Aquasart® Plus XL

Validation Guide

SARTORIUS

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1. Introduction

Sartorius Stedim Biotech developed filter cartridges to meet the needs of each specific food & beverage application. Only an optimised membrane structure can compensate any difference in the quality of raw materials.

In these optimised membranes, the radius of each pore decreases in the direction from the upstream, or unfiltrate, area to the downstream, or filtrate, region. As a result of this asymmetry, the pores of the filter membrane do not become clogged so quickly by the constituents of the beverage and undergoing filtration.

All raw materials of filter cartridges used in the food and beverage industry must comply with the list of component materials authorised by EU regulation No. 10/2011. Only then, they meet the requirements of the EU regulation (EC) No. 1935/2004 on materials and articles intended to come into contact with food. This is why each Sartorius Stedim Biotech filter cartridge is supplied with an up-to-date certificate specifying its current lot number and date of manufacture.

An additional especially important point in ensuring constant product quality is the validation of the filter cartridge used as well as a quality assurance system defined for the final filter membrane and the prefilter materials employed. This entails that all raw materials used in membrane production and final assembly and packaging of filter cartridges are tested. In compliance with the requirements of this quality system.

Following membrane production, each membrane roll is tested for conformance with the required specifications before it can be approved for use in further filter cartridge production. The plastic materials needed for manufacturing a filter cartridge – outer cage, core and adapters – also undergo quality testing before use.

Each filter cartridge manufactured is assigned with a unique lot number that can be tracked throughout the entire production process all the way down to the incoming raw materials initially supplied for the membrane manufacture. As both the membrane production process and the subsequent filter cartridge assembly and final packaging are done at one factory site, all manufacturing steps can be exactly traced in the unlikely event of complaint. This lot traceability is thus identical to product traceability implemented by the food and beverage industry.

During incoming goods inspection of the prefilter and membrane filter cartridges as the final user, their respective product numbers, the quantity of filters and their unique lot numbers are recorded at the bottling plant. When the filter cartridges are installed in housings, their specific lot numbers and date of installation are logged in the process documentation files. In many plants, the last membrane filtration stage upstream of bottling is additionally defined as a critical control point according to the HACCP concepts. Thus, the process sequences and traceable lot numbers of the filter cartridges used must be documented in compliance with the pertinent standards.

To guarantee the protection of food & beverage products during several manufacturing steps, filtration is a necessary process step in order to remove contaminants or particles, which can influence the quality of the product a lot. Therefore, a filtration step can ensure the physical, chemical and microbiological safety.

Physical safety means, that there are no particles in the product that could injure the customer. A product is chemical safe, when it is free of chemical contaminants like cleaning agents or other food plants remaining in the product.

The most important aspect of filtration is to control the microbiological quality. Bioburden reduction or the sterilization of a product can be achieved by choosing the right membrane pore size for your filtration process.

Product validation compromises the systematic testing of essential production steps and equipment in the production departments, including testing and inspection of food and beverage 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 procedure.

We have compiled this validation guide so users of Aquasart® Plus XL filter cartridges can plan, implement and document their own validation procedures.

1.1 cGMP Quality Assurance from Sartorius

Consistent high quality of Sartorius Membrane Filters and Filter Cartridges is assured by careful selection of the raw materials, well-planned and validated production technologies and an exceptionally efficient Quality Assurance Department, all of which results in high batch-to-batch reproducibility. The test procedures used are based both on external standard methods and on in-house methods which are the result of Sartorius' experience over the past 60 years.

1.2 Quality Assurance

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

1.3 Prevention of Contamination

Aquasart® Plus XL Filter Cartridges are sealed in protective plastic bags in a controlled production area. During production Aquasart® Plus XL Filter Cartridges are heat treated with steam and dried to reliably prevent microbial growth, and thus rule out the possibility of pyrogen synthesis during shipping and storage.

1.4 Complete Traceability

The pore size, type and lot number are printed on the label of the protective plastic bag and on the label of the box in which the cartridge is packed. In addition, the information about filter type, pore size, lot number and individual number are indicated on the top adapter of the cartridges. The traceable lot number allows convenient retrieval of all data complied on the materials used, production steps and QC tests.

1.5 Quality Management Systems

Sartorius Stedim Biotech implemented Quality Management Systems to assure consistent high quality of Membrane Filters and Filter Elements.

Exemplary Quality Systems Certificates:
- Quality Management System ISO 9001

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

1.6 Test Methods for the Quality Assurance of Aquasart® Plus XL Filter Cartridges

Lot Related Tests 100 % Individual Testing

- Diffusion Value of the Cartridge
- Throughput of the Membrane
- Bacteria Challenge Testing of the Filter Membrane
- Bubble Point Testing only 10%

Routine Testing of Randomly Sampled Filter Cartridges

- Bacteria Challenge Testing
- Flow Rate Testing
- Steam Sterilizability

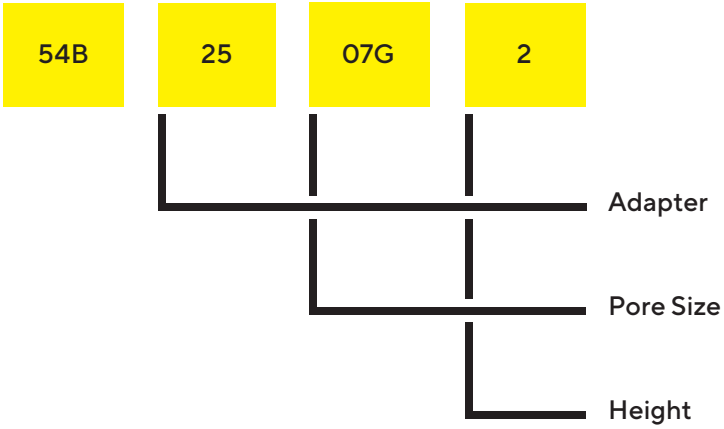
Testing Conducted for the Validation of the Filter Cartridges

- Correlation of Diffusion and Bubble Point Values with the HIMA Bacteria Challenge Tests
- Water Flow Rates
- Temperature and Pressure Resistance
- Sterilizability In-Line Steam Sterilization
- Evaluation of Integrity Test Values After Long Term Storage
- Test according the EU regulation 10/2011

2. Technical Specifications

2.1 Type and Part Number Overview

2.1.1 Cartridges



Explanation

54B
Aquasart® Plus XL, double layer PES membrane filter

Adapter
25 S-adapter top, locking bayonet adapter with 226 double O-ring bottom
28 S-adapter top, locking bayonet adapter with 222 double O-ring bottom

Pore Size
07aG 0.2 µm final membrane

Height	Filtration Area
2	20" 1.6 m²|17.2 ft²
3	30" 2.4 m²|25.8 ft²

2.2 Filter Material

Hydrophilic highly asymmetric; heterogeneous double layer Polyethersulfone membrane filters, with the upstream filter membrane having a larger pore size than the final membrane.

2.3 Mechanism of Filtration

The retention of particles and microorganisms is achieved by a sieving mechanism through the polyethersulfone filter membrane. The throughput is enhanced through the use of fractionated filter membrane combinations where the two membranes have different retention ratings.

2.4 Pore Size Combinations

0.8 µm + 0.2 µm

2.5 Materials of Construction

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.

Upstream Support Layer:
Polypropylene

Filter Membrane:
Polyethersulfone, double layer

Downstream Support:
Polypropylene

Outer Cage:
Polypropylene

Inner Core:
Polypropylene

Endcaps:
Polypropylene

O-rings|Gaskets:
Silicone

2.6 Fiber Release

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

All raw materials which are used to produce these filter products are in accordance with the EU regulation 1935/2004/EC or listed in the EU-Directive 2002/72/EC.

2.7 Height and Diameter

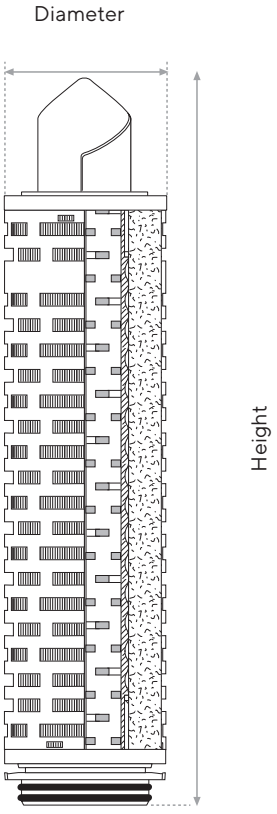
Adapter	Height 10" [mm]	Height 20" [mm]	Height 30" [mm]	Diameter [mm]
25	321	568	817	70
28	328	574	820	70

± 3 mm per 10"
Overall length include adapter and S-top where indicated in the diagram.

2.8 Maximum Allowable Differential Pressure

The maximum allowable differential pressure depends on the temperature at which the pressure is exerted. Maximum allowable differential pressures in the direction of filtration.

Temperature [°C]	20	80	121
Pressure [bar]	5	2	1.5
Pressure [psi]	72.5	29	22



2.9 Wetting the Filters for Integrity Testing

For each filter element, rinse the filters in the direction of flow for 5 minutes with a differential pressure of 0.3 bar|4 psi backpressure 0.5 bar|7 psi in order to assure that the filters have been wetted completely. Generally, filters are wetted with water. In cases where a different wetting medium is used, if the surface tension of the fluid is different from water (> 70 dynes/cm), different integrity test values than indicated on the next page may be required.

2.10 Sterilization

Autoclaving of wet filter cartridges up to a maximum temperature of 121 °C, for 30 minutes, min. 25 Sterilization Cycles
or
In-line steam sterilization of wetted cartridges with a maximum of 1 bar|14.5 psi inlet pressure and 1 bar|14.5 psi outlet pressure (max. Δp= 0.3 bar|5 psi) and up to a maximum temperature of 121 °C.

2.11 Integrity Test Limits

Cartridges

Pore Size of the Final Membrane	Height	TestPressure [bar|psi]	Maximum Diffusion [mL/min]	Minimum Bubble Point [bar|psi]
0.2 µm	20"	1.5|22	50	2.8|40.5
	30"	1.5|22	75	2.8|40.5

3. Flow Rates

Background
Test filter elements are placed into individual Sartorius filter housings. Capsules are directly installed into the piping system, using sanitary flanges. The piping system to and from the filters has an inner diameter of 25 mm|1 inch resp. 15 mm|0.6 inch. The water inlet is opened and the filter housings are completely vented.

The filters are rinsed for approximately 5 minutes at 0.3 bar|4 psi differential pressure to assure complete wetting. The filter cartridges are then integrity tested to assure that only integral filters are tested. The inlet pressure (Pi) is held constant at 1.5 bar|22 psi.

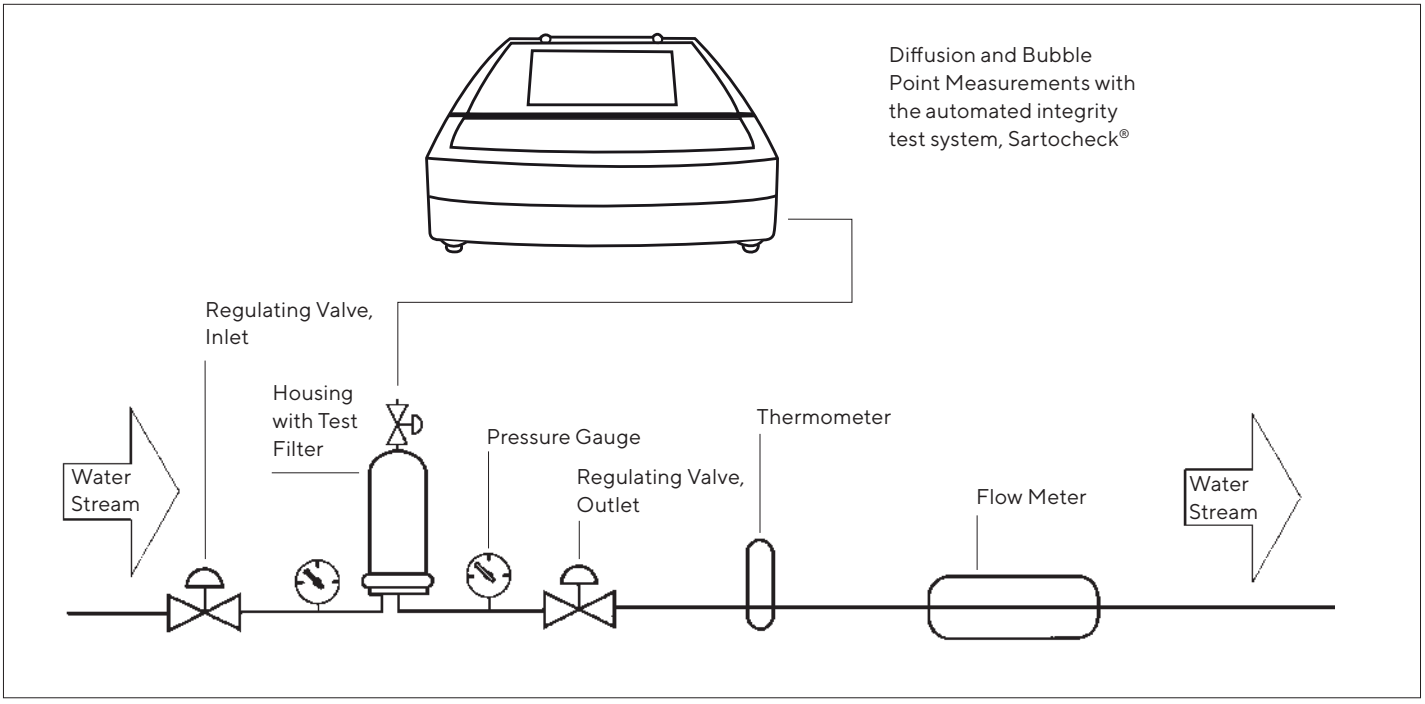
Through the adjustment of valves on the downstream side of the filter housing, the required differential pressure for the test measurements is established. After achieving a constant differential pressure, the flow rate is recorded from the flow meter and the temperature is noted. The flow meter used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

Results
The flow rate curves for water through Aquasart® Plus XL cartridge is displayed on the following page.

Note
The flow rate is strongly influenced by the viscosity of the medium being filtered. For this reason, all flow rate measurements are taken at 20 °C so that the influence of temperature on viscosity is not a factor.

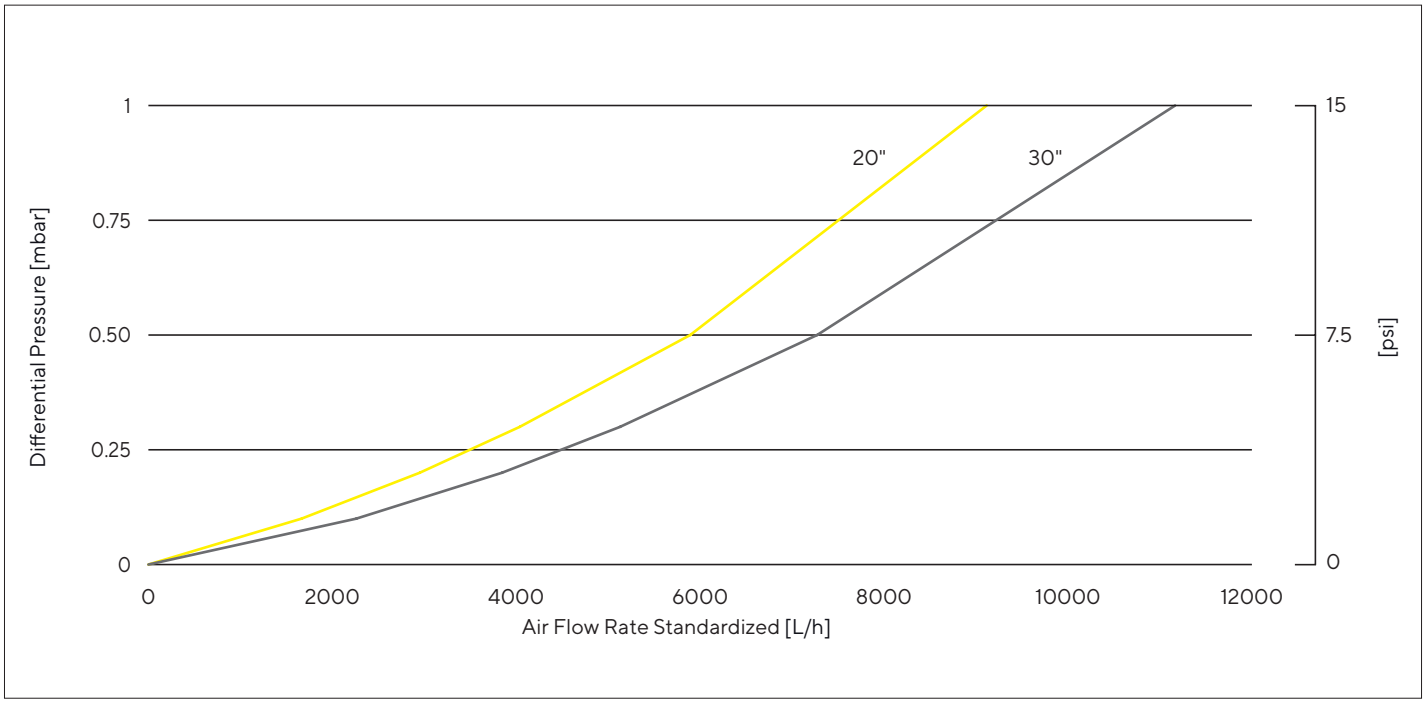
For flow rate measurements of 20" and 30" filter elements, the flow rates reach a point where the geometry of the piping and the filter housing begin to contribute to the overall differential pressure (resistance to flow). At a flow rate of approximately 7000 L/h (120 L/min), the filter membrane surface area is no longer the flow limiting factor, but the housing and piping system begin to have increasing effects on differential pressure. For this reason the flow rates are only recorded at limited differential pressures.

Test Set-up



3.1 Aquasart® Plus XL with 0.2 µm Final Membrane

Water Flow Rates for Cartridges



4. Chemical Stability

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

	Silicone
Acids:	
HCL, 30 %	– –
HCL, 25 %	– –
HNO_3, 10 %	■
HNO_3, 65 %	□
H_2SO_4, conz.	– –
H_2SO_4, 25 %	□
H_3PO_4, 25 %	□
Formic acid, conz.	– –
Formic acid, 25 %	□
Acetic acid, conz.	□
Acetic acid, 25 %	– –
Trichloracetic acid, 25 %	□
Trichloracetic acid, 10 %	□
Citric acid	■
Tartaric acid	■
Lactic acid	■
Bases:	
Ammonia, 10 %	□
Ammonia, 30 %	– –
NAOH, 1 M	□
NAOH, 2.5 M	– –
KOH, 1 M	□

	Silicone
Solvents:	
Acetone	– –
Cyclohexanone	– –
Methylethylketone	– –
Methylisobutyketone	– –
Diethylether	□
Methanol, 98 %	■
Ethanol, 10 %	■
Ethanol, 98 %	■
Isopropanol	■
n-Propanol	■
n-Amylalcohol	■
n-Butanol	■
Glycerol	■
Etyleneglycol	■
Methyleneglycol	■
Dioxane	– –
Tetrahydrofuran	– –
Dimethylsulfoxide	– –
Dimethylformamide	– –
Triethanolamine	□

	Silicone
Miscellanous:	
Aniline	– –
Sodium hypochlorite	□
Benzylalcohol	– –
Phenol, 10 %	– –
Formalin, 30 %	■
Hexane	□
Xylene	– –
Toluene	– –
Benzene	– –
Tetralin	– –
Dekalin	□
Methylenchloride	– –
Chloroform	– –
Carbontetrachloride	– –
Trichloreethylene	– –
Perchloreethylene	– –
Monochlorbenzol	– –
Methylacetate	– –
Ethylacetate	– –
Amylacetate	□
Propylacetate	□
Terpentine	□
H_2O_2, 0.3 %	■
Ammoniumpersulfat, 25 %	■
Sodiumhypochloride, 300 ppm	■
Starch solution	■
Water	■

Legend

■ = Compatible

□ = Limited compatibility depending on concentration, temperature etc.

– – = Not compatible

Test Specifications

7 days contact at 20 °C

Important

Compatibility is influenced by various factors, such as temperature, concentration, etc. If necessary, test the compatibility with the solution you wish to filter before performing the actual filtration run.

5. Integrity Test Limits

5.1 Basis for the Determination of Integrity Test Values

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

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

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

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

Test-Method
Several Aquasart® Plus XL filter cartridges with 0.2 µm pore size membranes, from numerous production lots were tested according to a Bacterial Challenge Test in accordance with the current ASTM F838 Guideline, and DIN 58356, Part 1.

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

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

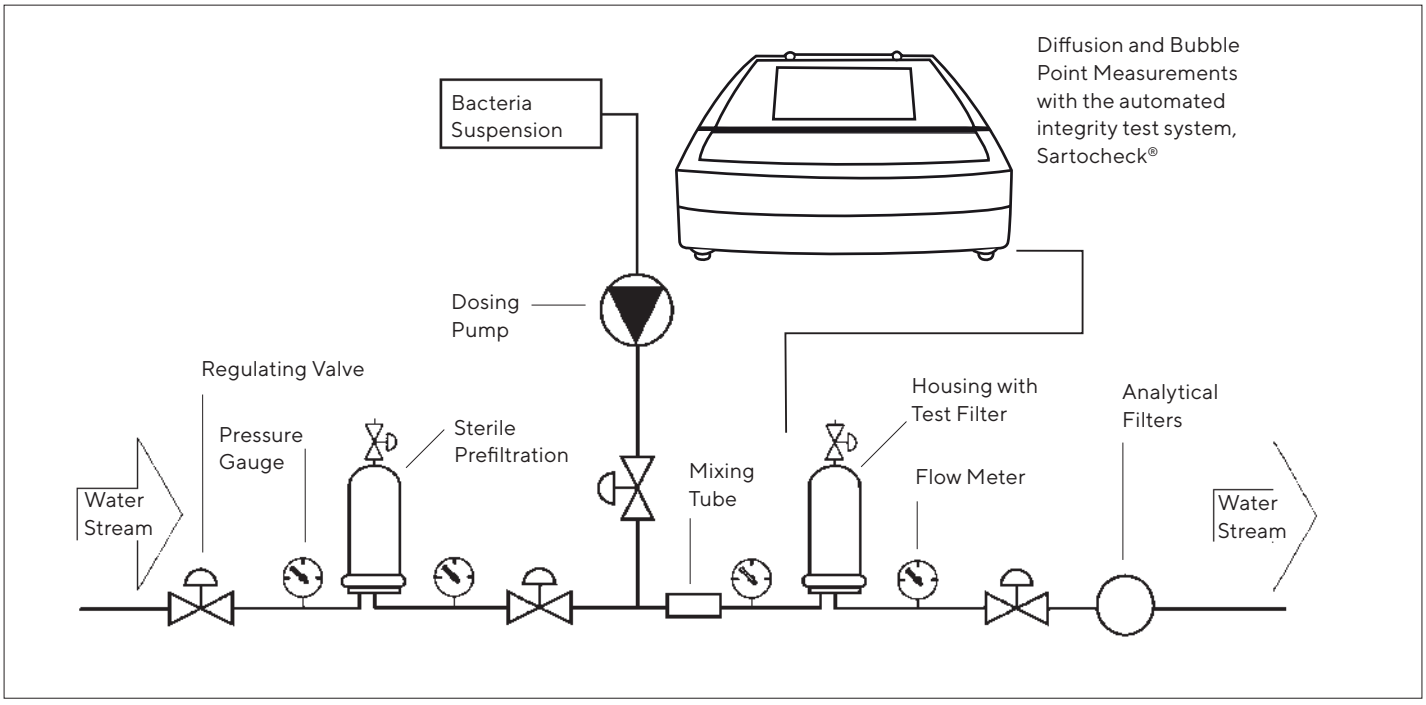
Integrity Test
The Aquasart® Plus XL filter elements were integrity tested by diffusion and bubble point test methods in order to correlate the results of the destructive Bacteria Challenge Test with these non-destructive integrity tests.

The Diffusion Test and the Bubble Point Test are performed utilizing a Sartocheck® automated integrity test unit.

The diffusion values are determined at a test pressure of 1.5 bar|22 psi for 0.2 µm rated filters. For the determination of the bubble point, air pressure is slowly increased on the upstream side of the filter housing by the Sartocheck® integrity tester.

5.2 Bacteria Retention Test

Test Set-up



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

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

Test Procedure

The Aquasart® Plus XL Filter Cartridges are installed and wetted as described in the operating instructions. The filter system is then sterilized.

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

5.3 Diffusion Test Limits for Aquasart® Plus XL Filter 10" Elements, 0.2 µm

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

Lot Number	Diffusion [mL/min]	Bioburden [CFU]*	Filtrate Quality
180035783	12.5	9.1×10^{10}	sterile
180035783	13.2	9.1×10^{10}	sterile
180035783	12.6	9.1×10^{10}	sterile
180035783	12.7	9.1×10^{10}	sterile
180035783	16.1	9.1×10^{10}	sterile
180035883	12.7	9.1×10^{10}	sterile
180035883	12.0	9.1×10^{10}	sterile
180035883	12.7	9.1×10^{10}	sterile
180035883	7.8	9.1×10^{10}	sterile
180035883	7.5	9.1×10^{10}	sterile
190004583	11.8	7.8×10^{10}	sterile
190004583	10.6	7.8×10^{10}	sterile
190004583	10.3	7.8×10^{10}	sterile
190004583	11.8	7.8×10^{10}	sterile
190004583	15.1	7.8×10^{10}	sterile
180035783	7.5	1.68×10^{11}	sterile
180035783	7.2	1.68×10^{11}	sterile
180035783	7.6	1.68×10^{11}	sterile
180035783	7.7	1.68×10^{11}	sterile
180035783	7.1	1.68×10^{11}	sterile
180035883	7.1	1.54×10^{11}	sterile
180035883	6.9	1.54×10^{11}	sterile
180035883	6.7	1.54×10^{11}	sterile
180035883	6.2	1.54×10^{11}	sterile

Lot Number	Diffusion [mL/min]	Bioburden [CFU]*	Filtrate Quality
180035883	6.4	1.54×10^{11}	sterile
190004583	9.1	8.4×10^{10}	sterile
190004583	9.2	8.4×10^{10}	sterile
190004583	9.4	8.4×10^{10}	sterile
190004583	9.4	8.4×10^{10}	sterile
190004583	9.0	8.4×10^{10}	sterile

* CFU = Colony Forming Units

Cartridges 0.2 µm

Conclusion

Aquasart® Plus XL 0.2 µm Filter Cartridges of various lengths have the following maximum allowable diffusion values at a test pressure of 1.5 bar|22 psi at 20 °C:

for a 20" Filter Cartridge:
50 mL/min

for a 30" Filter Cartridge:
75 mL/min

Bubble Point: ≥ 2.8 bar|40.5 psi

Note

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

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

6. Testing According to USP

Test Purpose
The tests for extractable substances and particle release of Aquasart® Plus XL filter elements are performed in dynamic extraction mode. This methodology provides the best representative of actual filtration applications determining levels of extractable substances and particles present in varying filtrate volumes. The samples for all tests are taken after 1, 5 and 10 liters flush volume for standard filter elements.

According to the specifications given in section "Sterile Water for Injection" of the current USP, filtrate samples of Aquasart® Plus XL filter elements are analyzed for Particulate Matter, Oxidizable Substances, pH and conductivity, Ammonia, Sulfate and Chloride. The tests are performed according to the descriptions given in the current USP. The test results obtained are compared to the relevant USP specifications and for Particulate Matter also to the specifications of the European Pharmacopoeia (EP).

6.1 Particle Content of the Filtrate

Purpose
In general, the particle release from the filters should be minimized. For parenteral solutions, the requirements are define in the USP Monographs, which set maximum limits for particle content based on defined particle sizes.

Limits
From the current USP, the following limits have been set as a maximum number of particles per mL of product (in this case, large volume injections for single dose infusion):

25 particles/mL ≥ 10 µm
3 particles/mL ≥ 25 µm

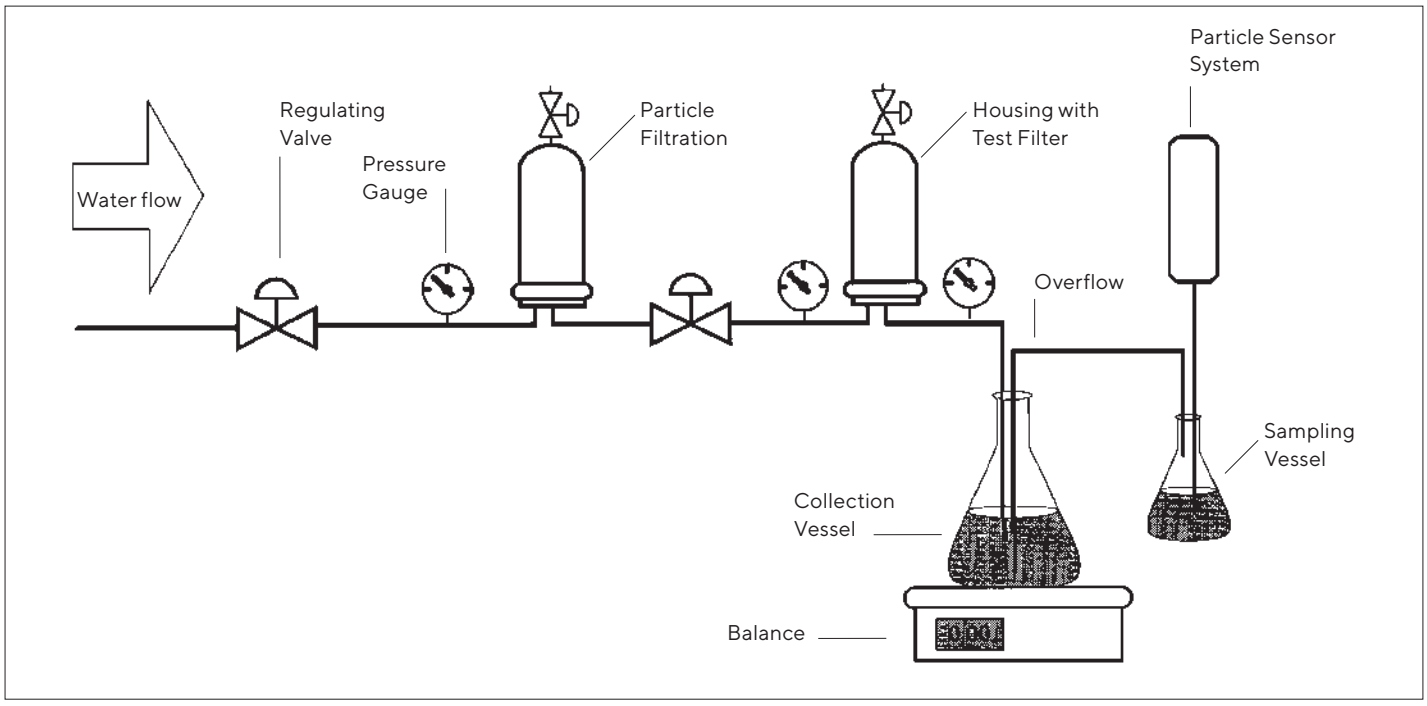
Test Procedure
Two standard filter elements from three production lots were wetted and autoclaved prior to being tested. The wetting of the filters is achieved through a static soak, not through fluid flow, in order to avoid removing potential particles that may be present. As a wetting and flushing medium, Reverse Osmosis (RO) generated water is used during the testing. An integrity test is performed to assure that only integral filters are used for this testing. In order to generate particle-free water, the water is first filtered through two 0.2 µm membrane filter cartridges. This water is used to flush the filter housing and all contact surface to remove surface particles prior to testing. The filter elements that have been autoclaved and integrity tested are then installed in the pre-rinsed system.

After attachment of the collection vessel that was also pre-rinsed with the filtered water, the inlet valve is opened and the water is filtered through the test filter elements. The samples for all tests are taken after 1, 5 and 10 liters flush volume for all elements tested. The balance is used to determine gravimetrically when a sample should be taken. Particle analysis of the samples is conducted utilizing a particle sensor system. This system consists of a Pacific Scientific Hiac Royco sampler (Model 3000 SOS, serial No. 93023007), in which a particle sensor (Model HRLD 150, serial No. 9208-012) is installed to analyse the filtrate in accordance with the current USP requirements. The system also incorporates a particle counter (Model 8000, serial No. 91078805). The particle sensor system is calibrated twice a year in line with USP Standards.

A sampling vessel is placed into the sampler. The sample medium is drawn in through a glass bulb and a sample volume of 25 mL/min is set exactly on the sampler. The particle count begins automatically when the sampler is started. The average particle value is calculated from a total of six measurements, 25 mL each.

Summary of Results
In order to have an overview of the particle content of filtrates of the tested filters the following table contains the average values for the test performed. These averages are for the three different production lots previously noted.

Test Set-up



Cartridges

Particle Size [µm]	Particle Count per mL after 1 L Flush	Particle Count per mL after 5 L Flush	Particle Count per mL after 10 L Flush	Limits according to USP
≥ 10	0	0	0	≥ 25
≥ 25	0	0	0	≥ 3

Conclusion

The table above shows that for Aquasart® Plus XL filter, the requirements of the current USP and BP for particle content are met in the first liter of rinse volume. This shows that the initial filtrate conforms to these standards, as it is not technically feasible to test the first mL of solution filtered. Accordingly, the Aquasart® Plus XL do not have to be rinsed prior to being able to produce a filtrate that conforms with the current USP and EP for particle content.

6.2 Determination of Oxidizable Substances of the Filtrate

Test Procedure
Two Standard Aquasart® Plus XL filter elements from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

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

Then 0.2 mL of 0.1 N potassium permanganate were added and the solution was boiled for 5 minutes. If a precipitate forms, it is cooled to room temperature. If the precipitate remains its color after cooling to room temperature, the test sample and respectively the tested filter element meets the USP specifications for oxidizable substances.

Test Results of the Determination of Oxidizability Substances of the Filtrate

Blank	passed		
Lot Number	**Test Results after 1 L Flush**	**Test Results after 5 L Flush**	**Test Results after 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

Conclusion
The Aquasart® Plus XL filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for Oxidizable Substances for "Sterile Water for Injection".

6.3 Determination of pH Values and Conductivity of the Filtrate

Test Procedure
Two Aquasart® Plus XL filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

Conductivity and pH value of the samples were measured using appropriate calibrated pH meters and conductivity meters according to the USP regulations.

Test Limits
The following table lists the limits for pH and conductivity given by the current USP in conjunction with "Sterile Purified Water" and the filters were tested in the specified pH range of 5 to 7.

The relationship between the pH value and the maximum allowable conductivity for "Sterile Water for Injection" according to the current USP is:

pH Value	Maximum Allowable Conductivity [µS/cm]
5	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8–6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

6.3.1 Test Results for the pH Values

Blank	pH 5.8		
Lot Number	**pH after 1 L Flush**	**pH after 5 L Flush**	**pH after 10 L Flush**
8044983	5.6	5.7	5.8
8045083	5.7	5.8	5.8
8045183	5.7	5.7	5.7

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

6.3.2 Test Results for the Conductivity

Blank	0.8 µS/cm		
Lot Number	**Conductivity after 1 L Flush [µS/cm]**	**Conductivity after 5 L Flush [µS/cm]**	**Conductivity after 10 L Flush [µS/cm]**
8044983	0.9	0.8	0.8
8045083	0.9	0.8	0.8
8045183	0.9	0.8	0.8

Conclusion
Both parameters, pH and pH dependent conductivity of the filtrate, when filtering with the Aquasart® Plus XL filter elements are well below the limit requirements of the current USP.

6.4 Determination of Chloride, Sulfate, Ammonia and Calcium in the Filtrate

6.4.1 Determination of Chloride

Test Procedure
Two Aquasart® Plus XL filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and 20 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 20 mL samples 5 drops of nitric acid and 1 mL of silver nitrate are added and gently mixed. If the turbidity formed within 10 minutes is below the control reagent consisting of 20 mL of high purity water containing 10 µg of Chloride the test is passed.

Test Results for Chloride

Blank	**passed**		
Lot Number	**Test Results after 1 L Flush**	**Test Results after 5 L Flush**	**Test Results after 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

Conclusion
Aquasart® Plus XL standard filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for Chloride for "Sterile Water for Injection".

6.4.2 Determination of Sulfate

Test Procedure

Two Aquasart® Plus XL filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

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

Test Results for Sulfate

Blank	passed		
Lot Number	**Test Results after 1 L Flush**	**Test Results after 5 L Flush**	**Test Results after 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

Conclusion

Aquasart® Plus XL filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for Sulfate for "Sterile Water for Injection".

6.4.3 Determination of Ammonia

Test Procedure
Two Aquasart® Plus XL filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 100 mL samples 2 mL of alkaline mercuric-potassium iodide is added. If any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in High Purity Water the test is passed.

Test Results for Ammonia

Blank	passed		
Lot Number	**Test Results after 1 L Flush**	**Test Results after 5 L Flush**	**Test Results after 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

Conclusion
Aquasart® Plus XL filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for Ammonia for "Sterile Water for Injection".

6.4.4 Determination of Calcium

Test Procedure
Two Aquasart® Plus XL filter from three different production lots were wetted (by soaking) and autoclaved. After installation into the filter housings the filter elements were flushed with Water for Injection and 100 mL samples were taken after 1, 5 and 10 L flush volumes for standard filter elements.

To the 100 mL samples 2 mL of alkaline mercuric-potassium iodide is added. If any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in High Purity Water the test is passed.

Test Results for Calcium

Blank	passed		
Lot Number	**Test Results after 1 L Flush**	**Test Results after 5 L Flush**	**Test Results after 10 L Flush**
8044983	passed	passed	passed
8045083	passed	passed	passed
8045183	passed	passed	passed

Conclusion
Aquasart® Plus XL filter produced filtrates that, when measured by this method, were below the requirements set by the current USP Limits for Calcium for "Sterile Water for Injection".

6.5 Biosafety

Purpose
These tests are to determine that all components used in the manufacture of Aquasart® Plus XL filter elements are biosafe and meet or exceed the requirements for the current USP Class VI Plastics Tests.

Test Method and Results
Aquasart® Plus XL filter 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 (Extraction at 121 °C)
- Systemic Injection test
- Implantation test (7 days)

Quality Assurance Certificate

AQUASART Plus XL

Order no.	54B2507G2
Use before	11 / 2024
Pore size	0.2 µm
Lot no.	SAMPLE.

This document certifies that the designated product was manufactured by Sartorius in conformance with applicable Current 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 is registered with the Food and Drug Administration (FDA) under the Drug Master File No. 5967.

Complete filter documentation: All data concerning materials used and production data are documented and accessible under the individual batch number which is embossed on every filter element.

Integrity test values: Each membrane filter element has been individually tested for integrity by means of diffusion and each lot randomly by bubble point testing. These tests have been performed according to the procedures stated in the corresponding SOP.

This product meets the requirements laid down in the Framework Regulation (EC) No 1935/2004 and Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.

For best filtration results, please follow the instructions given in the "Directions for Use".

2019-11-27

Date

QA released

sartorius stedim

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