100 kDa [%] | 300 kDa [%] |
|---|---|---|---|---|---|
| Vitamin B12 | 1,200 | – | – | – | – |
| Cytochrome C | 12,400 | > 95 | 60–90 | – | – |
| Albumin | 67,000 | – | – | < 80 | – |
| γ-Globulin | 169,000 | – | – | ≥ 98 | < 70 |
| Dextran | 2,000,000 | – | – | – | > 95 |

– = not measured

## 9.3.1 Polyethersulfone (PES) Microfilter Microfiltration Static Conditions

| Marker | Retention |
|---|---|
| Mammalian cells | > 99 % |
| Bacteria | > 99 % |
| Mycoplasma | LVR ≥ 7 (PES 0.1 µm) |

# 9.4 Dextran

## 9.4.1 Purpose

The dextran method is agreed to be a procedure to evaluate pore size and pore size distribution in ultra-filtration membranes. As dissolved dextrane molecules are non-charged and exhibit low non-specific interactions, only molecule size determines the sieving effect.

The rejection profile was determined with dextran standard markers of different size.

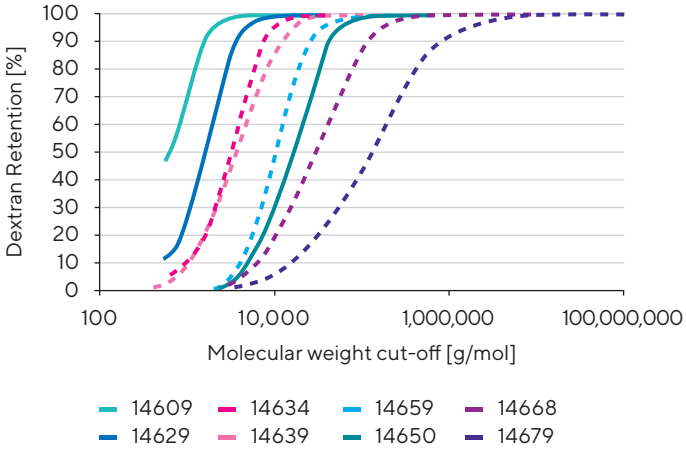
## 9.4.2 Materials and Methods

A Gel Permeation Chromatography (GPC) system was used to determine the different sizes and amount of dextran in the samples. The range is from 100 to 4,000,000 Da. The eluent used was 0.05 M potassium phosphate buffer at a flow rate of 1 mL/min. and a column temperature of 30 °C.

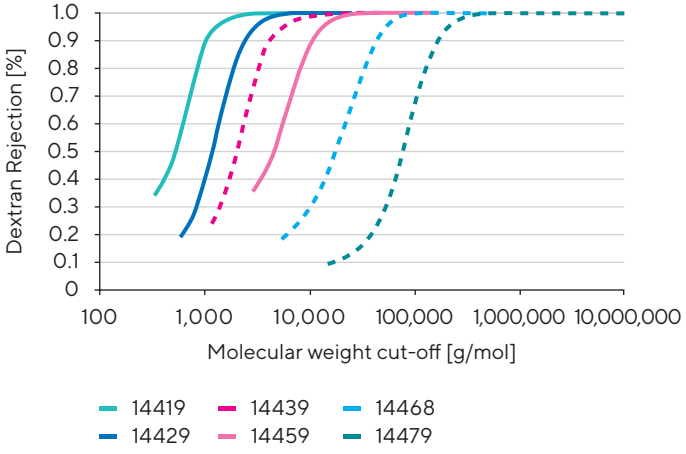
The filters were challenged with a mixture of Dextran markers in a stirred cell (≤ 10 kDa at 4 bar, > 10 kDa at 1 bar) with a cross speed of 0.8 m/s. The retentate was analyzed using the GPC-method.

## 9.4.3 Rejection Profiles of Different Membrane Cut-Offs

**Polyethersulfone**




**Hydrosart®**



# 10. Sterilisation Validation

A sterilisation validation study according to ISO 11137 has been performed in order to demonstrate the effectiveness of the gamma radiation sterilisation method applied to Sartocon® Slice and Sartocube® SCU with AseptiQuik® connectors, Sartocon® Slice bag loop assemblies and Sartocube® self contained filter assemblies, as well as Opta® and custom filter assemblies.

## 10.1 Evaluation of Bioburden Before Sterilisation

### 10.1.1 Purpose

ISO 11137 defines how the safety assurance level (SAL) of a sterilization process is calculated. The microbial load of all self contained assembly configurations is determined before sterilization to ensure a reliable sterilization process.

All self contained assembly devices are flushed with purified water during the manufacturing process and packed in two PE | PA pouches. Thereafter, the self contained configuration is sanitized within seven days at 60 °C. As long as the gamma radiation has not been conducted, the bioburden load can increase. For that reason, the bioburden contamination is evaluated for a storage time of seven days.

Acceptance criteria is < 1000 CFU per filter assembly.

### 10.1.2 Test Procedure

The bioburden contamination was determined as follows:

The bioburden was determined of all inner and outer surfaces by filling, shaking and rinsing the unit consecutively. The rinsing solution collected was filtered through a girded 0.45 µm membrane filter. Each filter was transferred to a plate count and incubated at 30 – 35 °C for five to seven days. The sum of the colony-forming units results in the bioburden.

### 10.1.3 Results

Bioburden evaluation was conducted on the self contained devices. The storage scenarios are as follows:

The self contained devices are sanitized for 24 h at 60 °C and stored at room temperature for 10 days.

| Filter Configuration | < 1000 CFU |
|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Yes |
| Opta® filter assembly with slice and Sartocube® self contained | Yes |
| Filter assembly with Sartocube® self contained | Yes |
| Bag loop assembly with Sartocon® Slice self contained | Yes |
| Custom filter assembly | Yes |

### 10.1.4 Conclusion

The storage analysis of 10 days shows that the bioburden concentration is low enough to ensure complete sterility after gamma radiation. As a worst-case scenario all self contained assemblies have been tested for a storage time of 10 days instead of seven days.

# 10.2 Minimum Dose Verification

## 10.2.1 Purpose

Verification of the minimum dose is performed by irradiation with the corresponding dose resulting from the bioburden analysis. After irradiation with this minimum dose, a sterility test according to EP and USP is performed to verify sterility.

## 10.2.2 Test Procedure

The self contained units are gamma radiated with a minimum dose of 5–10 kGy depending on the bioburden result. After irradiation, all parts of the self contained assemblies have been tested for sterility according to USP and EP.

Under sterile conditions, two of each assembly configuration have been filled with soybean casein digest medium (BO0509M Lot 108191), and two of each assembly configuration have been filled with thioglycollate medium (BO0510M Lot 1089160). The soybean casein digest medium-filled filter assemblies have been incubated at 22.5 ± 2.5 °C for 14 days. The thioglycollate broth-filled assemblies have been incubated at 32.5 ± 2.5 °C for 14 days. The medium in all assemblies has been tested for sterility thereafter.

## 10.2.3 Filter Configuration

| | Soybean Casein Digest Medium | Thioglycollate Broth |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Sterile | Sterile |
| Opta® filter assembly with slice and Sartocube® self contained | Sterile | Sterile |
| Filter assembly with Sartocube® self contained | Sterile | Sterile |
| Bag loop assembly with Sartocon® Slice self contained | Sterile | Sterile |
| Custom filter assembly | Sterile | Sterile |

## 10.2.4 Conclusion

With a radiation dose of 5 kGy, all self contained filter assembly configurations have shown a Safety Assurance Level (SAL) of $10^{-2}$ according to ISO 11137. A SAL of $10^{-6}$ results in a radiation dose of 25 kGy.

## 10.3 Dose Mapping

The radiation sterilization standards EN 552 and ISO 11137 require that dose mapping in real or simulated product has to be carried out. Dose mapping verifies the dose of gamma radiation within a grid pattern throughout the product. The dose at any spot within the grid pattern has to ensure a minimum radiation of 25 kGy.

Dose mapping for all self contained filter configurations have been performed and a SAL of $10^{-6}$ can be guaranteed.

## 10.4 Performance Test After Irradiation and Accelerated Aging

### 10.4.1 Purpose

The physical properties of different membrane types may be affected by high-dose gamma irradiation. To ensure physical stability of the membrane after irradiation and storage, a functional test of Hydrosart® is performed after a worst-case gamma irradiation of 50 kGy and accelerated storage.

### 10.4.2 Test Procedure

The units as mentioned below have been irradiated with a minimum dose of 50 kGy. After sterilisation and accelerated aging equivalent to 6, 12 and 24 months of storage, diffusion and water flux have been evaluated. One membrane per cut-off was analyzed for protein rejection, after radiation and accelerated aging equivalent to 6, 12 and 24 months of storage. All data has been compared with the acceptance criteria.

| Filter | Diffusion Test | Water Test | Membrane Protein Rejection |
|---|---|---|---|
| Hydrosart® filtration unit | Passed | Passed | Passed |
| PES filtration unit | Passed | Passed | Passed |

### 10.4.3 Conclusion

Irradiation with 50 kGy has shown no change in physical functionality.

## 10.5 Sterilisation Validation Summary

Gamma irradiation with 25 kGy has proven to ensure a SAL of $10^{-6}$ according to ISO 11137. Sartorius performs gamma irradiation of all self contained filter assembly configurations with a minimum level of 25 kGy to a maximum level of 50 kGy.

# 11. Validation of Extractables After Gamma Irradiation

Sartorius has proven that the Sartocon® Slice bag loop assemblies and standalone units, as well as Sartocube® self contained filter assemblies with Hydrosart® and PES membrane, are within the applicable specification of the USP, EP as well as within our stringent in-house test limits. The data shown in this chapter is based on evaluations performed on the Sartocon® Slice and Sartocube® self contained assemblies after gamma irradiation of 25-50 kGy.

**Substantial equivilance of product family**
Within one membrane filter configuration, one cut-off was chosen to be the reference material. The largest filtration area available within this configuration was then completely analyzed. Substantial equivalence within the different cut-offs available allows us to reference a representative filter cut-off.

## 11.1 Particulate Matter in the Retentate and Permeate

### 11.1.1 Purpose

Particle release from filters must be minimized. For injectables solutions, the requirements are defined in the current USP monographs, which set maximum limits for particulate matter based on defined particle sizes. The release of all self contained cassettes are below the limits set forth in the current USP for "Sterile Water for Injection for single-dose Infusion".

### 11.1.2 Limits

Using the method "Light Obscuration Test Particle Count" the following limits have been set by the current USP <788> and EP 2.9.19 as the maximum number of particles per mL of product (in this case, containers with a normal content of more than 100 mL):
25 per mL ≥ 10 µm
3 per mL ≥ 25 µm

## 11.1.3 Test Set-Up

Purified water in compliance with the current USP section on particulate matter, endotoxins, and extractables were used for the tests.

A self contained assembly is installed into a cleaned test apparatus. The installed self contained assembly must be flushed with 10 L for a Sartocon® Slice and 50 L for a Sartocube® of purified water as described in the user manual, at an inlet pressure of 1 bar. Both retentate and permeate valves have to be adjusted in setting to accommodate the flow ratio, given in the table below:

| Cassette Type | Ratio of Retentate to Permeate |
|---|---|
| All ultrafilters | Approx. 1 : 1 |

After 33 % of the flush volume has passed the self contained, the pump is stopped. Flushing is continued after 15 minutes soaking time. Permeate and retentate are disposed of.

Subsequently, the slice self contained assembly is filled with 10 L purified water and the Sartocube® self contained assembly is preflushed with 50 L purified water. The extraction liquid is thereafter recirculated within the system for 15 minutes under the same pressure conditions as mentioned above.

The conclusion is that all slice self contained assemblies must be flushed with 10 L purified water and all Sartocube® self contained assemblies must be preflushed with 50 L purified water in order to meet the extractables. The custom filter assembly (SFA-LY-1466814) was evaluated using a custom flush procedure.

## 11.1.4 Procedure

A sample of 250 mL is subjected to particle analysis. The particle sensor system consists of a Pacific Scientific Hiac Royco sampler (Model 3000), in which a particle sensor (Model HRLD 150) was used until December 2015. Since then, a Klotz particle system with a LDS 45/50 sensor has been used to analyze the sample in accordance to the current USP requirements. The particles sensor is calibrated in line with the USP standards. The system also incorporates a particle counter (Model 8000).
The sample was drawn through the sensor at a rate of 25 mL/min. The average values of particle size and particle count were calculated from a total of six measurements of 25 mL volume each.

## 11.1.5 Summary of the Results

**Particulate Matter**

| Component | Particles per mL ≥ 10 µm | Permeate ≥ 25 µm | Particles per mL ≥ 10 µm | Retentate ≥ 25 µm |
|---|---|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed | Passed | Passed |
| Custom filter assembly | Passed | Passed | Passed | Passed |

## 11.1.6 Conclusion

The requirements of the current USP <788 > and EP 2.9.19 in respect of particulate matter are met after a preflush with 10 liters purified water for each slice self contained assembly and 50 liters purified water for each Sartocube® self contained assembly.

# 11.2 Determination of Extractable Substances in the Retentate and Permeate

**Purpose**
Extractables are determined to establish the minimum rinse volume required before using self contained devices. As a limit, the current USP | EP requirements for "Sterile Water for Injection" are used. The samples of retentates and permeates are taken for analysis of non-volatile residues, oxidizable substances, chloride, sulfate, calcium, ammonium, and bacteria endotoxins, as well as pH, conductivity changes and TOC.

## 11.2.1 Determination of Non-Volatile Residues in the Retentate and Permeate

A one-liter sample was taken from each of the permeate and retentate. Two hundred mL from each samples was evaporated. The residue was dried for an additional 60 minutes at 105 °C. The sample vessel was then weighed and the weight was compared with the original tare weight of the sample vessel. The data in the next section shows the average extractables values for all configurations.

### 11.2.1.1 Limits

Maximum allowable limits for non-volatile residue applicable to "Sterile Water for Injection" described in the current EP in relation to the volume of parenteral dose sizes:

| Vessel Volume | Non-Volatile Residue in % [w/v] |
|---|---|
| > 10 mL | < 0.003 |

### 11.2.1.2 Results for Extractable Substances

| Component | NVR% Permeate 10 µm | NVR% Retentate 10 µm |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed |
| Custom filter assembly | Passed | Passed |

### 11.2.1.3 Conclusion

The requirements of the current EP "Sterile Water for Injection" in respect of non-volatile residues are met after a preflush with 10 liters of purified water for each slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.2 Determination of Oxidizable Substances in the Retentate and Permeate

### 11.2.2.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from permeate and retentate.

As described in the current EP (for containers with a nominal volume equal or greater than 50 mL), to 50 mL to 5 mL 2 N sulfuric acid was added of the sample. The mixture was heated to boiling, and then 0.1 mL of 0.1 N potassium permanganate was added. This mixture was heated for 10 min. at 100 °C. If the solution retained its color, the sample passed the current EP test for Oxidizable Substances in "Sterile Water for Injection" and the test result is negative.

### 11.2.2.2 Results for Oxidizable Substances

| Filter Configuration | Permeate | Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.2.3 Conclusion

The requirements of the current USP "Sterile Water for Injection" in respect of oxidizable substances are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 of liters purified water for Sartocube® self contained assembly.

## 11.2.3 Determination of Conductivity in the Retentate and Permeate

### 11.2.3.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. A one-liter sample was taken from the permeate and retentate.

The limits for the conductivity values are based on the current USP <645> and EP. A 100 mL solution was tested for conductivity. The solution has to be regulated to 25 °C ± 1 and stirred for two to three minutes. A conductivity reading is taken. If the conductivity is below 5 µS/cm, the test has passed.

### 11.2.3.2 Results for Conductivity Analysis

| Component | Conductivity [µs/cm] Permeate | Conductivity [µs/cm] Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed |
| Custom filter assembly | Passed | Passed |

### 11.2.3.3 Conclusion

The requirements of the current USP <643> in respect of conductivity are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.4 Determination of the Ammonium Content in the Retentate and Permeate

### 11.2.4.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from the permeate and retentate.

As described in the current EP, the solutions were prepared by the addition of 1 mL of alkaline mercuric-potassium iodide solution. The ammonium content of these samples was measured and, as any yellow color produced immediately was not darker than that of a control containing 0.2 ppm $NH_4^+$ in high-purity water, the test result was negative.

### 11.2.4.2 Results for Ammonium Analysis

| Component | Ammonia Permeate | Ammonia Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.4.3 Conclusion

The requirements of the current EP "Sterile Water for Injection" in respect of ammonium are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.5 Determination of the Chloride Content in the Retentate and Permeate

### 11.2.5.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from the permeate and retentate.

As described in the current EP, the solutions were prepared by the addition of five drops of 2 N nitric acid and 1 mL of 0.1 N silver nitrate solution. The chloride content of these samples was qualitatively measured, and as no turbidity wasproduced, the test result is negative and the test is passed.

### 11.2.5.2 Results for Chloride Analysis

| Component | Chloride Permeate | Chloride Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.5.3 Conclusion

The requirements of the current EP "Sterile Water for Injection" in respect of chloride are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.6 Determination of the Sulfate Content in the Retentate and Permeate

### 11.2.6.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from each of the permeate and retentate.

As described in the current EP, the solutions were prepared by the addition of 1 mL of barium chloride. The sulfate content of these samples was qualitatively measured, and as no turbidity was produced, the test passed and thetest result is negative.

### 11.2.6.2 Results for Sulfate Analysis

| Component | Sulfate Permeate | Sulfate Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.6.3 Conclusion

The requirements of the current USP "Sterile Water for Injection" in respect of sulfate are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.7 Determination of the Calcium Content in the Retentate and Permeate

### 11.2.7.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from the permeate and retentate.

The solution was prepared by the addition of 1 mL ammonium oxalate to 100 mL samples. The calcium content of these samples was qualitatively measured, and as no turbidity was produced, the test has passed and the test result is negative.

### 11.2.7.2 Results for Calcium

| Component | Calcium Permeate | Calcium Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.7.3 Conclusion

The requirements of the current USP "Sterile Water for Injection" in respect of calcium are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.8 Determination of the Nitrate Content in the Retentate and Permeate

### 11.2.8.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. One-liter samples were taken from permeate and retentate.

As described in the current EP, 0.4 mL potassium chloride solution and 0.1 mL di-phenylamine solution were added to the sample. 5 mL concentrated sulfuric acid was added during shaking the mixture. The vessel containing the mixture is transferred to a water bath at 50 °C. A reference solution containing 2 ppm nitrate is treated in the same manner as the sample. If after 15 min, any blue color in the solution is not more intense than that in the reference solution, the test is passed and the test result is negative.

### 11.2.8.2 Results for Nitrate

| Component | Nitrate Permeate | Nitrate Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Negative | Negative |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Negative | Negative |
| Filter assembly (4XC...) | Negative | Negative |
| Sartoflow® bag loop assembly (SFA-SUM...) | Negative | Negative |
| Custom filter assembly | Negative | Negative |

### 11.2.8.3 Conclusion

The requirements of the current USP "Sterile Water for Injection" in respect of nitrate are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.9 Determination of the pH Values Content in the Retentate and Permeate

### 11.2.9.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling have been followed as described in chapter 11.1.3. One-liter samples is taken from the permeate and retentate.

As described in the current USP <791>, all solutions have to be regulated to 25 °C ± 2 °C. If the pH is between the range of 5 – 7, the test has passed.

### 11.2.9.2 Results for pH Analysis

| Component | pH Permeate | pH Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed |
| Custom filter assembly | Passed | Passed |

### 11.2.9.3 Conclusion

The requirements of the current USP <791> in respect of pH are met after a preflush with 10 liters of purified water for slice self contained assembly, and 50 liters of purified water for Sartocube® self contained assembly.

## 11.2.10 Total Organic Carbon Analysis of "Sterile Water for Injection"

### 11.2.10.1 Test Procedure

Selected master products and reference assemblies after irradiation were analyzed.

The system set-up and sampling have been followed as described in chapter 11.1.3. One-liter samples is taken from the permeate and retentate.

The solution used has a pH between 5 and 9, a salt quantity of < 1000 ppm. After 100 µl of 2 % HCl is added and the sample is purged by $O^2$ to evaporate the inorganic TOC, the sample is analyzed with a Shimadzu 5000A.

### 11.2.10.2 Results for TOC

| Component | TOC Permeate | TOC Retentate |
|---|---|---|
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed |
| Custom filter assembly | Passed | Passed |

### 11.2.10.3 Conclusion

All loop assemblies and self contained assemblies tested under the conditions of the previously mentioned method yielded results below or equal to 500 ppb TOC.

## 11.2.11 Bacterial Endotoxins Test

**Purpose**
The goal of this test is to determine that the amount of endotoxins released in the permeate and retentate of Sartocon® Slice and Sartocube® self contained assemblies is less than 0.25 EU/mL (in compliance with current USP <85> and EP 2.6.14).

### 11.2.11.1 Test Procedure

Selected master products and reference assemblies were analyzed.

The system set-up and sampling method have been followed as described in chapter 11.1.3. Samples were taken from the permeate and retentate extraction liquid.

The endotoxin level is determined by kinetic turbidimetric LAL assay according to the current USP and EP guidelines.

### 11.2.11.2 Results

| Component | Endotoxine [in compliance with USP <85> and EP 2.6.14] | |
|---|---|---|
| | Permeate | Retentate |
| Sartocon® Slice and Sartocube® self contained with AseptiQuik® connectors | Passed | Passed |
| Opta® filter assembly with slice and Sartocube® (SFM-...) | Passed | Passed |
| Filter assembly (4XC...) | Passed | Passed |
| Sartoflow® bag loop assembly (SFA-SUM...) | Passed | Passed |
| Custom filter assembly | Passed | Passed |

### 11.2.11.3 Conclusion

All loop assemblies and self contained assemblies tested under the conditions of the previously mentioned method yielded results of less than 0.25 EU/mL bacterial endotoxins.

# 11.3 Pressure Resistance Test

## 11.3.1 Purpose

To prove pressure stability, a wet test at maximum temperature and pressure is performed.

## 11.3.2 Test Procedure

Selected master products and reference assemblies are installed into a system. Water is recirculated at a temperature of 35 °C ± 5 °C for 20 hours. The pressure is set to the maximum pressure specified. Thereafter, all filter assemblies are tested for diffusion and water flux.

## 11.3.3 Results

| Device | Pressure | Integrity Test | Water Flow |
|---|---|---|---|
| 4XC...<br>SFM-OP...<br>SFB-LY...<br>3D5... | 3 bar ± 0.3 bar | Passed | Within specification |
| SFA-SU... | 2.5 bar ± 0.25 bar | Passed | Within specification |
| SFM-AQ-144...<br>≤ 1.4 m² | 4 bar ± 0.4 bar | Passed | Within specification |
| SFM-AQ-146...<br>SFM-AQ-144...<br>≥ 1.4 m² | 3 bar ± 0.3 bar | Passed | Within specification |

## 11.3.4 Conclusion

All assemblies and self contained devices tested under the conditions of the previously mentioned method have proven to show a water flux within the specification, and have passed the integrity test.

# 11.4 Shelf Life Stability

## 11.4.1 Purpose

The objective of the test is to evaluate the shelf life stability of self contained assemblies after gamma radiation.

## 11.4.2 Test Procedure

Selected master products and reference assemblies have been gamma radiated at a minimum dose of 50 kGy and stored for two years. All devices have thereafter been tested for integrity and the water flux was determined. The master products were also tested for the complete series of extractables (in analogy as described in chapter 6.2).

## 11.4.3 Results

All assemblies, including self-contained standalone units radiated at 50 kGy, have passed the integrity test, flux evaluation and the extractable test after two years of storage.

## 11.4.4 Conclusion

All filter assemblies, including standalone units, show no change in physical functionality after radiation at 50 kGy and storage.
For filtration units 4XC... , SFA... , SFB... and SFM... the latest date of usage is 2 years from date of manufacture.
Only Exception is 4XC48, for which the latest date of usage is 1year from date of manufacture.

# 11.5 External Tests for Biosafety

## 11.5.1 Biosafety

## 11.5.2 Purpose

These tests were designed to determine that all components used in the manufacture of Sartocon® Slice and Sartocube® self contained are biosafe and meet or exceed the requirements for the current USP Biological Test (classification VI/121 °C).

## 11.5.3 Test Method

All filter loop and bag loop assemblies, as well as the self contained units themselves were supplied to an independent facility for evaluation according to the requirements of the current USP <88> Biological Test (classification VI/121 °C), which included the following tests:

- Intracutaneous test
- Systemic injection test
- Implantation test (seven days)

## 11.5.4 Results

The certificates issued for the following tests were approved for release based on the test results. All materials used in the construction of the loop assemblies, as well as the self contained devices meet or exceed the requirements of the current USP <88> Biological Test (classification VI/121 °C).

# 11.6 Cytotoxicity Tests

## 11.6.1 Purpose

The tests were designed to determine whether the assemblies or self contained units release cytotoxic materials after cleaning or flushing with water.

## 11.6.2 Test Method

All loop assemblies as well as self contained components, were tested according to ISO 10993-1, (-5)-12, (EN 30993-1, (-5)-12).

MRC5 | L929 cells were incubated with these samples. The cells were analyzed with regard to their viability.

## 11.6.3 Results

All components showed no cytotoxicity after a flushing volume of 50 L for Sartocube® self contained standalone or loop assemblies, or 10 L for slice self contained standalone or loop assemblies.

# 12. Quality Assurance

## 12.1 Quality Control Measures

**Quality assurance**
Consistent high quality of Sartorius Separation Technologies consumables is ensured by careful selection of the raw materials, well-planned and validated production technologies, and an exceptionally efficient Quality Management System in compliance with ISO 9001 standards. Theses standards apply to all manufacturing facilities (www.sartorius.com/qm-certificates) resulting in high batch-to-batch reproducibility.

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

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

Consequently, our products are qualified according to most stringent performance and safety industry standards as described in this Validation Guide. Our engineering change request management and centralized documentation system ensure product and process consistency while enabling continuous improvement.

**Sartorius herewith certifies that more than one membrane lot can be implemented in one cassette lot. However, each single cassette always contains only one membrane lot.**

**Prevention of contamination**
Slice and Sartocube® self contained devices are flushed with purified water, drained and then packed and sealed in two PE | PA pouches. The units are sanitized at 60 °C for 24 hours and subsequently gamma irradiated before they are placed in a cardbord box.

**Complete traceability**
The order number, type, pore size, cut-off, lot number and serial number are laser-printed onto the silicone frame of the Slice and Sartocube® self contained. The identical information, as well as the latest date for initial use (expiry date), is printed on the label of the PE | PA bag and the cardboard box.

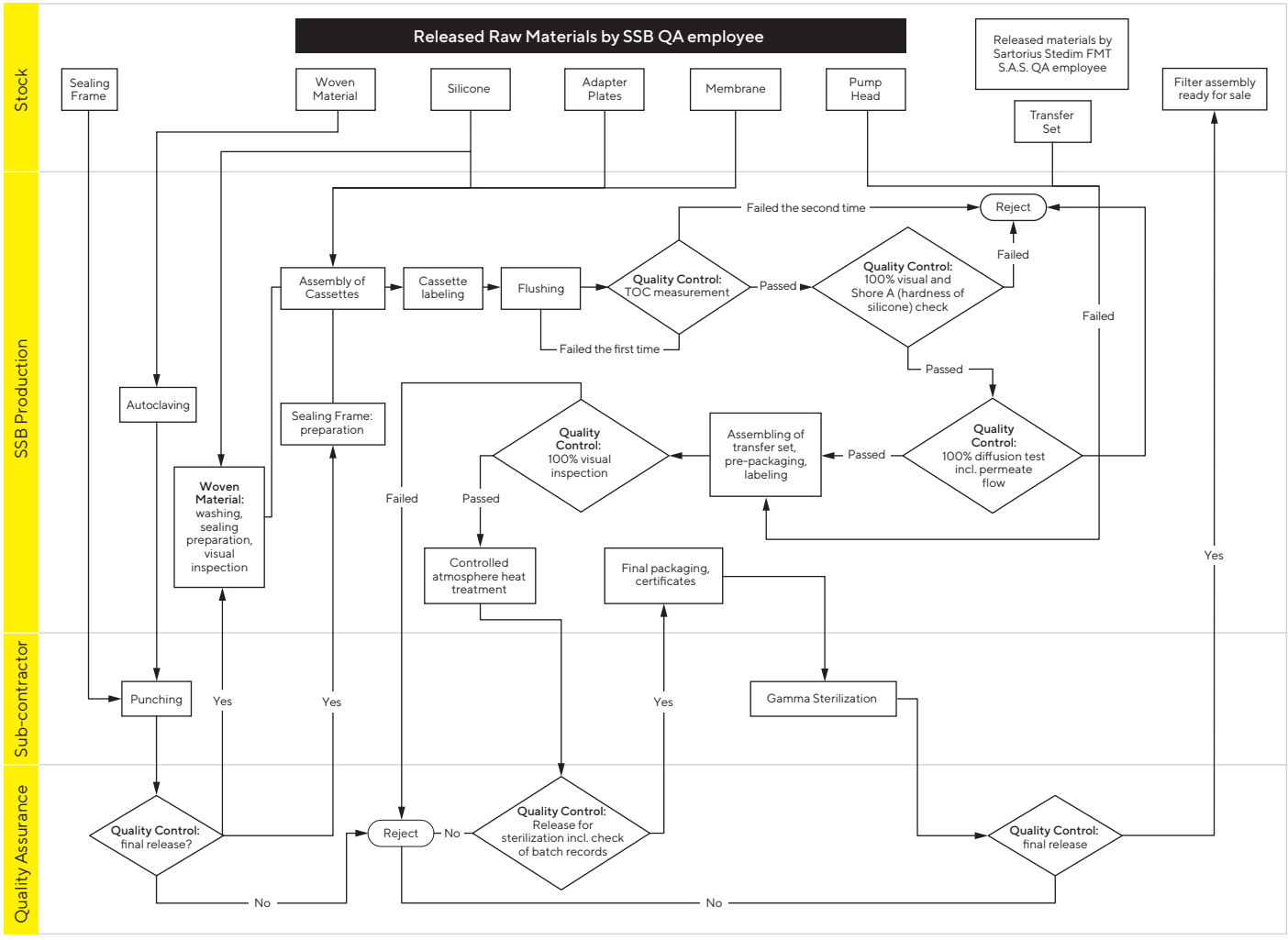
**Facility audit**
Sartorius Stedim encourages customers to audit its manufacturing facility and quality program. Please contact your Sartorius Stedim representative for more information.

**Product release criteria**
All incoming raw materials undergo inspection and testing by the Sartorius Quality Assurance Department. All membranes and cassettes are tested throughout the complete production process. Performance data is used as product release criteria for membranes and cassettes.

**Membrane:**
- Water flux
- Protein solution flux
- Retention | Rejection profile (bacteria retention for MF, protein retention for UF)
- Integrity test (air diffusion for UF and MF, bubble point for MF)
- Burst pressure to evaluate mechanical strength
- Membrane thickness

**Self contained filter assemblies:**
- Each membrane sheet is visually inspected before installation
- Individual air diffusion test to confirm integrity
- Individual module integrity to confirm seal tightness
- Durometer test of silicone frame (Shore A)
- Permeate flux for each cassette batch
- TOC monitoring after preflush
- 100 % visual inspection of the final product
- Gamma tag verification. Color change from yellow to red
- Gamma certification is checked and documented

## Process of Sartocon® self contained | filter assembly




Date: 20.02.2015

# 13. Packaging and Labeling

## 13.1 Packaging

Self contained units are packed and sealed in two PE | PA pouches and packaged into a sturdy cardboard box. A QC certificate and instructions for use are placed into the cardboard box. A label is placed on the outside of the cardboard box.

## 13.2 Transportation and Packaging Tests

Shipping package and transportation test is validated and documented according to:

- ASTM D 4169 DC Level 2,
- ASTM D 7386 Level 2 or
- ASTM 4169 Level 1.

# 14. Appendix

## 14.1 Biocompatibility Certificate

SARTORIUS

Sartorius Stedim Biotech GmbH, 37070 Göttingen

To whom it may concern

09 March 2021

Statement on Biocompatibility

| | |
|---|---|
| Test material: | The product families of Sartocon® \| Sartocube® Cassettes [302*/305*/306*/308*/3M2*/3M5*/3M8*/3D9*] components and membrane types |
| Studies performed: | The following studies have been performed by an external, accredited institute in order to determine the biocompatibility of every cassette component.<br><br>– CYTOXICITY in accordance with ISO 10993-5<br>– USP <88> BIOLOGICAL REACTIVITY TEST (Plastic class VI/121 °C) |
| Results: | All test materials did not show any effect in the performed studies and thus meet the USP Plastic Class Test VI criteria.<br><br>No leachable substances were released in cytotoxic concentrations. |

The information provided in this document is given to the best of our knowledge and belief and is based on the information available at the time this document was issued.

Sincerely
Sartorius Stedim Biotech GmbH

Product Compliance Officer

Aida Santos

Quality Assurance

i.A.

Miriam Giersemehl

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Uwe Becker,
Bettina Berendsen

Chairman of the Supervisory Board:
Dr. Joachim Kreuzburg

# 14.2 Quality Assurance Certificate Example

SARTORIUS

## Quality Assurance Certificate

**AQ Filter Assembly**
with 3D21467914MFFSG

| | |
|---|---|
| **Order no.** | SFM-AQ-1467914 |
| **Filter material** | Polyethersulfone |
| **Use before** | 06 / 2022 |
| **Cut off** | 300 kD |
| **Lot no.** | 210878123 |

This document is to verify that the designated product was manufactured by Sartorius in conformance with established Good Manufacturing Practice (cGMP) standards.

This product is developed, produced and distributed according to a Quality Management System that is certified for compliance with DIN/ISO 9001.

This product was sterilized using a validated process in accordance with DIN/EN ISO 11137 regulations.

Shipping package and transportation test was validated according to ASTM D7386 Level II.

**This product has passed Sartorius' inhouse tests and thus meets Sartorius' stringent quality control standards.**

**The following specified investigations are executed during the validating phase for each product type:**

The investigation of the current USP Class VI Biological Test for Plastics was executed by an independent accredited institute. All components of this product are biosafe and meet the requirement of the current USP Biological Reactivity Tests <88> for Plastic Class VI.

The product has passed the Bacterial Endotoxin test according to USP <85> with an acceptance criteria of ≤ 0.25 EU/ml.

This product releases particulate matter in quantities below the requirement for Large Volume Injections established by the current USP <788> Particulate Matter in Injections. The sample preparation complies with the test if the average number of particles present in the units tested does not exceed 25 per ml equal to or greater than 10 µm and does not exceed 3 per ml equal to or greater than 25 µm.

The products are irradiated between a minimum dose of 25 kGy and a maximum dose of 50 kGy. The efficiency of the minimum dose of 25 kGy has been validated according to ISO11137 recommendations in order to obtain a $10^{-6}$ Sterility Assurance Level.

**The Self Contained Cassette has passed Sartorius' inhouse tests and thus meets Sartorius' stringent quality control standards.**
Before membrane material is approved for incorporation into a cassette, the flow rates and retention capacities, including other physical characteristics, of each respective membrane lot are tested for compliance with the applicable standards. Once a membrane lot has been approved for release and cut, each membrane is visually inspected before incorporation into a cassette.

Each completed filter cassette has passed multiple documented visual inspection steps and has been individually tested for integrity. Air diffusion tests were performed for each cassette. The filtrate flow rate performance was determined for each lot. The results of these tests were found to meet or exceed the minimum requirements set forth by our Quality Assurance Department. Quality control test results can be traced for each membrane lot as well as for each cassette.

Diffusion rate measured for this filter was found to be ≤ 50.0 ml/min, at a test pressure of 1.0 bar.

Sartorius complies with the highest standards available in the manufacture of the membranes incorporated into this cassette. This along with Sartorius' rigorous quality standards for finished products results in the lot-to-lot reproducibility that is required. In addition, this enables Sartorius to guarantee the performance of this cassette when it is used in accordance with the accompanying instruction manual.

2021-06-29
Date

Dr. Anna Vreemann
Site Quality Manager

Manufactured by Sartorius Stedim Biotech GmbH
37070 Goettingen, Germany

# 14.3 Quality Systems Network Certificate: IQ NET DIN EN ISO 9001:2000

Sartorius implemented quality management systems to ensure consistently high quality of membrane filters, ultra filters, filter cartridges and disposables.

**Exemplary Quality Systems Certificates:**

- Global Quality Systems Certificates | Quality Certificates (ISO 9001:2000)
- Global Quality Systems Certificates | Quality Certificates for Medical Devices (ISO 13485:2003 and directive 93|42|EEC)

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

# 10. Document History

| Version Number | Description of Change | Version Date |
|---|---|---|
| 00 | Update to new Sartorius brand design. Renaming of document to include DIR number. | October 2021 |
| 01 | Adjustment of wrong irradiation dose from 45 to 50 kGy.<br>Correction of wrong connector sizes.<br>Removal of Drug Master File.<br>Correction of typos.<br>Update of imagery. | October 2022 |
| 02 | Update regarding the shelf life extension (please refer to Change Notification of ECR 36281 "Product Shelf Life Extension for Tangential Flow Filtration (TFF) Self Contained Units (SCU)"). | July 2023 |
| 03 | Removal of cGMP claim and update of chapter Quality Assurance (please refer to Change Notification of ECR 33619 "Removal of cGMP claim"). | Oktober 2024 |

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DIR No.: 2554012-000-03
Status 10 | 2024