QRM Handbook
Conducting FMEA Using the Sartocheck® 5 Plus Filter Tester

Valid for software version 2.3.1

Contents

Introduction

Failure Modes and Effects Analysis (FMEA) is commonly used in a variety of industries for Risk Management, where simple quantification of risk is insufficient, and where identification of root causes of risks and means of mitigation are paramount. FMEA is one of the most useful and effective tools for developing designs, processes and services. The goal of FMEA is to align the risks as closely as possible with the source. This enables the determination of the root cause of the risk, and allows the selection of ways to detect the occurrence of a particular failure and | or to find options to prevent or mitigate the effects of a particular failure. Good FMEA methodology allows for the identification and documentation of potential system failures of a system and their resulting effects. It also allows for the assessment of the potential failures to determine actions that would reduce severity, reduce occurrence, and increase detection.

1. Purpose and Scope

The purpose of this FMEA is to improve the Quality Risk Management of integrity testing for compliance with ICH Q9 and the new Annex1 draft as the request for QRM has been greatly enhanced in the latter as compared to the previous version. More specifically, this FMEA focuses on:

Identifying possible conditions that could generate false passed or false failed filter integrity test results, where existing laid-down controls or measures require further strengthening by e.g. training, SOPs or optional hardware.

The following aspects are considered for the evaluation of the risk:

- The Sartocheck® 5 Plus Filter Tester
- Environmental conditions
- The setup of filters being tested and their preparation

Analyzing the risks for the operator when using the Sartocheck® 5 Plus for integrity testing of sterilizing grade filters in the manufacturing process, when cleaning the Sartocheck® 5 Plus Filter Tester internally and externally and when moving the Sartocheck® 5 Plus Filter Tester from one location to another.

Analyzing the risk for momentarily of irreversibly damaging the Sartocheck® 5 Plus Filter Tester that may or may not impact the reliability of the test result.

This FMEA is a comprehensive generic documentation and should be used as a basis for a user-specific FMEA. The user-specific FMEA should provide evidence to assure that the manufacturing process is capable of producing the quality level required to meet pre-determined specifications when using the Sartocheck® 5 Plus Filter Tester for integrity testing of filters.

In addition this documentation also includes directives and concrete examples for setting the program-specific safety parameters that will prevent false passed and false failed test results.

1.1 Responsibility

This FMEA has been produced by Sartorius Stedim Biotech and may be used as the basis for user-specific quality risk but it is not designed to be user-specific. Sartorius Stedim Biotech may not be held responsible for misinterpretation or translation errors.

It is the responsibility of the concerned end-user to review the document and ask for clarification if needed.

1.2 Documentation Updates Related to Software Releases

When new software versions are released, we will update this documentation. The new version will be communicated together with the software upgrade information. As new functionalities are implemented, this may be of high interest.

1.3 Specific Risk Assessments Related to Software Upgrades

The validation binder of the Sartocheck® 5 is updated for each new software release. The validation binder contains the recapitulative changes for all the previous software versions, each change being classified as "announcement", "minor change" or "major change". Based on the classification of changes, the risk assessment conclusion advises if a re-qualification is recommended or not.

Add-on features typically do not require a re-qualification of already qualified features.

Add-on features can typically be qualified by performance qualification.

2. Documentation Authors

This Failure Mode Effects Analysis was elaborated by Sartorius Stedim Biotech Product Management, Research and Development, and by Application Support.

3. System Description

The Sartocheck® 5 Plus Filter Tester (reference 26787---FT---P) is a filter integrity tester. It was exclusively developed, constructed, built exclusively and commercial purpose of conducting filter integrity tests in pharmaceutical and biotechnological production and laboratory operations and leak testing of rigid vessels.

The Sartocheck® 5 Plus Filter Tester has been designed for use in or with explosive atmospheres according to the following standards:

- Sartocheck® 5 Plus Filter Tester without Accessory Kit for External Venting:
  - IECEx, ATEX Zone 2, Groupe II-B
  - FM (USA) Class 1 Zone 2 Group II-B*

- Sartocheck® 5 Plus Filter Tester Accessory Kit for External Venting:
  - IECEx, ATEX Zone 1 Group II-B
  - FM (USA) Class 1, Div. 1, Zone 1 Group II-B

* Note that FM (USA) compliance for the device requires a special kit (26787---AK---FM) with additional insulated cable cover.

The Sartocheck® 5 Plus Filter Tester uses compressed gas and electricity and must be handled with the same precautions as all electrical IP64 devices. Operators must also wear protection glasses.

The Sartocheck® 5 Plus Filter Tester is able to perform the following integrity tests:

- Diffusion test (with or without automatic test time)
- Bubble point test (standard or accelerated)
- Combined diffusion (with or without automatic test time) and bubble point test (standard or accelerated)
- Water intrusion test (with or without automatic test time)
- Pressure drop | leak test (also applicable for tanks)

Additionally, it can perform a separate volume measurement. The volume measurement by itself is not an integrity test.

The Sartocheck® 5 Plus Filter Testers requires operating at temperatures between 0 °C to +40 °C at a relative humidity in compliance to IEC 61010-1. When operating outside standard room temperature e.g. in a cold room specific integrity test parameters must be validated.

This FMEA does not cover intended misuse of the Sartocheck® 5 Plus Filter Tester.

The Sartocheck® 5 Plus Filter Tester has not been designed to test singl se bags.
For testing of single-use bags, please refer to the Sartocheck® 4 Plus Bag Tester and Bag Tester Multi-Unit.

3.1 Additional Information

- More detailed information about specific topics such as the impact from temperature can be found in published articles and | or guidance documents. Suggestions for additional reading can be found at "References and Recommended Reading".

- Critical instruments used for lot release must be qualified before use. The Sartocheck® 5 Plus Filter Tester can be qualified on site by certified Sartorius Service staff using established IQ OQ protocols. A water marked copy of these protocols can be obtained for revision by QA.
- PQ guidelines can be provided upon request.
- Sartorius Stedim will make updates of this Quality Risk Management document as new QRM related software features become available.

4. Risk Management Approach

This risk management approach has been developed as per principle of Failure Mode and Effects Analysis (FMEA). FMEA consists of the identification of hazards and the analysis and evaluation of the risk associated with the exposure to those unwanted events.

When the risk in question is well defined, an appropriate risk assessment tool and the type of information that will address the risk question will be more readily identifiable.

The following questions have been answered in the FMEA.

1. What might go wrong? (§4.1. Risk Identification | Unwanted Event)
2. What are the consequences? (§4.2. Severity | Impact)
3. What is the likelihood that the unwanted event will occur? (§4.3. Probability)
4. What is the likelihood of detecting the unwanted event? (§4.4. Detectability)

Linerar two to three-step scoring scales have been selected for severity, probability and detectability (1; 3; 5; 8 and 10). The two to three-step-value approach allows more distinction between ratings but is not as emphasized as nonlinear scoring scale sometimes used for the severity criteria (e.g. 1; 4; 9; 16; 25)

4.1 Risk Identification | Unwanted Event

We have based the risk identification matrix (see § 5 Risk Analysis & Risk Assessment matrix) on qualified claims from pharmaceutical customers regardless of whether the claims were due to inappropriate training of the users or not. We have also taken into account the extensive field experience of Sartorius Stedim Application Specialists.

4.2 Severity | Impact

The severity assesses how serious the effects would be if the unwanted event occurred, regardless of the probability. The impact may be felt by following "stakeholders":
- The integrity test result (reliability – false passed or false failed)
- The functionality of the integrity tester
- The data storage integrity
- The environment (e.g. particle release)
- The operator (safety | health issue)

Value	Description	Criteria
1	Very low	No impact on any of the stake holders. Irrelevant in general.
3	Low	Slight impact on the SC5 or on the reliability of the test value. No impact on the environment or on the operator.
5	Moderate	Moderate impact on the SC5 or the reliability of the test value or the data storage or the clean room air quality. No impact on the operator.
8	High	Strong impact on the SC5 and | or strong impact on the reliability of the test value and | or on the data storage or on the clean room air quality or slight health impact on the operator or the patient.
10	Very high	Serious damage on the SC5 and | or very high impact on the reliability of the test value and | or on the data storage or life threatening danger for the operator or the patient.

4.3 Probability

In general, the probability of occurrence evaluates the frequency that potential risk(s) will occur for a given system or situation. The probability score is rated against the probability that the effect occurs as a result of a failure mode.

Value	Description	Criteria
1	Very low	The unwanted event has not been seen or is very unlikely to happen.
3	Low	The unwanted event has been claimed in the past. In some cases it was due to inappropriate training of the operator.
5	Moderate	The unwanted event has been claimed several times but would have been avoided with appropriate training of the operator and | or the use of appropriate accessories.
8	High	The unwanted event may happen even if the operator has been appropriately trained and even if appropriate accessories are used.
10	Very high	The unwanted event will most likely happen sooner or later even if the operator has been appropriately trained and even if optional accessories are used.

4.4 Detectability

In general, detectability is the probability of the failure being detected before the impact of the failure to the system or process being evaluated is detected. The detectability score is rated against the ability to detect the effect of the failure mode or the ability to detect the failure mode itself.

Value	Description	Criteria
1	Very high	The SC5 will automatically detect the unwanted event and | or the operator will detect it.
3	High	The SC5 will automatically detect the unwanted event if it is significant enough and | or the operator may detect it.
5	Moderate	The SC5 may automatically detect the unwanted event or the operator | QA may detect it if he | she has been appropriately trained.
8	Low	The SC5 will not detect the unwanted event. The operator | QA may detect the unwanted event if he | she has been trained appropriately.
10	Very low	Neither the SC5 nor the operator | QA will detect the unwanted event.

4.5 Risk Score

The composite risk score for each unit operation step is the product of its three individual component ratings: severity, probability, and detectability. This composite risk is called a risk priority number (RPN).

$$RPN = S \times P \times D$$

The RPN is not absolute and should be considered in context with other factors that influence the reliability of the integrity test outside the scope of this evaluation. The RPN provides a relative priority for taking action: the bigger the RPN, the more important to address the corresponding failure being assessed. The risk ranking system includes severity, occurrence and detection.

4.6 Acceptability of Risk

If the RPN is higher than 100, we considered that measures should be taken to reduce risk. Recommended actions are given in the Risk Analysis Matrix following. The recommended actions should not be seen as the only way to reduce risk, but rather as a minimum recommendation.

For lower risks, there are also recommendations for general improvements of the integrity testing process.

	RPN	Action
Low	< 40	No mandatory action, but recommendations are given.
Medium	40 ≤ X ≤ 100	The FMEA team should decide if additional action is required, but recommendations are given.
High	> 100	Actions have to be defined to reduce the RPN. Recommendations are given.

Remark: We have used a two-to three-step value approach for severity, probability and detectability. Other scales (e.g. 1; 4; 9; 16; 25) or letter scales (e.g. A – J) may also be used. The end-user should decide what is the most appropriate for their quality system.

5. Risk Analysis Matrix

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
1a	Touch screen.	Failure of the touch screen (non-reacting).	**10.** All functions of the SC5+ are executed from the touch screen or remotely during automation. Data entry may also be done using the optional barcode reader. If the screen breaks, the device could theoretically still work remotely but it would be impossible to see the pressure status of the device. The device should therefore not be used. The screen may be changed by Sartorius Service and is available off the shelf locally.	**1.** The screen is very unlikely to break as long as the device operates within the predefined temperature range 0 – 40 °C. The use of sharp objects would not literally break the screen even if scratches would occur. It could reduce the regional reactivity however.	**1.** A non-working screen would be detected as soon as the device is to be used.	**10.**	Yes.	Only work within the predefined temperature range. Do not use sharp objects to press the touch screen and do not manipulate heavy objects above the screen.
1b	Touch screen.	Breaking the screen.	**10.** If the screen breaks due to e.g. a sharp or a heavy object falling on it the device must not be used. The screen may be changed by Sartorius Service.	**1.** The screen is made of thermally toughened glass DIN EN 12150-1; IEC 60068-2-75 Breaking the glass requires a significant impact e.g., a stainless steel part e.g. a filter housing.	**1.** A broken screen would be detected immediately.	**10.**	Yes.	Do not manipulate heavy objects above the screen. Subscribe to a service contract.
2	Power supply.	Accidentally high voltage supply.	**3.** The SC5+ resists to 265V. Two fuses protect the internal parts from being affected by even higher voltage. The fuses do not protect against lightning.	**1.** Very low.	**1.** The fuses break and have to be changed before being used again.	**3.**	Yes.	Put spare fuses on stock if you have experienced high voltage supply in your production facility.
3	Water.	Water splash on the unit.	**1.** The SC5+ is IP64. As long as the SC5+ is not flooded, there is no significant impact.	**10.** Water projections may happen on a regular basis as water is used for filter wetting.	**1.** Water can be spotted on the surface.	**10.**	Yes.	Use the SC5+ on a flat surface where the water may not accumulate to flood the device from below.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
4a	Pressure supply (too low).	Too low pressure supply.	**1.** The SC5+ must be fed by at least 4 barg or "test pressure + 500 mbar", whichever is higher all through the test sequence. If the pressure falls below during the test, an explicit error message is generated so there is no risk for false passed nor false failed test results related to the pressure supply. The pressure is required for the internal valves to be leak-proof.	**5.** Generally, the pressurized air and the nitrogen are at least 5 barg. We receive rare but regular reports about accidentally too low pressure supply.	**1.** The SC5+ is equipped with a pressure sensor on the inlet. The detection is automatic and instant.	**5.**	Yes.	Make sure no additional equipment requiring excessive amounts of compressed gas is used in parallel with the SC5+. Do not switch off the pressure supply while operating.
4b	Pressure supply (too high).	Too high pressure supply (Above 8 barg, below 12 barg).	**3.** The SC5+ can be fed with up to 8 barg. The internal pneumatics are designed for up to 12 barg. If the pressure supply is > 12 barg, a safety valve inside the unit opens up automatically.	**1.** Generally, the pressurized air and the nitrogen are limited to 7 barg.	**1.** The SC5+ is equipped with a pressure sensor on the inlet. The detection is automatic and instant. If the device is exposed to high pressure when being switched off, it is not detectable until the device, is switched on. In that case the self-test in the beginning of the test will verify if the device has been affected.	**3.**	Yes.	Do not supply higher pressure than 8 barg.
4c	Pressure supply (much too high).	Extreme pressure, beyond 12 barg.	**10.** The internal pneumatics are designed for 12 barg. If the pressure supply is even higher, a safety valve inside the unit opens up automatically. Extreme pressure may cause damage.	**1.** Generally, the pressurized air and the nitrogen are limited to 7 barg.	**1.** The SC5+ is equipped with a pressure sensor on the inlet. The detection is automatic and instant. If the device is exposed to high pressure when being switched off, it is not detectable until the device is again switched on. In that case the self-test will verify if the device has been affected.	**10.**	Yes.	Do not supply higher pressure than 8 barg.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
5a	Type of test gas (N_2 vs air).	Wrong test gas used (nitrogen instead of air) when performing a diffusion test with water or alcohol (e.g. IPA 60 or 70%) as wetting liquid.	**10.** The most common test gases are air and nitrogen (N_2). The test value of the bubble point test and the WIT/WFT are not influenced if using N_2 instead of air. The programmed maximum allowable diffusion value must be adapted due to the different solubility of air and N_2: Diff max N_2 = Diff max air x 0.82 No correction of the max value when using N_2 instead of air may lead to false passed diffusion, test results which is extremely critical.	**3.** Cases have been reported where operators have mixed up air and nitrogen. Questions arise on a regular basis concerning the quantification of the impact.	**10.** The SC5+ cannot detect the type of test gas. The operator must be trained. See comments.	**300.**	No. See comments.	The operator must be trained to understand the eventual impact on the integrity test value. Color coding must exist on gas pressure lines to differentiate between air and nitrogen and other gases. The test gas should be specified in the program data log.
5b	Type of test gas (Air vs N_2).	Wrong test gas used (air instead of nitrogen) when performing a diffusion test with water or alcohol (e.g. IPA 60 or 70%) as wetting liquid.	**8.** The most common test gases are air and nitrogen (N_2). The test value of the bubble point test and the WIT/WFT are not influenced if using air instead of N_2. The programmed maximum allowable diffusion value must be adapted due to the different solubility of air and N_2: Diff max N_2 = Diff maximum air x 0.82 No correction of the max value when using air instead of N_2 may only lead to false failed diffusion test results, generating a deviation, but will not cause the release of a non-sterile drug. In the worst case, it could generate a drug shortage due to unnecessary quarantine.	**3.** Cases have been reported in which operators have mixed up air and nitrogen. Questions arise on a regular basis concerning the quantification of the impact.	**10.** The SC5+ cannot detect the type of test gas. The operator must be trained. See comments.	**240.**	No. See comments.	The operators must be trained to understand the eventual impact on the integrity test value. Color coding must exist on gas pressure lines to differentiate between air and nitrogen and other gases. The test gas should be specified in the program data log.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
6a	Clean water backflow **without** the Accessory Kit for External Venting.	Water entering the pneumatics.	**3.** Clean water will have no functional impact on the internal valves but may generate additional bioburden if repeated.	**3.** Correct handling limits the risk of water getting back into the unit.	**5.** Droplets may be detected in the transparent test tubing.	**45.**	Yes.	Operators must be trained to connect the SC5+ at the highest point of the filter being tested. If water enters the device, it must be dried. As the drying function is not yet available, drying can be achieved by starting a test with an open-end connector.
6b	Clean water backflow **with** the Accessory Kit for External Venting.	Water entering the pneumatics.	**3.** Clean water will have no functional impact on the internal valves but may generate additional bioburden if repeated.	**1.** The use of the Accessory Kit for External Venting 26787---AK---EV (AKEV) prevents efficiently water from flowing back into the SC5+. If the AKEV has been ticked during programming, the program cannot be executed without the AKEV.	**5.** Droplets may be detected in the transparent test tubing.	**15.**	Yes.	Operators should be trained to connect the SC5+ at the highest point of the filter being tested even when using the AKEV. Maximum of 10 different AKEVs can be associated to one SC5+ due to calibration data.
6c	Liquid | product backflow **without** the Accessory Kit for External Venting.	Product entering the pneumatics.	**8.** Product may affect the functionality of the internal valves especially when dried out. Product can also generate cross contamination. Nutrient media will generate microbiological growth and uncontrolled bio-burden inside the pneumatics, which could contaminate filters being tested subsequently to the backflow.	**3.** Correct handling limits the risk of liquid product getting back into the unit. The use of the Accessory Kit for External Venting 26787---AK---EV prevents efficiently liquid, aerosols and other gases from contaminating the device and reduces the probability to 1.	**5.** Droplets may be detected in the transparent test tubing.	**120.**	No. See comments.	The operators must be trained to connect the SC5+ at the highest point. The internal pneumatics of the SC5+ may be cleaned with e.g., 0.5M NaOH using the cleaning program combined with the Accessory Kit for the Cleaning Kit (please look for your region specific reference) available in Q3 2022. A hydrophobic vent filter e.g., Sartofluor, may also be used between the SC5+ and the filter to be tested but must be sized so as not to impact the test value. Request support documentation from Sartorius Stedim.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
6d	Liquid | product back-flow **with** the Accessory Kit for External Venting.	Product entering the pneumatics.	**8.** Product may affect the functionality of the internal valves, especially when dried out. Product can also generate cross contamination. Nutrient media will generate microbiological growth and uncontrolled bio-burden inside the pneumatics, which could contaminate filters being tested subsequently to the back-flow.	**1.** The use of the Accessory Kit for External Venting 26787---AK---EV prevents efficiently liquid, aerosols, and other gases from contaminating the device and the operator. If the AKEV has been ticked during programming, the program cannot be executed without the AKEV.	**5.** Droplets may be detected in the transparent test tubing.	**40.**	Yes. See comments.	The Accessory Kit for External Venting prevents liquid, aerosols, and other gases from contaminating the device. A maximum of 10 different AKEVs can be associated to one SC5+ due to calibration data.
6e	Hazardous product back-flow **without** the Accessory Kit for External Venting.	Hazardous product entering the pneumatics; contamination of the operator and | or device.	**10.** If hazardous product enters the pneumatic, operators may become contaminated as the device depressurizes into the working area and cross-contamination will occur if the unit is used for testing another filter. Connecting the two outlets of the SC5+ to venting tubings (ref. 26787---VT---DE and 26787---VT---SA) and lead them towards an appropriate area prevents the operator from being affected but it does not protect the SC5+ from being contaminated.	**10.** Correct handling limits the risk of liquid product getting back into the unit, but it will not prevent vapors from flowing back.	**5.** Droplets may be detected in the transparent test tubing, but not aerosols and vapors.	**250.**	No. See comments.	A hydrophobic vent filter e.g. Sartofluor may be used between the SC5+ and the filter to be tested to efficiently stop aerosols (see separate publication for aerosol retention MS2 phages), but does not stop hazardous gases. The vent filter must be correctly sized not to impact the test value. Request support documentation from Sartorius Stedim. The internal pneumatics of the SC5+ may be cleaned with e.g. 0.5M NaOH using the cleaning program combined with the cleaning kit (please look for your region specific reference) available in Q3 2022. Please use the AKEV (see hereafter).

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
6f	Hazardous product backflow **with** the Accessory Kit for External Venting.	Hazardous product entering the pneumatics; contamination of the operator and | or the device.	**10.** If hazardous product enters the pneumatic, operators may get contaminated as the device depressurizes into the working area and cross-contamination will happen if the unit is used for testing another filter.	**1.** The use of the Accessory Kit for External Venting 26787---AK---EV prevents liquid, aerosols, and other gases from contaminating the device and the operator. If the AKEV has been ticked during programming the program cannot be executed without the AKEV.	**5.** Droplets may be detected in the transparent test tubing but not aerosols.	**50.**	It depends on the classification of the hazardous product. See comments.	Operators must be trained on using the Accessory Kit for External Venting (AKEV). As the AKEV itself gets contaminated, several AKEVs can be used for one SC5+ e.g., 1 AKEV per product or per filtration line. The AKEV should be equipped with venting tubings in order to direct the off-gas towards an appropriate place (ref 26787---VT---DE and 26787---VT---SA). A maximum of 10 different AKEVs can be associated to one SC5+ due to calibration data. The flow path of the AKEV can be cleaned with the Accessory Kit for cleaning (please look for your region specific reference) available in Q3 2022.
7a	Environmental temperature and wetting liquid (too high).	Too high environmental temperature (stable) above prerequisite conditions.	**5.** An environmental temperature that is too high affects the test result due to test gas solubility, surface tension and viscosity. The impact on the test result will amongst other factors, depend on the difference between the wetting liquid and the environment. If the wetting liquid and the environment are at the same temperature, too high temperature leads to a lower bubble point values and typically higher diffusion intrusion values with the risk for false failed test results. For unstable conditions please refer to 7c.	**3.** This value greatly depends on the training of the operators and QA personnel: 3 = trained staff with cleanroom temperature monitoring 5 = trained staff without cleanroom monitoring | untrained staff with cleanroom monitoring 8 = untrained staff and no cleanroom monitoring.	**3.** The internal temperature verification of the Sartocheck® 5 Plus Filter Tester is designed to verify the temperature of the electronics. Not the environment. In a GMP environment the temperature must be monitored. If the temperature is not monitored, the detectability increases to five.	**45.**	Yes. See comments	The SC5+ working range is from 0 to 40 °C but standard conditions for filter, integrity testing is between 18 and 25 °C and must be stable. The operators and QA personnel must be made aware of the great impact of temperature on the reliability of integrity test results and that performing integrity testing outside prerequisite conditions is a quality deviation.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
7b	Environmental temperature and wetting liquid (too low).	Too low an environmental temperature (stable) below prerequisite conditions.	**10.** Too low environmental temperature affects the test result due to test gas solubility, surface tension and viscosity. This may generate mainly false passed test results, which is the most severe deviation. If the wetting liquid and the environment are at the same temperature, too low a temperature leads to higher bubble point values and typically lower diffusion | intrusion values with the risk for false passed test results. For unstable conditions e.g., a difference between the wetting liquid and the environment, please refer to 7c.	**3.** This value greatly depends on the training of the operators and QA personnel: 3 = trained staff with cleanroom temperature monitoring 5 = trained staff without clean-room monitoring | untrained staff with cleanroom monitoring 8 = untrained staff and no clean-room monitoring	**5.** The internal temperature verification of the Sartocheck® 5 Plus Filter Tester is designed to verify the temperature of the electronics, not the environment. In a GMP environment, the temperature must be monitored.	**150.**	No. See comments.	The SC5+ working range is from 0 to 40 °C, but standard conditions for filter integrity testing is between 18 and 25 °C and must be stable. The operators and QA personnel must be made aware about the great impact of temperature on the reliability of integrity test results and that performing integrity testing outside prerequisite conditions is a quality deviation. Future software upgrade and accessories (environmental temperature sensor) will make it possible to avoid starting a test outside the defined range.
7c	Environmental temperature variations and temperature difference between wetting liquid and environment.	Temperature changes beyond prerequisite conditions.	**10.** Temperature variations affect the test result and may generate false passed and false failed test results. Most integrity testing technologies are based on the perfect gas law (pV= nRT) and are therefore influenced by temperature variations. In addition, temperature variations also impact the size of the housing | capsule by thermal contraction | expansion and may have a direct impact on the pressure.	**5.** The main risks are temperature regulating HVACs, process equipment close by being steamed in place, and, in some cases, direct sunlight. Also, temperature differences between the wetting liquid and the environment will have an impact.	**8.** Even minor local temperature changes of a few K may have a radical impact on the test value. This is often beyond the capacity of clean-room monitoring as this monitoring is not done next to the filter.	**400.**	No. See comments.	Integrity testing must not be performed right below HVACs, close to equipment being steamed, or exposed to direct sunlight. Future software upgrades and accessories (environmental temperature sensor) will make it possible to avoid starting a test outside the defined range and detect temperature fluctuations.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
7d	Too low temperature of the wetting liquid compared to the environment.	Wetting the filter with too cold liquid and running a test without waiting until it has reached environmental temperature.	**10.** During the test, the test gas will be cooled down by the filter housing | capsule. And the housing | capsule will be warmed up by the environment, thus giving an unpredictable setup. Temperature variations affect the test result and may generate false passed and false failed test results. Most integrity testing technologies are based on the perfect gas law (pV=nRT) and are therefore influenced by temperature variations. In addition, temperature variations also impact the size of the housing | capsule by thermal contraction | expansion and may have a direct impact on the pressure. In case the approach of cold wetting liquid in an ambient environment has been validated, this is no longer a hazard.	**5.** This event has been observed regularly even if not frequently. Operators must be made aware of the impact. Longer stabilization times for the integrity testing allows for thermal equilibration. In case the approach of cold wetting liquid in an ambient environment has been validated, this is no longer a hazard.	**8.** Even minor local temperature changes of a few K may have a radical impact on the test value. In case the approach of cold wetting liquid in an ambient environment has been validated, this is no longer a hazard.	**400.**	No. See comments.	Operators and QA personnel must be made aware of the great impact of temperature on the reliability of integrity test results and that performing integrity testing on an unstable setup may generate serious quality deviations. Future software upgrade and accessories (environmental temperature sensor) will offer the possibility to avoid starting a test outside the defined range. Putting it in direct contact to the housing | capsule would improve the detectability. In case the approach of cold wetting liquid in an ambient environment has been validated, this is no longer a hazard. Validation of such conditions are not easy. Please ask for support.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
7e	Too high temperature of the wetting liquid compared to the environment.	Wetting the filter with too warm liquid and running a test without waiting until it has reached environmental temperature.	**10.** During the test, the test gas will be warmed up by the filter housing | capsule, and the housing | capsule will be cooled down by the environment, thus giving an unpredictable setup. Temperature variations affect the test result and may generate false passed and false failed test results. Most integrity testing technologies are based on the perfect gas law (pV=nRT) and are therefore influenced by temperature variations. In addition, temperature variations also impact the size of the housing | capsule by thermal contraction | expansion and may have a direct impact on the pressure. In case the approach of warm wetting liquid in an ambient environment has been validated, this is no longer a hazard.	**5.** This event has been observed regularly even if not frequently. Operators must be made aware about the impact. Longer stabilization times for the integrity testing allows for thermal equilibration. In case the approach of warm wetting liquid in an ambient environment has been validated, this is no longer a hazard.	**8.** Even minor local temperature changes of a few K may have a radical impact on the test value. In case the approach of warm wetting liquid in an ambient environment has been validated this is no longer a hazard.	**400.**	No. See comments.	Operators and QA personnel must be made aware of the great impact of temperature on the reliability of integrity test results and that performing integrity testing on an unstable setup may generate serious quality deviations. Future software upgrade and accessories (environmental temperature sensor) will offer the possibility to avoid starting a test outside the defined range. Putting it in direct contact to the housing | capsule would improve the detectability. In case the approach of cold wetting liquid in an ambient environment has been validated this is no longer a hazard. Validation of such conditions are not easy. Please ask for support.
8a	Wrong test program | test parameters.	Selecting the wrong test program (wrong filter material and | or wrong filter size vs. program).	**10.** Executing the wrong integrity test program may generate false passed and false failed test results if no safety parameters are activated.	**5.** If the operator follows a SOP, the probability is reduced. Nevertheless regular requests for analyzing, the impact from end-users indicate that it happens on a rare but regular basis.	**5.** Without the security parameters on the SC5+, the detectability will depend on the training of the operator and the QA personnel.	**250.**	No.	Train the operators and QA personnel. Use the barcode scanner, Activate the safety parameters: ▪ Min net volume ▪ Max net volume ▪ Min diffusion/WIT/WFT ▪ Min flow at BPend Define and enter the correct values based on a risk assessment. See hereafter.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
8b	Wrong test program | test parameters whilst using the barcode scanner.	Selecting the wrong test program (wrong filter material and | or wrong size vs. program) while using a barcode scanner.	**10.** Executing the wrong integrity test program may generate false passed and false failed test results if no safety parameters are activated.	**3.** Using the barcode scanner does not reduce the risk to zero. Regular requests for analyzing the impact from end-users indicate that it happens on a rare but regular basis.	**5.** Without the security parameters on the SC5+, the detectability will depend on the training of the operator and the QA personnel to react if the net volume is abnormally low.	**150.**	No.	Train the operators and QA personnel. Define barcodes for all programs. Activate the safety parameters: ▪ Min net volume ▪ Max net volume ▪ Min diffusion/WIT/WFT ▪ Min flow at BPend Define and enter the correct values based on a risk assessment. See hereafter.
8c	Wrong test program | test parameters whilst using the safety parameters.	Selecting the wrong test program (wrong filter material and | or wrong size vs. program) and using safety limits.	**10.** Executing the wrong integrity test program may generate false passed and false failed test results if no safety parameters are activated.	**5.** If the operator follows a SOP, the probability is reduced. Nevertheless regular requests for analyzing the impact from end-users indicate that it happens on a rare but regular basis.	**3.** The security parameters on the SC5+ provide good detectability. A net volume outside the net volume span will interrupt the test immediately.	**150.**	No.	Train the operators and QA personnel. Use the barcode scanner to reduce the probability. Make sure safety parameters are appropriately defined based on a risk assessment. See hereafter.
8d	Wrong test program | test parameters whilst using the barcode scanner and the safety parameters.	Selecting the wrong test program (wrong filter material and | or wrong size vs. program) while using a barcode scanner and safety parameters.	**10.** Executing the wrong integrity test program may generate false passed and false failed test results if no safety parameters are activated.	**3.** If the operator follows a SOP, the probability is reduced. Nevertheless regular requests for analyzing, the impact from end-users indicate that it happens on a rare but regular basis.	**3.** The security parameters on the SC5+ provide good detectability. A net volume outside the net volume span will interrupt the test immediately.	**90.**	Yes	Train the operators and QA personnel. Define barcodes for all programs. Make sure safety parameters are appropriately defined based on a risk assessment. See hereafter.
9a	Faulty test set-up.	Test tubing not connected, wrong filter connected, manual | automatic valve closed between the test tubing and the filter, or closing the downstream valve.	**10.** Performing an integrity test on a faulty setup may generate false passed test results if no safety parameters are activated.	**3.** If the operator follows a SOP, the probability is reduced. Nevertheless regular requests for analyzing, the impact from end-users indicate that it happens on a rare but regular basis.	**5.** Without the security parameters on the SC5+, the detectability will depend on the training of the operator and the QA personnel to react if the net volume is abnormally low.	**150.**	No.	Train the operators and QA personnel. Activate the safety parameters: ▪ Min net volume ▪ Max net volume ▪ Min diffusion/WIT/WFT ▪ Min flow at BPend Define and enter the correct values based on a risk assessment. See hereafter.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
9b	Faulty test setup while using the safety parameters.	Test tubing not connected, wrong filter connected, manual | automatic valve closed between the test tubing and the filter, or closing the downstream valve.	**10.** Performing an integrity test on a faulty setup may generate false passed test results if no safety parameters are activated.	**3.** If the operator follows a SOP the probability is reduced. Nevertheless regular requests for analyzing, the impact from end-users indicate that it happens on a rare but regular basis.	**3.** The security parameters on the SC5+ provide good detectability. A net volume outside the net volume span will interrupt the test immediately.	**90.**	Yes.	The Sartocheck® 5 Plus Filter Tester 5 Plus will automatically detect: ▪ Too small systems ▪ Too big systems ▪ Too small filters (based on diffusion/WIT/WFT and BP flow) Define and enter the correct values based on a risk assessment. See hereafter. Future software features (test curve trend analysis) will improve the detectability even further to "1" for an overall RPN of 30.
9c	Faulty volume measurement due to out of boundary conditions | settings.	Under-estimation of the measured net volume.	**10.** Underestimating the net volume will have a direct impact on the calculation of the diffusion | intrusion value and could thereby generate a false passed test result.	**1.** The net volume measure-ment is accurate for all standard applications. Certain combinations of large volumes and low test pressures or large volumes and long test tubings must be avoided. See test limitations.	**10.** In the existing software version, one cannot detect out of boundary conditions. Refer to test limitations.	**100**	Yes, cf. comments	The test limitations are clearly defined and should be verified before using the Sartocheck® 5 Plus Filter Tester. Refer to test limitations.
10a	Too high diffusion or WIT test pressure e.g. due to mixing up of testing parameters from different suppliers.	Testing a filter from vendor "A" with diffusion or WIT parameters from vendor "B".	**8.** Performing a diffusion or intrusion test at too high a pressure is a quality deviation. Nevertheless, it will not generate a false passed. At the worst, it can generate a false failed result which could, in extreme cases, generate drug shortage due to unnecessary quarantine. It is possible to extrapolate linearly downwards and calculate what the diffusion | intrusion would have been at the correct test pressure.	**3.** Regular requests for analyzing the impact from end-users indicate that it happens on a rare but regular basis.	**10.** The SC5+ has not been designed to automatically detect faulty parameters during programming.	**240.**	No.	Make sure to review all test parameters and compare them to official information in technical documentation (e.g., validation guides) before releasing the program. In the meantime, the program can be locked inside the program management of the Sartocheck® 5 Plus Filter Tester, which prevents the program from being used.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
10b	Too low diffusion or WIT test pressure e.g., due to mixing up of testing parameters from different suppliers.	Testing a filter from vendor "B" with diffusion or WIT parameters from vendor "A".	**10.** Performing a diffusion or intrusion test at too low a pressure will generate a serious quality deviation. It may generate a false passed test result, which could generate a serious health risk for the patient. It is not possible to extrapolate linearly upwards and calculate what the diffusion | intrusion would have been at the correct test pressure.	**3.** Regular requests for analyzing the impact from end-users indicate that it happens on a rare but regular basis.	**10.** The SC5+ has not been designed to detect faulty parameters automatically during programming.	**300.**	No.	Make sure to review all test parameters and compare them to official information in technical documentation (e.g., validation guides) before releasing the program. Ask your device | filter supplier to review the parameters. In the meantime, the program can be locked inside the program management of the SC5+, which prevents the program from being used.
11	Pressure sensor calibration offset.	A pressure sensor calibration offset having a direct impact on the test result value.	**5 to 10** (Severity "5" is based on actually experienced sensor calibration offset from the SC4). Assuming there is no experience for the SC5 the severity could be set to "10". Performing an integrity test with a unit having a calibration offset may either overestimate or underestimate the test pressure, but the slope change typically counterbalances the impact. If a calibration offset occurs, the offset is commonly very low and the impact is negligible.	**3.** A calibration offset is unlikely to happen if the unit is used and stored under predefined conditions. Additionally, the self-test on the SC5+ allows to detect a severe pressure reading offset. Experience from the SC4 shows that large offsets are induced mainly by noncompliant adjustments that can easily be avoided by employing qualified personnel e.g., Sartorius Service.	**5.** Every time the SC5+ is started up with inlet pressure connected and in the beginning of every test the pressure reading is compared at one point between the 3 pressure sensors. The SSB Service and App. Spec. use software allowing an immediate estimation of the impact. Please see the corresponding publication in Bioprocess International November 2013 issue.	**75 - 150.**	No.	Regular calibration is fundamental and should be done at least annually by qualified personnel. If the unit has been stored outside its defined temperature and humidity range, or if it has been submitted to severe shock the unit should be recalibrated. The future extended self-test further enhances the detection of drifts.
12a	Particle release beyond ISO7 when printing.	Particle release in the clean room area above maximum allowed level ISO7 when printing.	**8.** Particle release beyond the defined limit in a clean room environment of level ISO7 would be a serious deviation.	**1.** The SC5+ does not have any fan or any other moving parts such an integrated printer that could generate particles. Using the optional external printer (YPD30) with thermal transfer, the particle release is below ISO7.	**10.** This may only be detected with a particle counter.	**80.**	Yes.	The YDP30 printer is conforming to ISO7. Additionally a network printer can be used

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
12b	Particle release in ISO6 or better when printing.	Particle release in the clean-room area above maximum allowed level ISO6.	**10.** Particle release beyond the defined limit in a clean room environment of level ISO6 would be a very serious deviation.	**1.** Particle release above ISO6 will happen only when using the optional printer. This function can be deactivated. Additional venting tubings can be used to lead the depressurized air towards a grey area.	**10.** This may only be detected with a particle counter.	**100.**	No.	Do not use the optional printer in a cleanroom of ISO6 or better. If printing is required, use a network printer at another location. Optional venting tubings can also be used in order to redirect the off-gas outside the critical area.
13	Loss of user credentials.	Losing the password or user identity making it impossible to use the unit.	**8.** Without a valid user ID and password, it is impossible to use the SC5+ as a standalone device. If the administrator still has their user ID and password, they may create new users.	**5.** Set to "5" based on customer feedback from SC4 user IDs. When using LDAP on the SC5+, the probability is reduced to "1".	**1.** The interface clearly indicates if the user ID or the password is wrong. A definable amount of wrong attempts will close the user account.	**40.**	Yes.	If all users lose their passwords, the administrator has to erase and recreate the user accounts on 1 unit. The new user accounts may then be transferred to remaining units. To reduce the probability and the severity, please use LDAP.
14	Battery failure.	Malfunction or loss of data due to battery failure on the MU board.	**8.** If the battery fails all, data will be kept as generated on the flash memory and the internally inaccessible SD card. If the device is switched off, the real-time clock would no longer work.	**1.** The battery has a life time of 10 years and will be changed before the due time by Sartorius Service.	**1.** When running the self-test, the device will indicate the battery is low.	**8.**	Yes.	Regular data back-ups should be performed even if the failure of the battery is unlikely and even if no data would be lost in case of failure.
15	SD card failure.	Malfunction or loss of data due to SD card failure.	**5.** If the SD card fails, there will be an error message the next time it is used by the SC5+ e.g., at the end of a test when the test result should be stored on the SD card. Even if the SD card fails all data will be retained on the flash memory.	**1.** The life of the SD card is estimated at 20 years. No power is required to keep the memory.	**1.** When running the self-test, the device will indicate the SD card is defective.	**5.**	Yes	Regular data back-ups can be performed even if the failure of the SD card is unlikely and even if no data would be lost in the case of failure.
16	Failure of both the flash memory and the SD card.	Malfunction or loss of data.	**10.** If both memories fail at the same time, data will be lost. There will be no additional malfunction such as false passed or false failed test results.	**1.** Both memories failing at the same time is considered extremely unlikely.	**10.** When booting, the device will indicate if the memory is defective. If both memories are defective, the data is already lost.	**100**	Yes because the likelihood of both memories breaking at the same time is extremely low.	Regular data back-ups should be performed even if the failure of both memories is extremely unlikely.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
17	Data overwriting.	Loss of test results due to overwriting the oldest test result file.	**10.** Uncontrolled overwriting of test result files would not be compliant with 21CFR part 11.	**1.** The SC5+ does not allow overwriting of files.	**1.** When the memory is full no more actions can be performed.	**10.**	Yes.	The SC5+ is fully compliant to 21CFR part 11. Its memory has been sized for eight years of intensive use without the need for emptying it. Please see risk n° 18 for more information.
18	Memory full.	Impossibile to run a test due to memory being full.	**3.** If the memory is full it does not impact the reliability of the existing data but it prevents additional tests from being executed.	**5.** If the memory is not emptied it will be full when around 22,900 results have been generated.	**1.** If the memory is full the SC5+ will not allow any additional testing to be done. The memory then has to be emptied.	**15.**	Yes.	The available memory space should be checked on a regular basis in the memory management and the administrator having the required rights should empty the memory after having verified that all data has been backed up.
19	Data virus infection.	Unreliable data and non-compliant lot release.	**10.** A data virus or malware may corrupt data.	**1.** The SC5+ is a closed system with inherent virus resistance. The SC5+ root file system is write-protected, making it impossible for a virus to reside in the system. The major update of the root file system in software version 2.1.1 has even further strengthened the data security aspects of the software.	**1.** The integrity of the root file system is constantly monitored. Corruption of the software would block the booting.	**10.**	Yes.	▪ Processor architecture not in use of mainstream desktop computers ▪ Custom Linux-based OS creates immunity ▪ Write-protected root file system with continuous integrity checking ▪ Disabled inbound connections ▪ Custom system architecture ensures obfuscation of internal components
20	Valve failure on the SC5+.	No de-pressurization of the housing at the end of the test.	**10.** If the operator opens a pressurized housing, there is a risk of serious harm.	**3.** Sticky product coming back into the pneumatic circuit may be the principal cause of blocked valves (see risk n° 6) if they are not cleaned afterwards. If the housing is equipped with self-closing connectors, pressure may remain in the housing if the operator disconnects the SC5+ before the SC5+ has completed the test and the de-pressurization.	**1.** De-pressurization is loud (below 70 dBA). The SC5+ will display an error message if the de-pressurization is not successful. Liquid in the SC5+ can be detected and also avoided.	**30.**	Yes, but operators must be sensitized to the hazard.	The housing to be tested should be equipped with an open connector. If the operator disconnects the unit before the SC5+ has de-pressurized, the housing will be automatically vented. The manual membrane valve (typically used on housings with open connectors) must not be closed before the SC5+ has been disconnected. The operator must use protective glasses.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
21	Unauthorized access.	Access to the SC5+ without the need to log on because of an administrator | user account being active.	**10.** Fraudulent, unauthorized access on the administrator level may result in loss of data or parameter change. Unauthorized access on the user level may result in tests being launched only with the inappropriate user name being printed which gives a lower score.	**1.** The SC5+ has got an auto log-off function that should be activated and set appropriately to a user definable time (1 – 120 min). When an administrator or a user leaves the unit, they should press the "log off" button even if a test is running. If the auto log-off time is set to e.g., three minutes and the test takes five minutes, the auto log-off takes place during the test without interrupting the test.	**3.** All changes (e.g. parameter changes, time and date settings, user account deleting) are recorded in the audit trail. An administrator may access the audit trail at any time the SC5+ is not running a test and verify changes.	**30.**	Yes, but only if the auto log off function is activated and if the administrators have been appropriately trained.	Administrators must be trained to log off after having used the SC5+ so that nobody can access the unit within the laps of time the account is still active (before the auto log off function logs off automatically after e.g., three minutes).
22	Software bugs.	Faulty test evaluation or mis-reading of a test evaluation due to software bugs.	**10.** Faulty test evaluations or mis-reading of a test evaluation due to software bugs could lead to both false passed and false failed test results.	**1.** Virtually all software-based products have bugs. Every software version of the SC5+ is extensively tested by our testers, and the bugs are classified by severity. No software version is released with any critical bugs that could have an impact on the calculation of the test value or an impact on the readability of the value.	**3.** Known software bugs can be identified by cosmetic flaws on the graphical user interface or too long text strings in specific languages.	**30.**	Yes.	Every software release reduces the number of bugs. For optimal user experience and additional features, ask for your upgrade. Each software upgrade comes with a risk assessment which allows your QA to evaluate the impact on your qualified devices in case of upgrade. The upgrade can easily be accomplished with the system administrator or by Sartorius support.
23	Outdated software.	Suboptimal user experience and/or discrepancy between several devices.	3. All software versions have been qualified. Discrepancies between devices may nevertheless be confusing for both the operator and the end-user IT-support.	8. The SC5+ is always delivered with the latest software version. New device will therefore not have the same software version as older devices, unless these latter ones have already been upgraded.	1. The software version can easily be seen by all SC5+ users.	24	Yes.	The device administrator should ask his | her regular Sartorius contact for information on the latest upgrades. Upgrades are included in the price until the release in Q4 2023 and come with a risk assessment. Software upgrades are also announced on the official SC5+ web page.
24	Microbiological contamination building up on the surface of the device.	Contamination of the cleanroom.	8. Dirty surfaces could spread microbiological contaminants in the cleanroom.	1. Cleaning of surfaces is standard in GMP cleanrooms, including all sides of the device. SC5+ can also be used with gloves. Insufficient training of the operators would increase the probability to 3 or 5.	10. Microbiological contaminants would only be detected once the quality deviation is a fact.	80	Yes – Rotational cleaning of the surface should be implemented on all instruments in a GMP environment.	The SC5+ resists to a multitude of cleaning agents cf. data sheet. The SC5+ has also been designed to resist to VHP.

Risk N°	Identification | Component	Unwanted Event | Hazard	Severity	Probability	Detectability	RPN	Risk Accepted	Recommended Actions | Comments
25	Too many conclusive test attempts when no automatic blocking of abusive test attempts is implemented.	The operator performs too many test attempts e.g., more than 3.	**10.** Too many test attempts on a specific filter before having a passed test result may be considered as fraud by regulatory authorities and a sign of bad data integrity.	**5.** If there is no automatic verification of how many test attempts are done, it may be left to the operator to decide what is a conclusive test attempt.	**8.** It is possible to track the number of test attempts in the audit trail, but it is not automatically done.	400	Only if the operator is educated to understand the impact of conducting too many conclusive test attempts and if the QA is trained to count the number of conclusive test attempts.	Update to software version 2.1.1 or higher and implement the automatic blocking of abusive test attempts.
26	Too many conclusive test attempts when automatic blocking of abusive test attempts is implemented.	The operator performs too many test attempts e.g., more than 3.	**10.** Too many test attempts on a specific filter before having a passed test result may be considered as fraud by regulatory authorities and a sign of bad data integrity.	**1.** The automatic detection of abusive test attempts will prevent the operator from doing abusive test attempts. It will also define what a conclusive test attempt is.	**1.** The SC5+ will automatically detect the number of conclusive test attempts and prevent the operator from exceeding the defined number, provided the serial number and the individual number of the filter cartridge is entered appropriately.	10	Yes.	Still makez sure to educate operators about the regulatory impact of too many conclusive test attempts.
27	AU board	Lost calibration data in previous SW versions	10	1	1	10	If this has already been experienced, please upgrade.	The double backup of calibration data reduces the severity to 3 and the improved code reduces the likelihood virtually to zero. Upgrade to SW version 2.3.1 to prevent this from happening.
28	Testing	False failed bubble point due to pressure stabilization a decimal below the BPmin	8	4	1	32	If this has already been experienced frequently, please upgrade.	Certain filters with a highly exponential increase of the bulk-flow right at the BPmin generates a high probability, especially if not perfectly wetted before testing. Upgrade to SW version 2.3.1 to prevent this from happening.

6. The Different Program Specific Safety Values – General Information

The Sartocheck® 5 Plus Filter Tester allows an operator to set so-called "safety values" when the "advanced" mode is activated during programming. The safety values increase the detectability of faulty setups, operator errors, and environmental influences in order to avoid false passed and false failed test results.

6.1 Minimum and Maximum Upstream Net Volume

The Sartocheck® 5 Plus Filter Tester performs automatic upstream net volume measurement during the following integrity test types, unless a fixed value for the net volume has been entered:

- Diffusion
- Bubble point
- Combined diffusion and bubble point
- Water Intrusion

During programming of the above test types in the advanced mode, it is possible to enter a minimum and maximum value and a maximal expected value. The activation of automatic test time (for diffusion, combined diffusion and bubble point, and water intrusion) and | or accelerated test (for bubble point and the combined diffusion and bubble point) does not have any impact on the safety values for volume measurement.

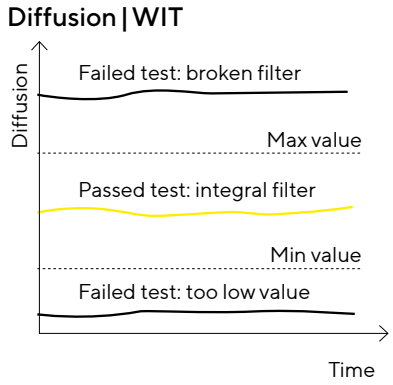
If the measured net volume falls below the minimum or above the maximum, the test is immediately interrupted with an explicit on-screen error and on the optional printout.

Reasons for an upstream net volume to fall outside the specified range:

- The wrong filter size being tested (too large or too small volume)
- The right filter being tested in the opposite direction (too small volume)
- A closed valve between the Sartocheck® 5 Plus Filter Tester and the filter to be tested (too small volume)
- A broken filter, yet correct reference, with a closed downstream valve (too large volume)
- Incorrect setup (e.g., the setup is supposed to contain a protective hydrophobic filter between the Sartocheck® 5 Plus Filter Tester and the filter to be tested, but the operator forgets to install it)

6.2 Minimum Diffusion

During programming of a diffusion test or a combined diffusion and bubble point test in the advanced mode it is possible to enter a minimum expected diffusion value per filter | sample, in addition to the validated maximum diffusion value. The activation of automatic test time (for diffusion or combined diffusion and bubble point) and | or accelerated test (for the combined diffusion and bubble point) does not have any impact on the safety value for minimum diffusion.



If the measured diffusion value is below the min. at the end of the test, the test is considered as failed and an explicit error message is displayed and optionally printed.

The reason for the diffusion to fall below the expected minimum value could be:

- Too small a filter size being tested
- A closed valve between the Sartocheck® 5 Plus Filter Tester and the filter to be tested (would already have been detected by the volume measurement)
- The wrong filter type being tested (e.g. double layer membrane instead of single layer)
- A valve on the downstream side being closed, with pressure building up on the downstream side
- An abnormally clogged membrane
- The filter being tested with the wrong wetting liquid (temperature or type)

6.3 Minimum Water Flow (not taken into account for software version 09-04-01.02.04.191023 – corrected in software version 09-04-01.03.05)

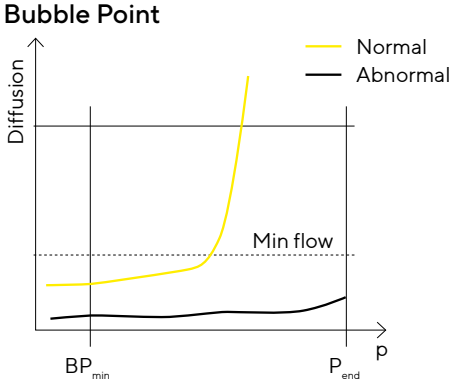
During programming of a Water Intrusion Test in the advanced mode, it is possible to enter a minimum expected water flow value per filter | sample. The activation of automatic test time does not have any impact on the safety value for minimum water flow.

If the measured water flow value is below the minimum at the end of the test, the test is considered as failed and an explicit error message is displayed and, optionally, printed. For illustration, refer to "Minimum Diffusion" above.

The reason for the water flow to fall to fall below the expected minimum value could be:
- Too small a filter size being tested
- A closed valve between the Sartocheck® 5 Plus Filter Tester and the filter to be tested (would already have been detected by the volume measurement)
- The wrong filter type being tested (e.g., double-layer membrane instead of single-layer)
- A broken filter, yet correct reference, with a closed downstream valve (no water flow)
- The filter being tested with water that is too cold

6.4 Minimum Flow at End of Test

During programming of a bubble point test or a combined diffusion and bubble point test, it is possible to enter a minimum flow expected at the end of the test. The activation of automatic test time (for combined diffusion and bubble point) and | or accelerated test (for the bubble point or the combined diffusion and bubble point) does not have any impact on the safety value for minimum flow at end of the test. "End of test" means the end pressure (Pend) that is defined during programming.

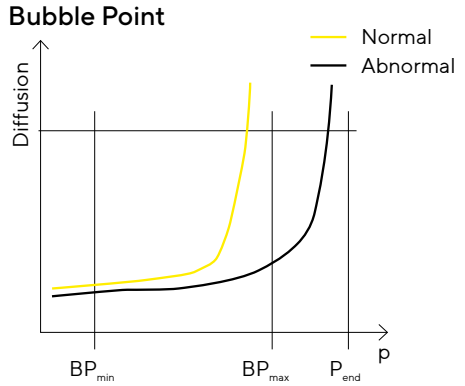


If the measured flow is below the min when "P_{end}" is reached, the test is considered as failed and an explicit error message is displayed, and optionally, printed.

The reasons for the flow to fall below the limit at the end of the test could be:
- The wrong filter type being tested (e.g., too small a pore size thus having a higher BP-value)
- A closed downstream valve, with pressure building up on the downstream side
- An abnormally clogged membrane
- The filter being tested with the wrong type of wetting liquid

6.5 BP_{max} Set to Lower Than P_{end}

During programming of a bubble point test or a combined diffusion and bubble point test, a default BP_{max}-value is set to same pressure as the end pressure. The BP_{max}-value can be set to a lower value than P_{end} with the purpose of detecting abnormally high BP-values.



If the actual BP is detected above BP_{max}, the test is considered as failed and an explicit error message is displayed and optionally printed. Remember that BP_{max} can be deactivated if set to the same value as P_{end}.

Reasons for the BP being abnormally high could be:
- The wrong filter type being tested (e.g., too small a pore size thus having a higher BP-value)
- A closed downstream valve, with pressure building up on the downstream side
- An abnormally clogged membrane
- The filter being tested with the wrong type of wetting liquid (temperature or type)

7. Setting Program-Specific Safety Values

Program-specific safety parameters must be set appropriately in order to allow efficient detection of faulty setups and operator errors. Sartorius Stedim will provide typical water-based values (see the following) but wetting conditions and the type of wetting liquid (e.g., product) may have a great impact on measured diffusion and bubble point values. Setting the safety parameters too tightly could generate unwanted error messages.

To set the safety values correctly it is important to identify the hazard e.g., "Should the minimum and maximum volumes be set to detect the absence of protective back-flow filter in the test setup or in the mixing of two different filter sizes?"

The standing values shown below were achieved by executing a combined diffusion and bubble point test on a limited number of filters (three filters from the same lot of each filter size*) with wetting in between every test with one Sartocheck® 5 Plus Filter Tester.

Sartopore® Platinum Gamma 0.2 µm	Lot n° _ Individual n°	Net Volume (2 m standard test tubing) (mL)			Diffusion Values (mL/min) at 2500 mbar			Bubble Point Values (mbar)		
5495307H7G--SS	839005203_11	192	192	193	1.39	1.37	1.39	4399	4449	4400
	839005203_10	191	194	194	1.44	1.38	1.35	4150	4350	4399
	839005203_15	194	194	196	1.40	1.41	1.21	4100	4249	4350
5495307H8G--SS	913000503_19	250	250	254	2.64	2,62	2.64	4299	4300	4300
	913000503_18	257	258	258	2.60	2.65	2.52	4050	4199	4250
	913000503_20	253	252	256	2.73	2.71	2.63	3950	4199	4250
5495307H9G--SS	734003703_5	354	355	356	3.90	3.90	3.89	4400	4450	4450
	734003703_10	354	356	358	3.98	3.83	4.14	4150	4450	4400
	734003703_8	354	352	356	4.03	4.14	3.84	4150	4450	4500
5497307H1G--SS	907011113_38	1183	1202	1190	16.08	15.21	16.32	4150	4300	4300
	907011113_21	1210	1194	1214	16.52	16.01	15.98	4149	4250	4299
	907011113_5	1201	1212	1210	16.78	16.82	16.12	4200	4299	4300
5497307H2G--SS	849011713_9	2140	2073	2103	32.50	31.84	29.61	3900	4050	4100
	849011713_12	2081	2148	2101	33.21	31.02	30.39	3949	4100	4150
	849011713_5	2096	2125	2141	34.01	33.05	33.18	3900	4100	4100

* Size 7, 8 , 9, 10 inch and 20 inch

The values in the table here above will be completed with test values on other filter lots and Sartocheck® 5 Plus devices as they become available. Even if the test values here above are not comprehensive enough for a statistical study, they give a clear overview of expected test values and reproducibility under defined conditions.

Note that these values have been obtained using Sartopore® Platinum Gamma capsules. Sartopore® filters of same size but with different capsule design may give different net volumes.

7.1 ±3 Sigma

A typical approach for setting safety values is to gather historical values and apply the “3 Sigma rule” which says that 99.7 percent of all results should be within the range of ±3 Sigma. Applying the 3 Sigma rule to the values gives the following results:

Volume

Sartopore® Platinum Gamma 0.2 µm	Lot n° _ ind. n°	Actual Net Volume (mL)			Average (Individual)	Average (Global)	STD Dev.	Recommended Min Volume (Average - 3σ)	Recommended Max Volume (Average +3 σ)
5495307H7G--SS	839005203_11	192	192	193	192	193	1.500	189	198
	839005203_10	191	194	194	193				
	839005203_15	194	194	196	195				
5495307H8G--SS	913000503_19	250	250	254	251	254	3.193	245	264
	913000503_18	257	258	258	258				
	913000503_20	253	252	256	254				
5495307H9G--SS	734003703_5	354	355	356	355	355	1.732	350	360
	734003703_10	354	356	358	356				
	734003703_8	354	352	356	354				
5495307H1G--SS	907011113_38	1183	1202	1190	1192	1192	10.849*	1169	1234
	907011113_21	1210	1194	1214	1206				
	907011113_5	1201	1212	1210	1208				
5495307H2G--SS	849011713_9	2140	2073	2103	2105	2112	27.455*	2030	2194
	849011713_12	2081	2148	2101	2110				
	849011713_5	2096	2125	2141	2121				

* The relatively high STD deviation was due to the variating positioning of the capsule thus leaving some residual liquid into the capsule which altered the net volume.

Diffusion

Sartopore® Platinum Gamma 0.2 µm	Lot n° _ ind. n°	Actual Diffusion (mL/min)			Average (Individual)	Average (Global)	STD Dev.	Test Pressure* (mbar)	Validated Max Diffusion	Recommended Min Diffusion* (Average - 3σ)
5495307H7G--SS	839005203_11	1.39	1.37	1.39	1.38	1.37	0.065	2500	4.00	1.17
	839005203_10	1.44	1.38	1.35	1.39					
	839005203_15	1.40	1.41	1.21	1.34					
5495307H8G--SS	913000503_19	2.64	2.62	2.64	2.63	2.64	0.061	2500	5.00	2.46
	913000503_18	2.60	2.65	2.52	2.59					
	913000503_20	2.73	2.71	2.63	2.69					
5495307H9G--SS	734003703_5	3.90	3.90	3.89	3.90	3.96	0.119	2500	7.00	3.60
	734003703_10	3.98	3,83	4.14	3.98					
	734003703_8	4.03	4.14	3.84	4.00					
5497307H1G--SS	907011113_38	16.08	15.21	16.32	15.87	16.20	0.490	2500	25	14.73
	907011113_21	16.52	16.01	15.98	16.17					
	907011113_5	16.78	16.82	16.12	16.57					
5497307H2G--SS	849011713_9	32.50	31.84	29.61	31.32	32.09	1.478	2500	50	27.66
	849011713_12	33.21	31.02	30.39	31.54					
	849011713_5	34.01	33.05	33.18	33.41					

* These values, related to the diffusion test, are used hereafter for calculating the minimum flow at Pend for the bubble point test.

Bubble Point

Sartopore® Platinum Gamma 0.2 µm	Lot n° _ ind. n°	Actual BP (mbar)			Average (Individual)	Average (Global)	STD Dev.	Recom. BP_{max} (Average +3 σ)	Pend in mbar	Min Flow at Pend**
5495307H7G--SS	839005203_11	4399	4449	4400	4416	4316	122,237	4683	5000	2,35
	839005203_10	4150	4350	4399	4300					
	839005203_15	4100	4249	4350	4233					
5495307H8G--SS	913000503_19	4299	4300	4300	4300	4200	122,373	4567	5000	4,91
	913000503_18	4050	4199	4250	4166					
	913000503_20	3950	4199	4250	4133					
5495307H9G--SS	734003703_5	4400	4450	4450	4433	4378	132,550	4775	5000	7,21
	734003703_10	4150	4450	4400	4333					
	734003703_8	4150	4450	4500	4367					
5497307H1G--SS	907011113_38	4150	4300	4300	4250	4250	86.603	4509	5000	29.47
	907011113_21	4149	4250	4299	4233					
	907011113_5	4200	4299	4300	4266					
5497307H2G--SS	849011713_9	3900	4050	4100	4017	4017	104.083	4329	5000	55.31
	849011713_12	3949	4100	4150	4066					
	849011713_5	3900	4100	4100	4033					

** Minimum flow at P_{end} is calculated by: (recommended minimum diffusion) x P_{end} / (diffusion test pressure)

7.2 ±3 Sigma ± Device Accuracy

All integrity test devices, regardless of manufacturer, have a certain tolerance in terms of accuracy. Identical devices may differ between each other in terms of measured values within the defined tolerance. Using data from all devices would automatically include the device accuracy and reproducibility. The benefit is statistical reliability from the important amount of data.

7.3 Safety Values Based on Failure Mode

Another frequently used approach for determining safety values is based on identified failure modes e.g., choosing the wrong capsule size or testing the filter capsules in reverse direction. The advantage of this approach is that there is a sound rational for setting the safety values for clearly identified hazards. In the table hereafter, the same filter capsules as previously used were tested by a combined diffusion and bubble point test in the reverse direction. The obtained values in reverse direction were compared to the values obtained in the normal direction. The differences between the values are identified hereafter as "deviation" with the respective unit of measurement and also percentage wise.

Sartopore® Platinum Gamma 0.2 µm	Lot n° _ ind. n°	Vol. (mL)	Average (mL)	STD Dev.	Deviation in mL	%-age deviation	Diffusion (mL/min)	Average (mL/min)	STD Dev.	Deviation in mL/min	%-age Deviation	BP (mbar)	Average (mbar)	STD Dev.	Deviation in mbar	%-age Deviation
5495307H7G--SS	913000503_19	126	126	0.0	-67	-34.8	0,89	0,813	0,142	-0,56	-40.9	4299	4283	29,160	-34	-0.8
	839005203_10	126					0,65					4300				
	839005203_15	126					0,9					4249				
5495307H8G--SS	913000503_19	159	159	1.0	-95	-37.5	1,31	1,333	0,032	-1,30	-49.5	4249	4216	28,583	16	0.4
	913000503_18	160					1,32					4199				
	913000503_20	158					1,37					4200				
5495307H9G--SS	734003703_5	224	222	2.0	-133	-37.5	2,68	2,717	0,217	-1,24	-31.4	4350	4400	50,003	22	0.5
	734003703_10	220					2,95					4399				
	734003703_8	222					2,52					4450				
5497307H1G--SS	907011113_38	463	462	2.6	-740	-61.6	10,07	10.190	0.289	-6.01	-37.1	4249	4233	28.583	-17	-0.4
	907011113_21	459					9,98					4200				
	907011113_5	464					10,52					4250				
5497307H2G--SS	849011713_9	804	811	6.1	-1301	-61.6	18,42	18.457	0.466	-13.63	-42.5	4000	4016	28.290	0	0.0
	849011713_12	812					18,01					4049				
	849011713_5	816					18,94					4000				

Testing a filter in the reverse direction may damage the filter element, especially if tested by bubble point, due to excessive pressure. The official maximum pressure in the reverse direction for the Sartopore® Platinum is two bar. The potential risk would be to get a passed test result during the pre-use test but damaging the filter during the test itself, thus getting a failed test result during the post-use testing.

Comparing the obtained values shows excellent detectability by volume determination and diffusion for both the wrong filter being connected and also for filters being connected in the reverse direction. On the other hand, the bubble point remains the same.

The table below resumes the values that are used for setting the minimum and maximum volumes. These are set to half way between the average values of the normal condition and the values of the worst case failure modes. The worst case failure mode is identified as the one generating a value closest to the normal average value (see calculation below the table):

Sartopore® Platinum Gamma 0.2 µm	Normal Average Volume (mL) with 2m Standard Tubing	Failure Mode Reversed Capsule (mL)	Worst Case Failure Mode Low Volume (mL)	Worst Case Failure Mode High Volume (mL)	Recommended Min Volume to Program (mL)	Recommended Max Volume to Program (mL)
5495307H7G--SS	193	126	159 (reversed H8)	222 (reversed H9)	176[a]	208[b]
5495307H8G--SS	254	159	222 (reversed H9)	355 (normal direction H9)	238[c]	305[d]
5495307H9G--SS	355	222	254 (normal direction H8)	462 (reversed H1)	305[e]	409[f]
5497307H1G--SS	1192	462	811 (reversed H2)	2112 (normal direction H2)	1002[g]	1652[h]
5497307H2G--SS	2112	811	1192 (normal direction H2)	Not identified in this study	1652[i]	Not identified in this study

[a] (193+159)/2 = 176 mL
[b] (193+222)/2 = 208 mL
[c] (254+222)/2 = 238 mL
[d] (254+355)/2 = 305 mL
[e] (355+254)/2 = 305 mL
[f] (355+462)/2 = 409 mL
[g] (1192+811)/2 = 1002 mL
[h] (1192+2112)/2 = 1652 mL
[i] (2112+1192)/2 = 1652 mL

7.4 Historical Safety Values

Generating statistically reliable values with the Sartocheck® 5 Plus Filter Tester requires time and effort and may not be possible when there is a timeline to respect. If the Sartocheck® 5 Plus replaces a Sartocheck® 4, the historical values of the Sartocheck® 4 can be used to determine safety values for the Sartocheck® 5 Plus until enough integrity test values and net volume measurements have been generated with the Sartocheck® 5 Plus under real operating conditions. The safety values can then be adjusted.

7.4.1 Diffusion and Bubble Point Values

Sartocheck® 4 diffusion and bubble point test values should take into account the potential difference in accuracy (+/- 5% & +/- 50 mbar) between two devices to avoid generating false error messages. The Sartocheck® 5 minimum diffusion value should be reduced by 10 percent (twice the accuracy) and the maximum bubble point should be increased by 100 mbar (twice the accuracy).

Examples:

	Sartocheck® 4 Values	Sartocheck® 5 Adjusted Values
Defined Minimum Diffusion	5 mL/min	4.5 mL/min
Defined Maximum Bubble Point	3700 mbar (53.664 psi)	3800 mbar (55.114 psi)

7.4.2 Water Intrusion Values

The Sartocheck® 4 can display water intrusion results as gas-based or water-based intrusion rates. The Sartocheck® 5 only displays intrusion results as water-based intrusion rates. Sartocheck® 4 gas-based intrusion rates in mL/10 min must be divided by the absolute test pressure in bar and then by 10 to convert into water-based intrusion values in mL/min. Then 10 percent should be subtracted so as not to generate false error messages.

Examples:

	Sartocheck® 4 Gas-Based Intrusion Values	Sartocheck® 5 Plus Water-Based Intrusion Adjusted Values
Defined Minimum Intrusion @ 2500 mbarg (3.5 bar absolute)	10.5 mL/10min	0.270 mL/min
Defined Minimum Intrusion @ 2600 mbarg (3.6 bar absolute)	10.5 mL/10min	0.263 mL/min

7.4.3 Minimum and Maximum Net Volume

The overall volume of the filter setup depends on the test tubing volume, so the larger diameter of the Sartocheck® 5 tubing must be taken into account.

Examples:

	Sartocheck® 4 (mL)	Sartocheck® 5 Plus (mL)
Net Volume With Respective Standard Tubing	35 to 36*	73 to 74*

*These values can also be determined individually for the Sartocheck® 4 being replaced and the Sartocheck® 5 Plus replacement.

Take into account that the volume measurement has an accuracy variance of +/- four percent.

Set the Sartocheck® 5 Plus Filter Tester minimum expected net volume to 37 mL higher (73 mL – 36 mL) based on historical values from the Sartocheck® 4 and then further adjusted for accuracy +/- four percent.

Set the Sartocheck® 5 maximum expected net volume 39 mL higher (74 mL – 35 mL) than Sartocheck® 4 historical values and then further adjusted for accuracy +/- four percent.

Examples:

	Historical Sartocheck® 4 Values	Sartocheck® 5 Plus Values
Defined Minimum Volume (mL)	250	277 (250 × 0.96 + 37)
Defined Maximum Value (mL)	350	403 (350 × 1.04 + 39)

7.5 Discussion

These values were obtained under stable conditions with the filter capsule in an upright or slightly tilted position, using a limited number of filter capsules, and one Sartocheck® 5 Plus Filter Tester. Therefore, this data may be insufficient for statistical purposes. Nevertheless, it shows the principle of determining safety values and the level of detectability.

In the study above, each filter was tested three times by the combined diffusion and bubble point test with re-wetting in between. It should be noted that the bubble point value specially can be subject to increase as the filter element is being wetted several times, which still represents the variability of achievable integrity test values.

It should also be noted that the net volume measurements of the small capsule were very easily reproducible due to the filter capsules always being placed in an upright position, thus leaving no residual liquid inside the capsule. The ±3 Sigma approach has an extremely tight minimum and maximum value setting for the net volume determination, which could generate unnecessary test aborts if e.g., the capsule is not always put in the same position. Safety values for net volume measurement based on failure mode show more robust values clearly demonstrating that all failure modes will be easily detected without the risk of unnecessary test aborts.

8. Summary

This FMEA for the Sartocheck® 5 Plus Filter Tester and for integrity testing of sterilizing grade filters in general, has been developed based, among other factors, on years of experience addressing end-user claims and technical support for end-users by our application specialists. This document should be used by the end-user as a guide for evaluating the need for additional standard operating procedures (SOP), for continuous training of operators and for additional accessories and procedures in order to reduce risk of false passed and false failed test results and operator injury. This document is generic but may serve as a basis for an end-user specific FMEA.

The result of any misinterpretation of the included information remains the responsibility of the end-user.

9. References and Recommended Reading

1. Risk Assessment for Thermal Influences on Filter and Container Closure Integrity Testing (M.A.Stering – Pharmaceutical Engineering – July-August 2017)
2. Failure Mode Effects Analysis for Filter Integrity Testing (M.A.Stering – Pharmaceutical Technology – April 2016)
3. Effects of Pressure Sensor Calibration Offset on Filter Integrity Test Values (M.A.Stering – BioProcess International – November 2013)
4. Pre-Use/Post-Sterilization Integrity Testing of Sterilizing Grade Filter (M.W.Jornitz & M.A.Stering – American Pharmaceutical Review – August 2017)
5. PDA Technical Report No. 26 Revised 2008 Sterilizing Filtration of Liquids (PDA Task Force – 2008)
6. Guidance for Industry Q9 Quality Risk Management (US FDA, CDER & CBER – June 2006)
7. Annex 1 Draft (EMA, FDA, WHO & PIC/s – 2020)

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For further contacts, visit
www.sartorius.com

Status: 06 | 2023