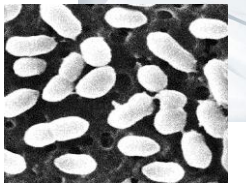
Annex 1
Impact on Filtration

Dr. Mathias Siebner, Product Specialist Separation Technology

Filter integrity test

+

Product and process specific validation

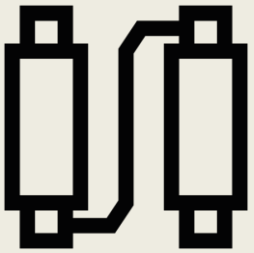


The filter integrity test confirms that the filter is flawless and does not say if the solution is sterile or not.

Filter Integrity Test Methods

Bubble Point
Diffusion Test (=Forward Flow), Pressure hold

Water Intrusion Test
(for hydrophobic membranes)



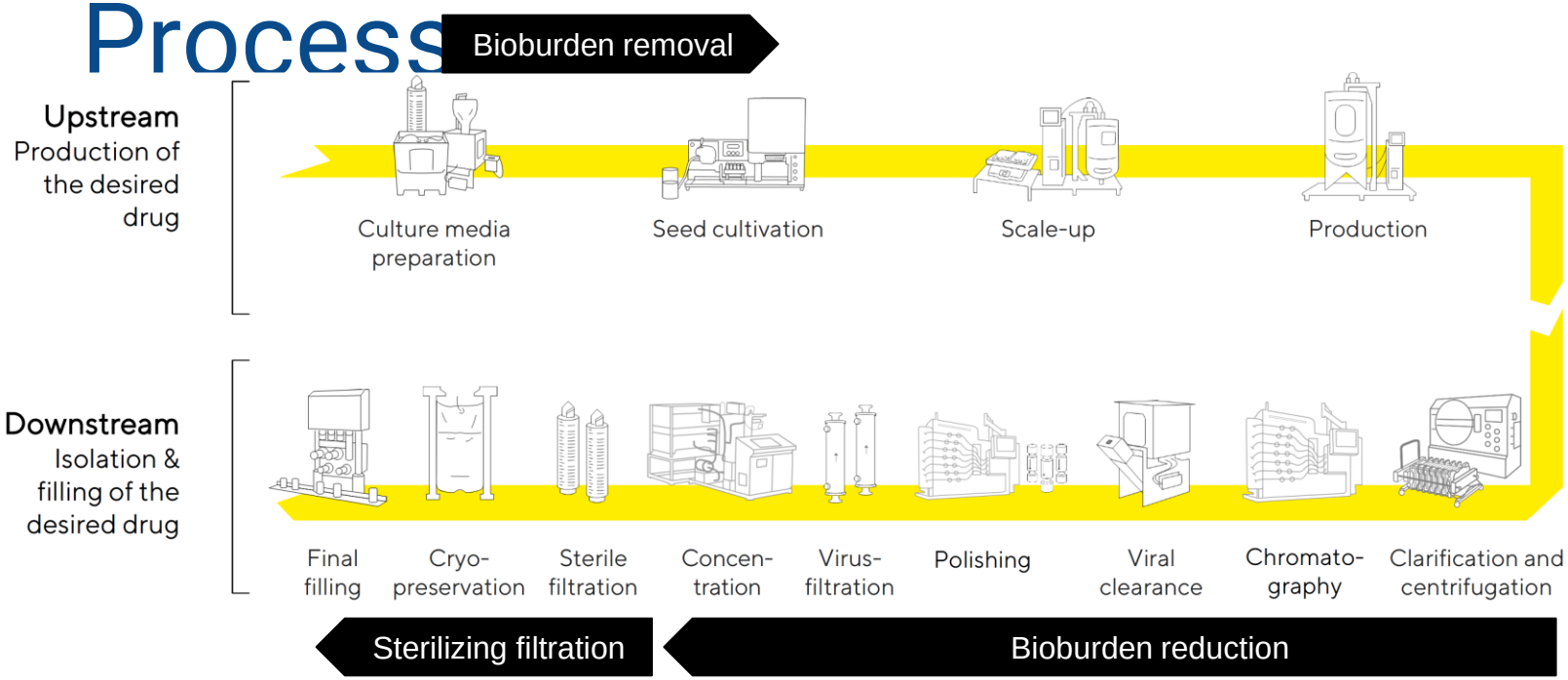
There is no regulatory preference for one filter test m

- Not all test methods are available
- Diffusion Test is usually more sen

Recommendation

- Diffusion Test
- Diffusion Test and Bubble Point Test
- For small filters only Bubble Point can be performed

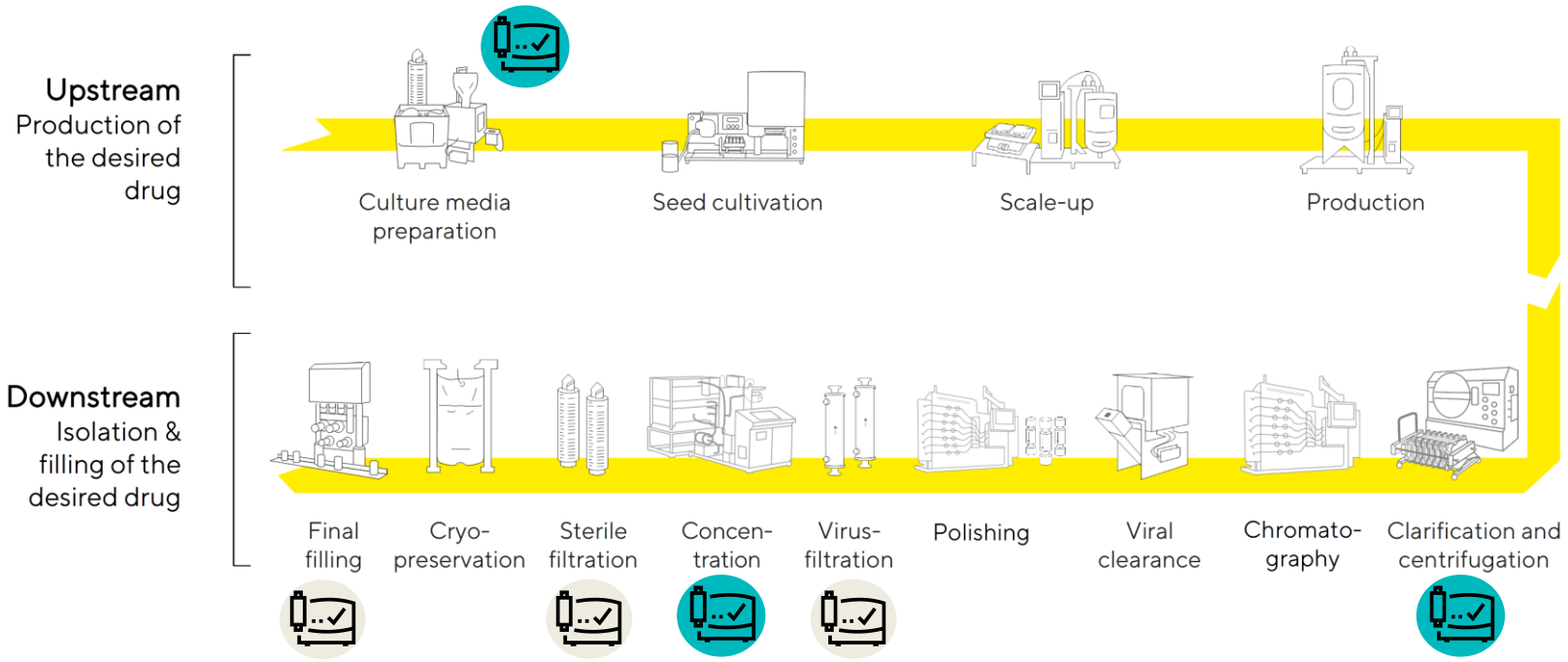
Integrity Testing in BioPharma - mAb Process



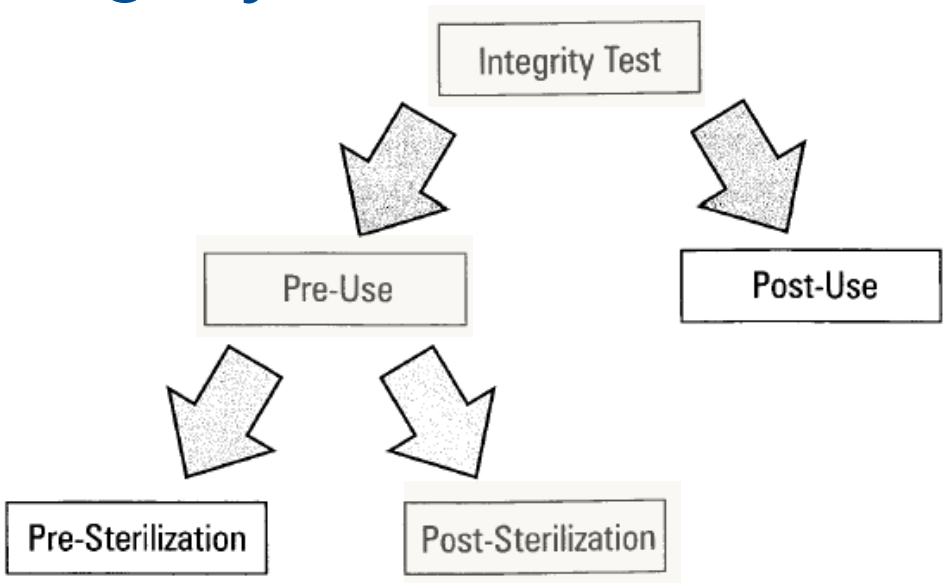
Integrity Testing in BioPharma - mAb Process

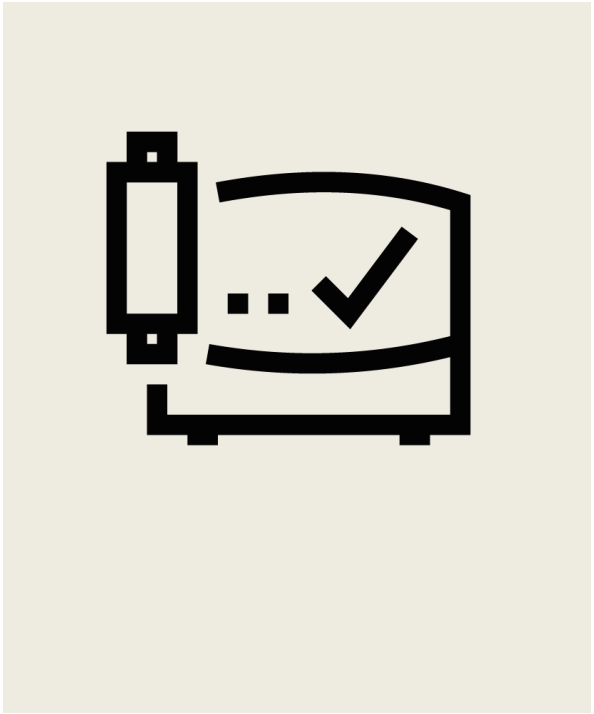
Regulatory required

Risk mitigation



When to Perform the Integrity Test?





Pre-Use Post-Sterilization IT (PUPSIT)

New Annex 1

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

Download Link

- Contamination Control Strategy (CCS)

What is CCS?

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.

Goal should be the creation strategy document

Contamination Control Strategy

CCS is about all contaminants in the process (bacteria, endotoxin, virus, leachables, particles …)

CCS is based on robust processes and validation rather than on control checks

Integrity testing helps to control the contaminations

QRM is used to make integrity testing more secure

QRM hat got a holistic approach…

This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs.

What is QRM and CCS related to filtration? Examples

- Sterilizing grade filtration
- Bioburden removal for media filtration
- Bioburden reduction in downstream (endotoxins)
- Virus retentive filtration
- (Critical) air filters
- Single-use of filters
- Use of redundant sterile filters
- Filtration process validation (BCT

2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex.

In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.

QRM in Integrity Testing

False failed IT

Still a deviation

VS

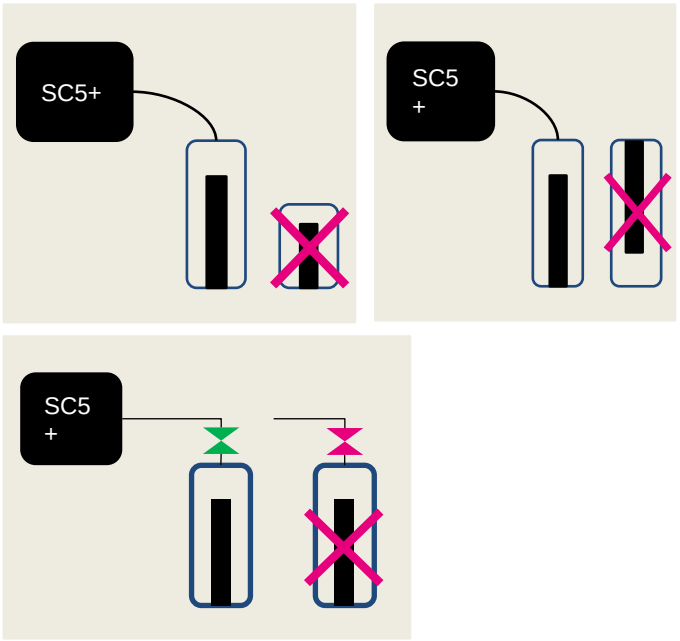
False passed IT

⚠ Potential danger for patients

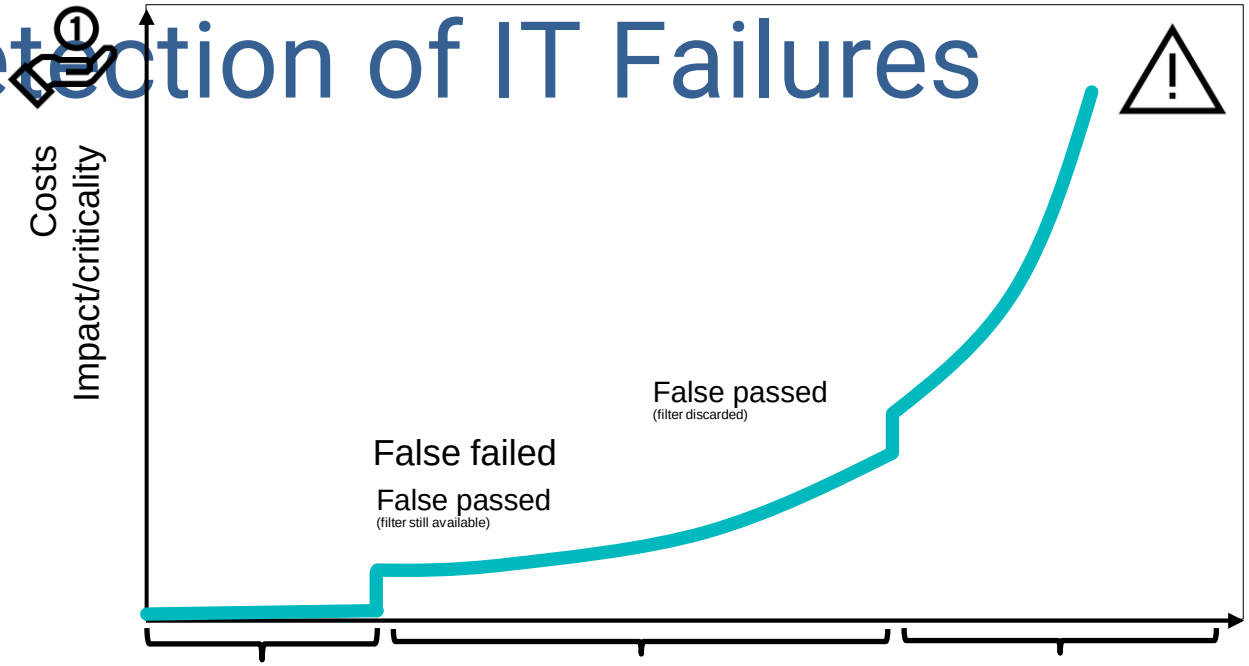
"False positive" and "false negative" should only be used for sterility testing.

Detection of

- Wrong filter size
- Filter in the opposite direction
- Closed valve between the upstream side
- Broken filter with a closed downstream valve
- Incorrect setups (any changes to standard setup)



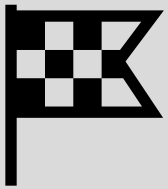
Benefits of Prevention and Early Detection of IT Failures



In case of detected false passed test danger for the patient

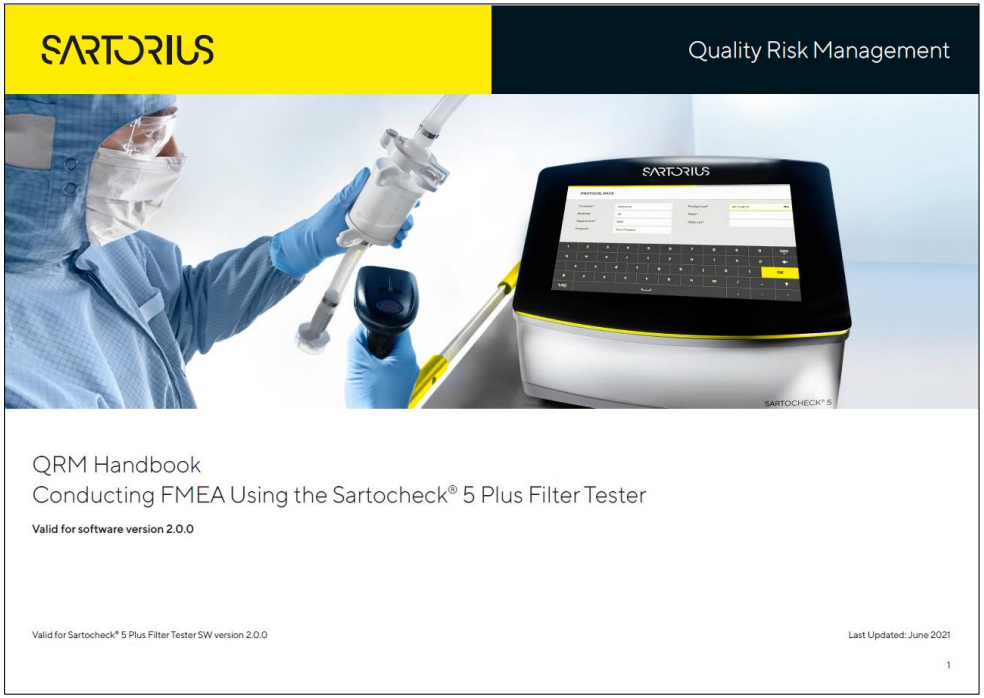
Detection by	SC5 Plus (automatic) or by operator	QA dept	Regulatory body

… to get a passed / conform integrity test result even if the/one filter is broken.



Multiround housings
Temperature variations
Operator mistake or SOP does not go into details

- Revise SOP
- Training / education
- Instrument maintenance
- Integrity tester self-test before every test
- FMEA (cf. QRM Handbook)

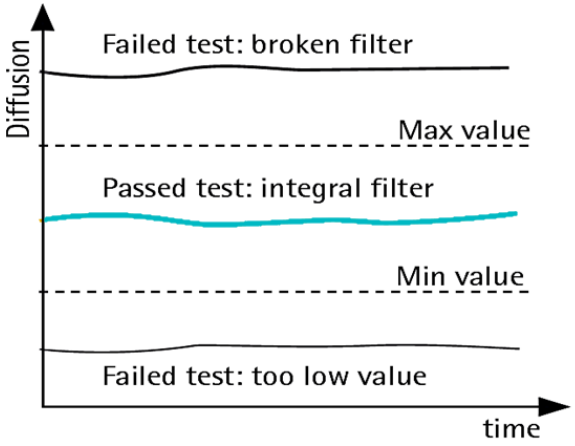


Risk score RPN = Severity * Probability * Detactability

	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.

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 measurement 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.

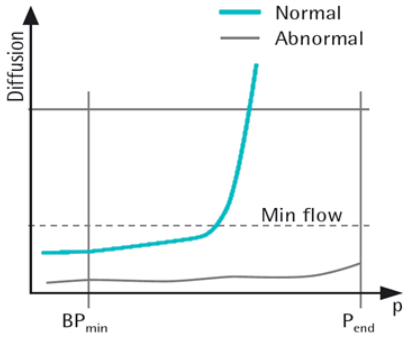
Diffusion | WIT



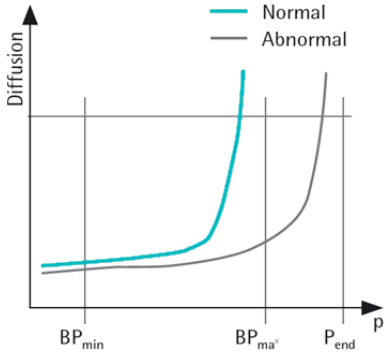
CHARACTERISTICS AND LIMITS

Pressure*	2,500 mbar	Tot. min. diffusion	2.00 mL/m
Max. diffusion/sample*	5.00 mL/min	Stabilization time*	3 min
Tot. max. diffusion	5.00 mL/min	Measurement time*	3 min
Min. diffusion/sample	2.00 mL/min	Auto. measurement time	✓

Bubble point



Bubble point



CHARACTERISTICS AND LIMITS

Meas. time/press. step	6 - 900 s	Min. flow at end of test	2.35 mL/min

CHARACTERISTICS AND LIMITS

Max. diffusion/sample*	5.00 mL/min	Max. bubble point*	4700 mbar

26

QRM - Blocking of Abusive Test Repeats by the Integrity Tester

A maximum of e.g. **three** (parameter setting) **tests** can be executed on a specific filter

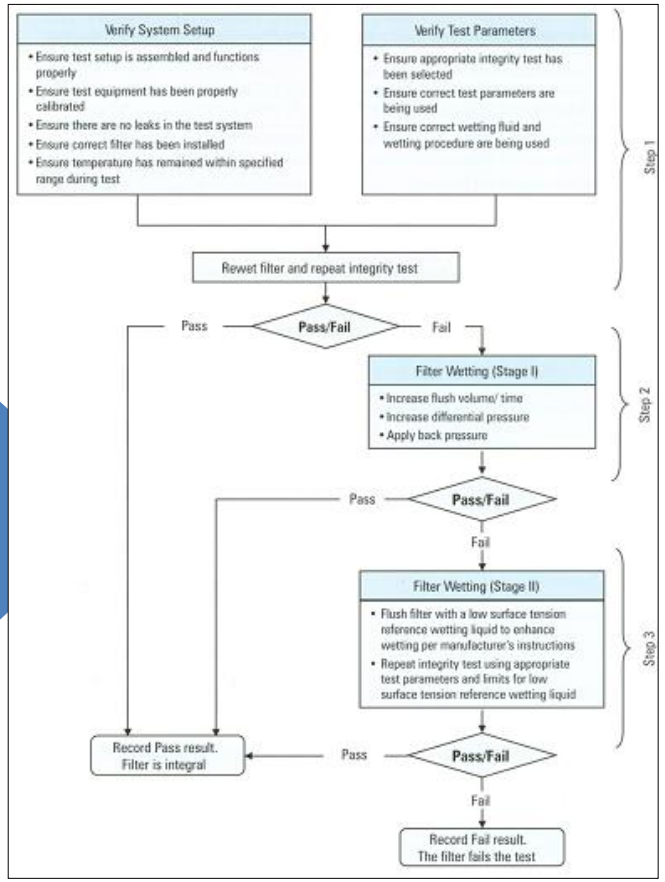
Tracking via

- lot number
- individual number

PDA Technical Report No.26 (2008) about Test Repetitions

1	Re-test after system check and re-wetting
2	Re-test after increased wetting conditions
3	Re-test using wetting solution with lower surface tension

Trouble shooting guides available



QRM – Barcode reader

Possibility to make

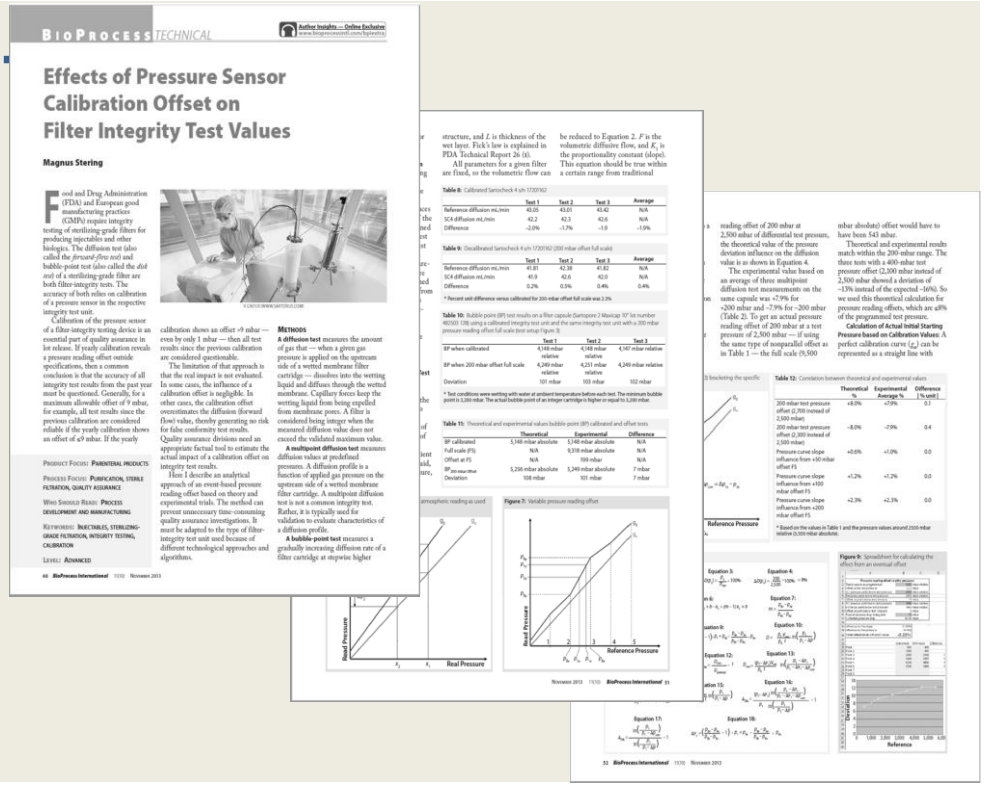
use of scanner mandatory)

Control of abusive test repetitions

QRM - Calculation Tool for Calibration Offset

Calibration offsets are very unlikely to happen but are generally considered to have a serious quality impact on the reliability of all test results since the last calibration

Evaluation of the hazard based of scientific knowledge



BioProcess TECHNICAL

Effects of Pressure Sensor Calibration Offset on Filter Integrity Test Values

Magnus Stering

29 https://bioprocessintl.com/downstream-processing/filtration/effects-of-pressure-sensor-calibration-offset-on-filter-integrity-test-values-347994

PUPSIT

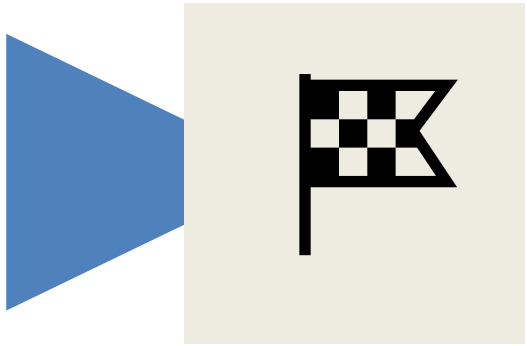
77. The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately after each use (it may also be useful to test the filter in this way before use). The	1989
85. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure	1996
8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:	2022

32

PUPSIT – when does it help?

All of the following factors have to be met:

1	Filter is damaged during or after the sterilization or prior to the use
2	Filtration of the product solution leads to flaw masking
3	Defect is not detected → false passed test after use



What is the issue with PUPSIT?

„A PUPSIT procedure may result in a higher risk to product quality ... due to downstream manipulation and/or the addition of equipment to the downstream process.“

Source: PDA Points to Consider for Aseptic Processing (Part1, Jan 2015)

35

PUPSIT

Stainless Steel Systems		Gamma Sterilized Systems
Depressurization after sterilization	VS	Requires higher pressures, single-use bags must not be pressurized
Downstream air filters integrity tested pre- or only post		Downstream air filters cannot be pre-tested
Dilution of product if not dried		Dilution, of product as usually cannot be dried

More complex setup

For manual systems more handling steps → errors more likely

PUPSIT – Exceptions (Annex 1)

"It is recognized that pre-use post sterilization integrity testing **(PUPSIT) may not always be possible** after sterilization due to process con

volu

In these cases, an alternative approach may be taken providing that a thorough **risk assessment**

As the Annex 1 is putting more emphasis on Risk Assessment, in more cases the PUPSIT will be avoided.

On the other hand more will look into the PUPSIT …

37

PUPSIT Risk

Stainless Steel Systems

Either Pre-Use-Pre-Steril.-IT or PUPSIT

VS

Gamma Sterilized Systems

Only PUPSIT

Following PDA TR 66 IT is less important

After Pre-Use-Pre-Steril.-IT Assembly and Transportation

FMEA

38

Benefits of PUPSIT

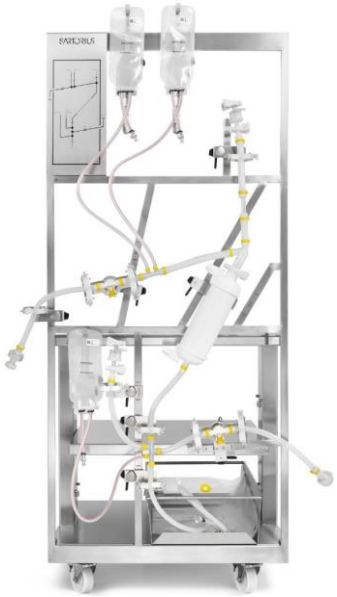
1. Commercial risk mitigation
2. Highest regulatory compliance

Solutions available for stainless steel as well as single-use manufacturing

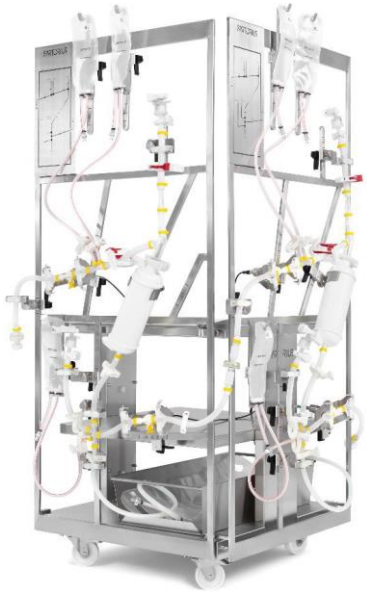
39

Implementation of PUPSIT in Single-Use Processes

- Easy installation
- Optimized dead space, minimal product loss
- Configurable setups:
  - Wetting
  - PUPSIT
  - Filtration
  - Recovery Step
  - Rinsing



Single Filtration



Redundant Setup

Critical Vent Filter Testing (Annex 1)

8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.

Critical vent filter:

Filtered air/gas comes into direct contact to the final product

- In place testing (WIT)
- After every use

Non-Critical Vent Filter Testing (Annex 1)

8.89 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/ sterilisation cycles permitted as applicable).

Risk assessment, for the event of an integrity test failure

- In place testing (-> WIT)
- Appropriate intervalls

42

- Holistic approach for Annex 1 is QRM
- Quality by design rather than by testing
- Decisions should be taken after risk assessment

Thank you

Dr. Mathias Siebner
Sartorius Stedim Biotech GmbH
August-Spindler-Str. 5
D – 37079 Göttingen
Mobile: +49.172.5664380
Email: mathias.siebner@sartorius.com