Filter Integrity Testing

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PDA
Parenteral Drug Association

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Agenda

Integrity test regulatory requirements

Bacterial Challenge Test (BCT) and correlation to IT

Integrity Test Methods

- Diffusion
- Bubble Point
- Water Intrusion Test (WIT)

Integrity Testers

- Quality Risk Management
- Data Integrity
- Usability
- Health, Safety and Environment (and Contamination Control Strategy)

Trouble Shooting of Integrity Tests

What is Integrity Testing?

A **non-destructive** physical test to determine the presence of oversized pores or other defects that may compromise a given filter's retention capability.

Regulations for Integrity Testing

EU GMP (Annex 1, Filtration of medicinal products which cannot be sterilised in their final container, (June 2001))

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 integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.“

Regulations for Integrity Testing

FDA Guideline on sterile drug products produced by aseptic processing, September 2004

“Integrity testing of the filter(s) can be performed prior to processing, and should be routinely performed post-use. It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration. Forward flow and bubble point tests, when appropriately employed, are two integrity tests that can be used. A production filter´s integrity test specification should be consistent with data generated during bacterial retention validation studies.”

Regulations for Integrity Testing

PDA Technical Report No. 26 Sterilizing Filtration of Liquids

"It generally is regarded as a GMP requirement that filter or filter systems routinely be integrity tested both prior to and after use.

If one filter has been validated to achieve sterilization with a specific product, then the single sterilizing filter must satisfactorily pass integrity testing before and after use."

Pre-use Post-sterlilization I-Test

Annex 1 : Manufacture of Sterile Products (DRAFT, 2020)

“It is recognized that pre-use post
1492 sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process
1493 constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative
1494 approach may be taken providing that a thorough risk assessment has been performed and compliance
1495 is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility.”

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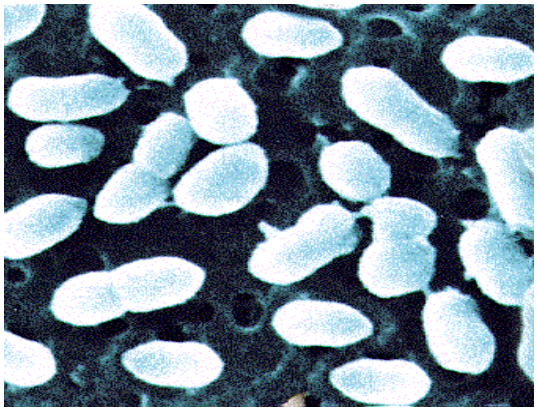
Correlation to Bacterial Challenge Test (BCT)

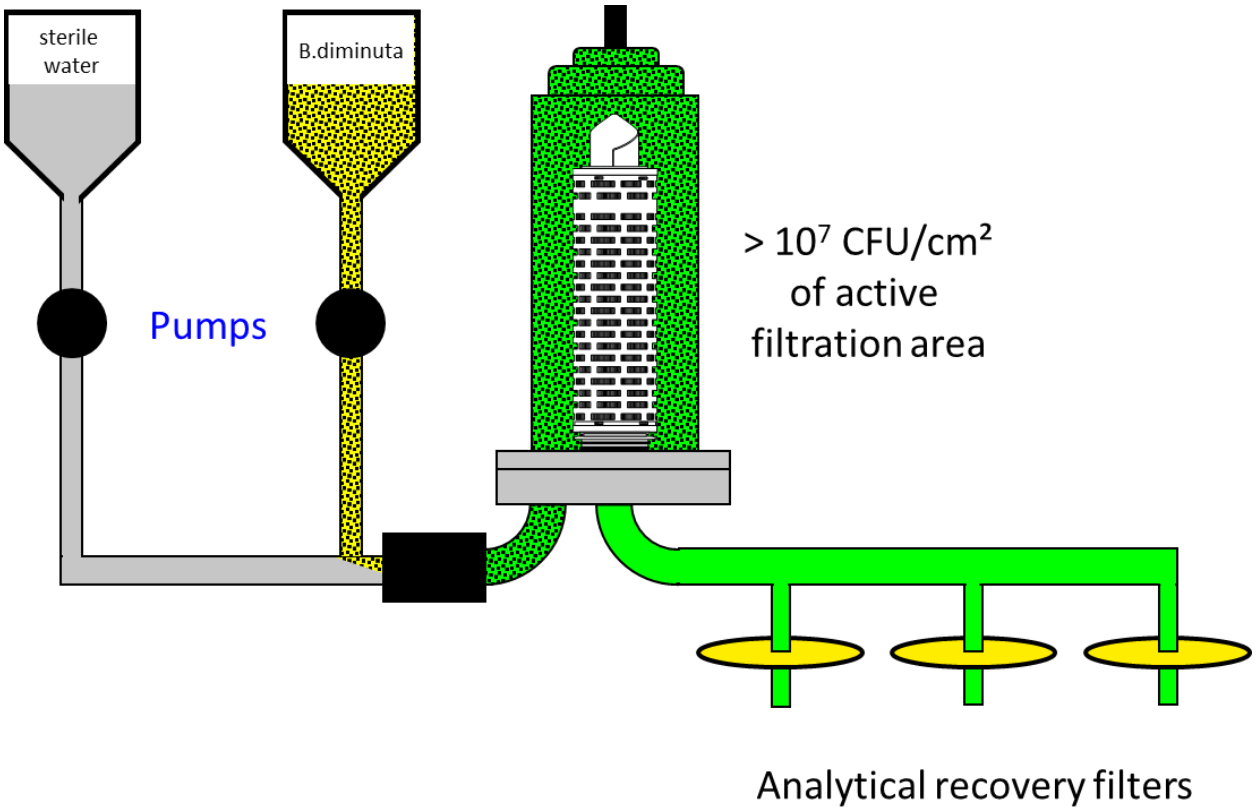
- A physical integrity test is only meaningful when it can be related to specific filter retention characteristics.
- For sterilizing grade membrane filters, the industry standard test is a micro-organism challenge using ***B. diminuta***.
- Since bacterial challenge tests (BCT) are **destructive**, they cannot be used on filters intended for production usage.
- Therefore, a correlation is established between bacterial retention and physical integrity testing.

BCT Organism: *Brevundimonas diminuta*

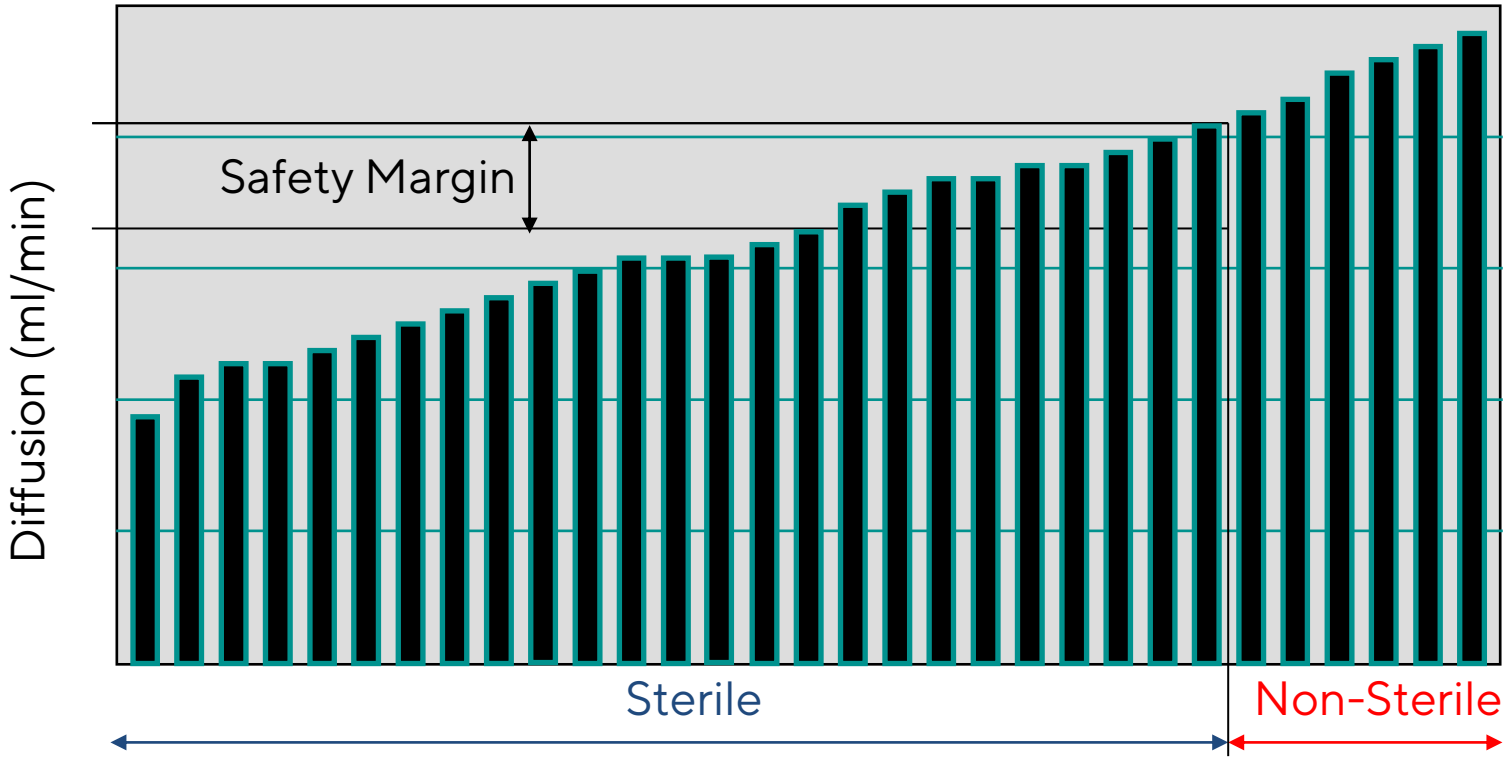


- Diameter: 0.3 - 0.4 µm
- Length: up to 1µm
- Concentration level greater than 10^7 CFU/cm^2

Bacterial Challenge Test (BCT)



Diffusion / BCT Correlation



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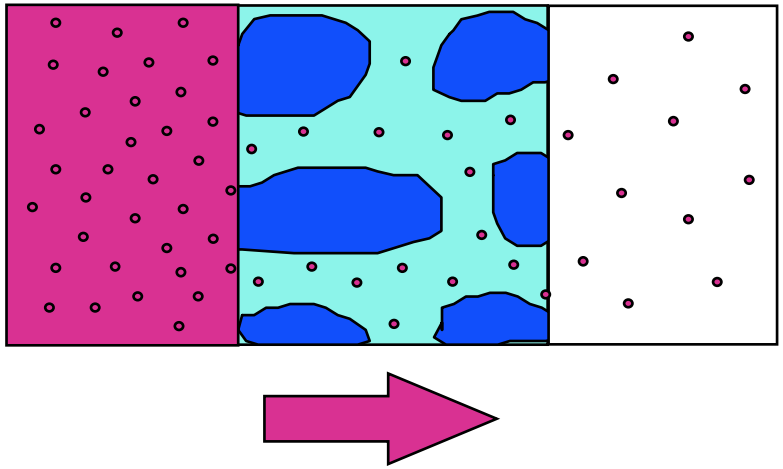
Trouble Shooting of Integrity Tests

Principle of Diffusion

Test pressure (e.g. 2.5 bar): good solubility of compressed air in the wetting medium



Atmospheric pressure: degassing

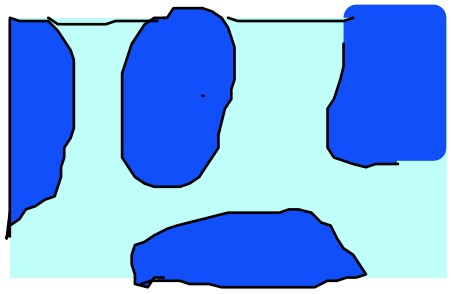
Henry 's Law:
The solubility of gases in liquids is dependant upon pressure (and temperature).

Diffusion Formula

$$N = \frac{D \cdot H \cdot P \cdot F}{L}$$

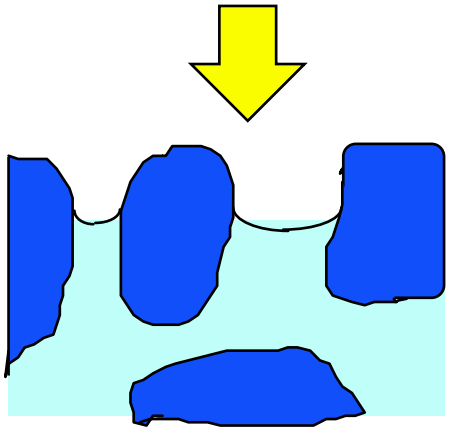
- **N**: Diffusive flux of the test gas
- **D**: Diffusivity of the test gas through the wetting fluid
- **H**: Solubility coefficient of the test gas through the wetting fluid
- P: Differential pressure applied
- **F**: Contact area between liquid and gas
- **L**: Thickness of the wet layer (membrane thickness corrected by a "tortuosity" factor)

Principle of the Bubble Point



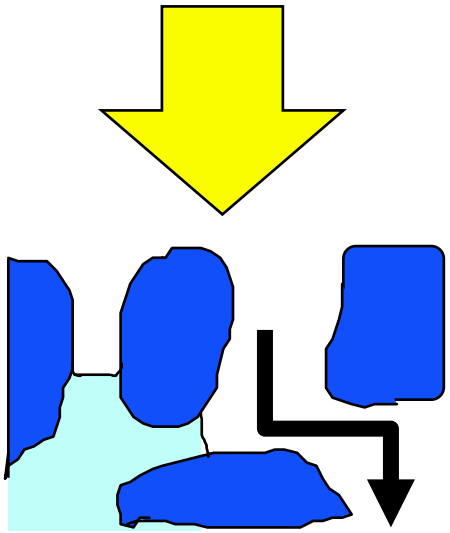
wetted membrane

compressed air



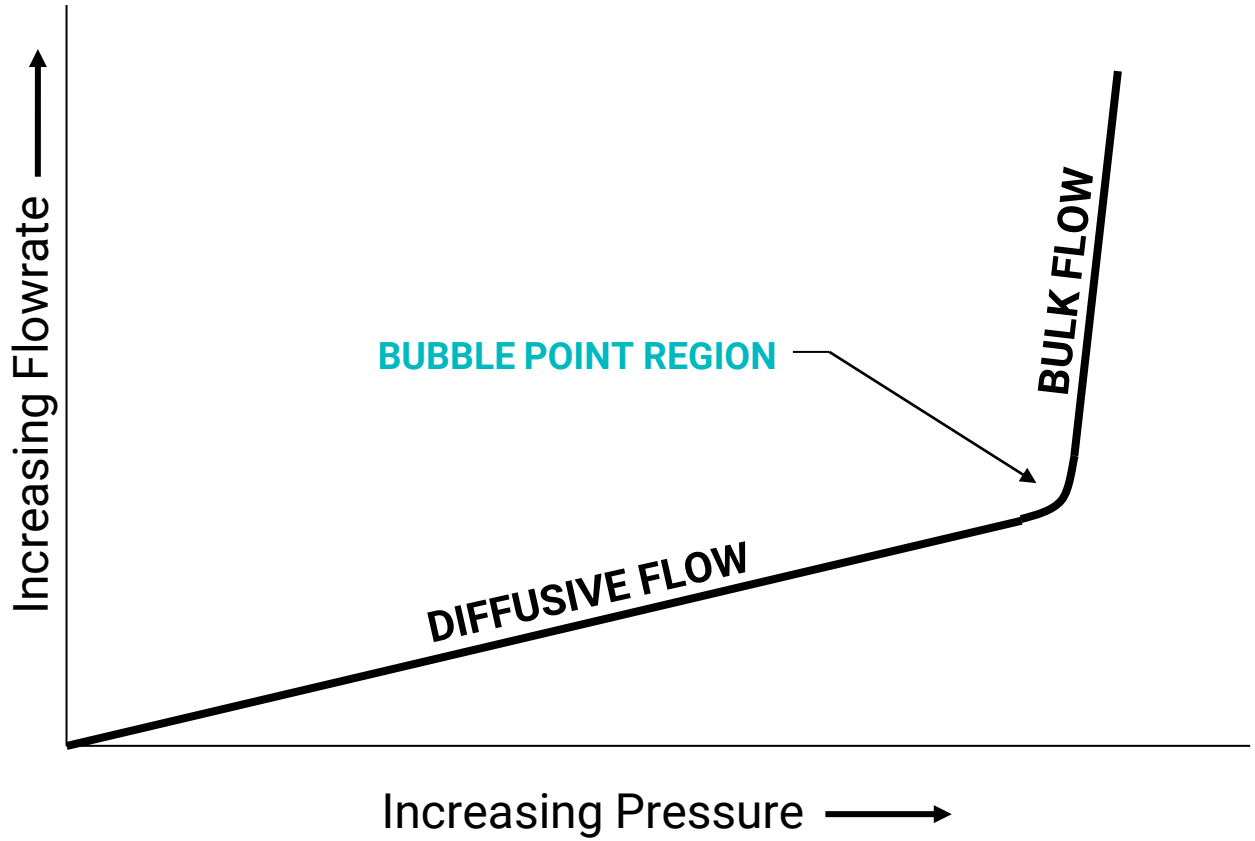
surface tension and capillary effect resist liquid expulsion from pores

compressed air



liquid forcibly removed from the largest pores first, resulting in bulk air flow

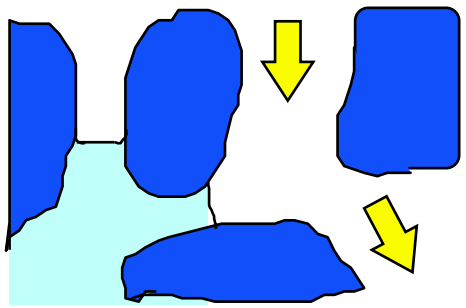
Flowrate vs. Pressure



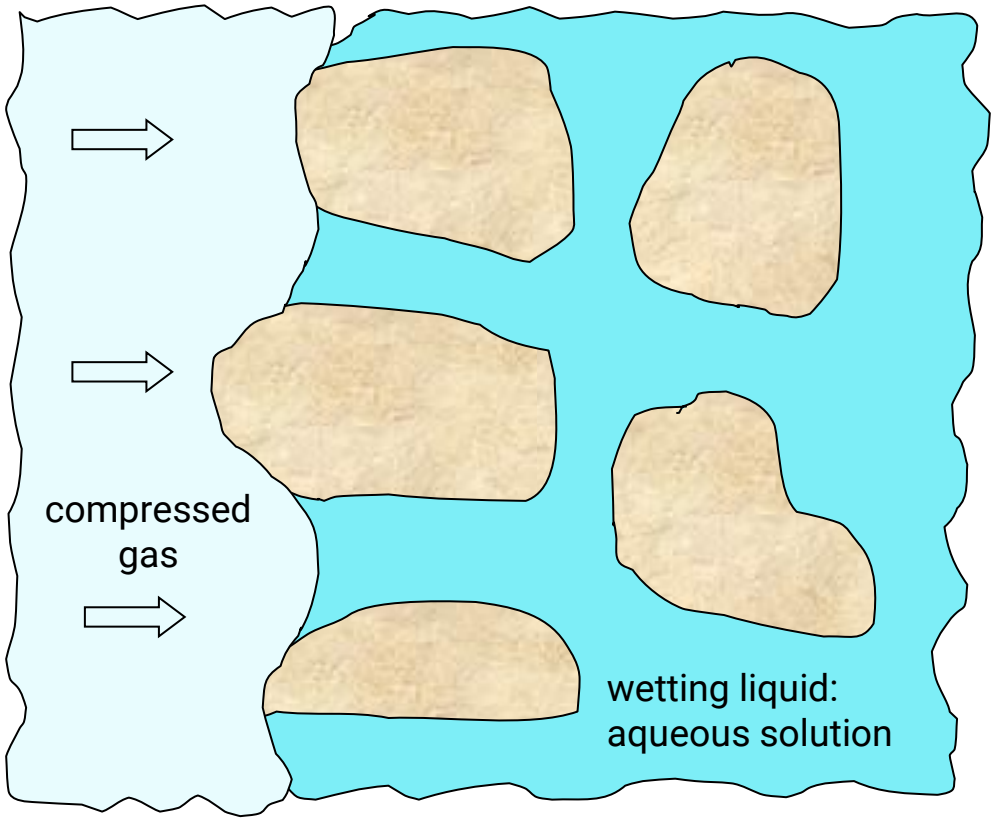
Bubble Point Equation

$$P = \frac{4 \cdot k \cdot \gamma \cdot \cos \theta}{d}$$

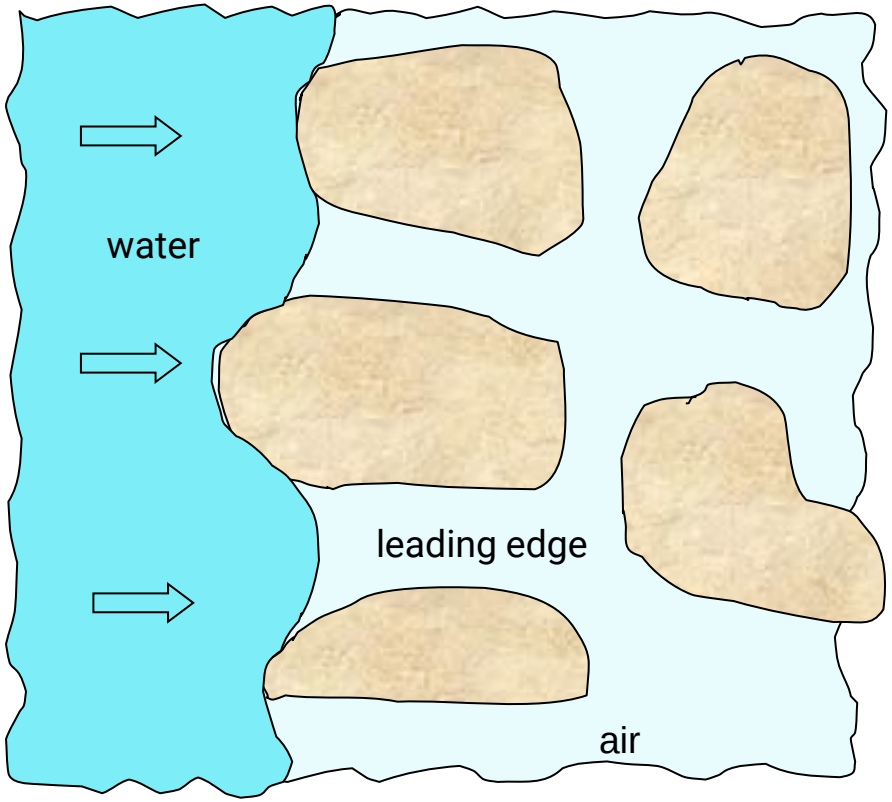
- **P**: Differential pressure at which largest pores will open
- **k:** Correction factor for the shape of the largest pores
- **γ:** Surface tension of the wetting fluid
- **cos θ:** Contact ("wetting") angle between the liquid and the membrane
- **d**: Diameter of the largest pores



Integrity Testing a Hydrophilic Membrane



Integrity Testing a Hydrophobic Membrane

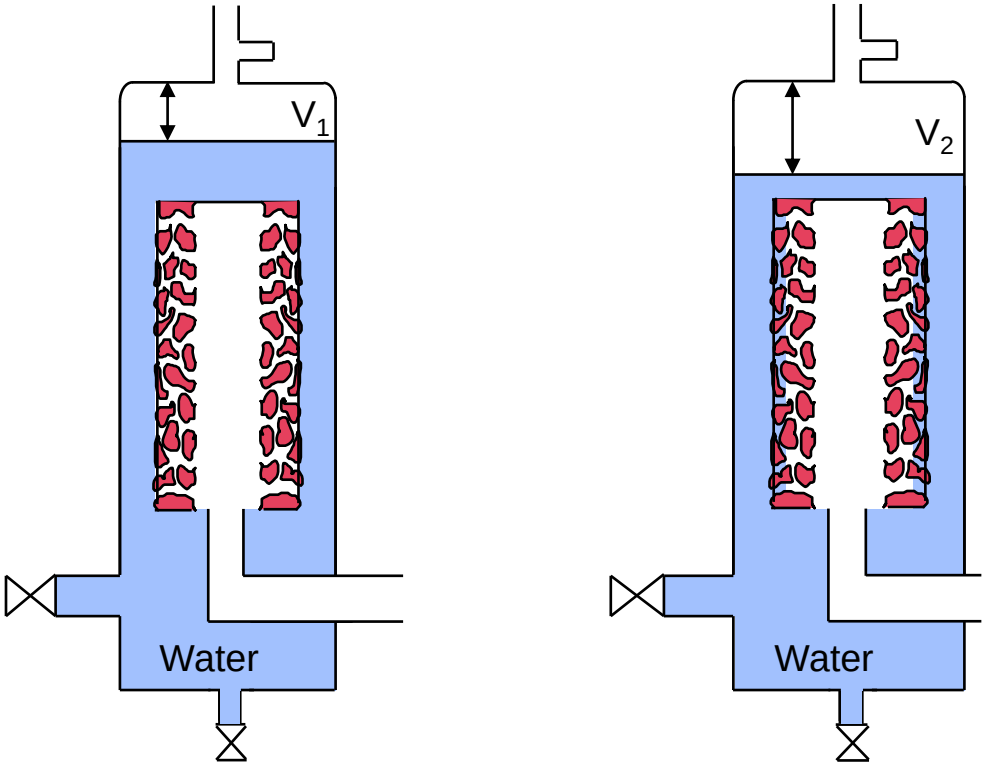


Water Intrusion Test

Water under pressure is forced to intrude into the pore matrix. The greater the overall porosity, the higher the rate of the intrusion.

The water vapor travels from the leading edge downstream through the filter membrane.

Water Intrusion Test



Water under pressure evaporates through the membrane and causes an increase in the headspace volume above the filter ($V_1 \rightarrow V_2$).

The resulting pressure drop from the volume increase is converted into a water flow rate.

Water Intrusion Test (WIT) Formula

$$\text{Intrusion (ml/min)} = \frac{\Delta p\ (\text{mbar}) \cdot \text{Volume (ml)}}{\text{Test Time (min)} \cdot \text{Test Pressure (mbar)}}$$

The limit values for intrusion are directly correlated to the Bacteria Challenge Test (ASTM F838).

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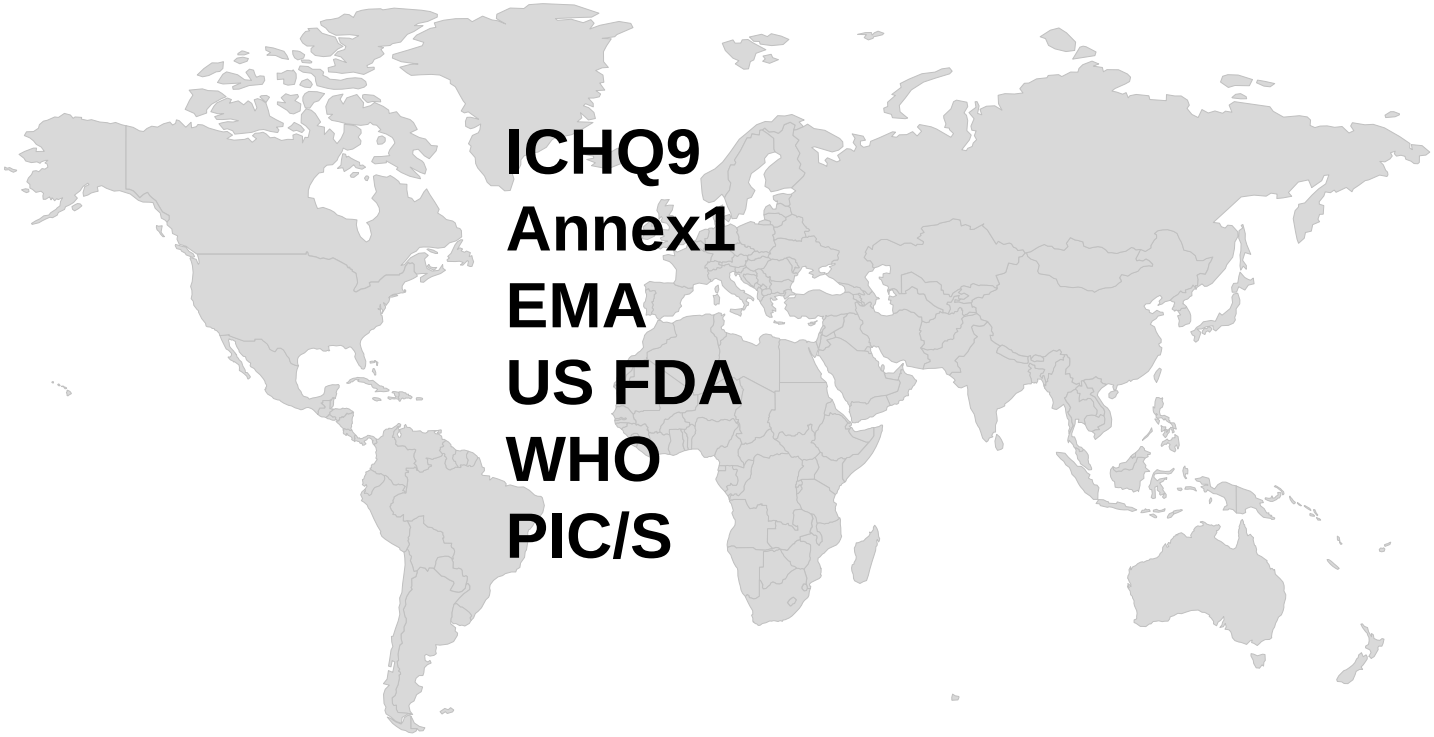
Trouble Shooting of Integrity Tests

Surpass the Requirements of Quality Risk Management (QRM)



ICHQ9
Annex1
EMA
US FDA
WHO
PIC/S

Quality Risk Management – Some hard Facts

- The regulatory focus on QRM is greatly increasing by the arrival of the new Annex1, expected to become effective in 2022
- “QRM” and “Risk Assessment” are mentioned already in the §-Scope and §-Principle
- The word "risk(s)" is used 101 times throughout the latest draft version (Feb 2020)
- QRM also applies to filter integrity testing:
  - *"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.“*
  - **False passed and false failed** integrity test results are indeed a risk to quality:
    - False passed test results puts the health of the patients in danger
    - False failed test results generate costly QA deviation and a risk for drug shortage
- The new Annex 1 was written by EMA and reviewed by US-FDA, WHO and PIC/S.
  - It should be applied virtually worldwide

Filter Integrity Tester – QRM

- Traditional QRM methods are essential
  - Operator training
  - Standard operating procedures
  - Possibility to use barcode scanner for program selection
- Rare but regular end-user complaints of false passed and false failed test results prove that traditional QRM methods are not enough

- Integrity Tester with improved QRM:
  - Possibility to make the barcode scanner mandatory
  - Automatic detection of operator errors by program specific safety parameters
  - QRM Handbook & FMEA documentation
    - Identifies hazards, calculates the RPN and suggests measures for Risk Control
    - Guidance for setting of safety parameters reduces the Likelihood and improves the Detectability

Data Integrity from a regulatory perspective

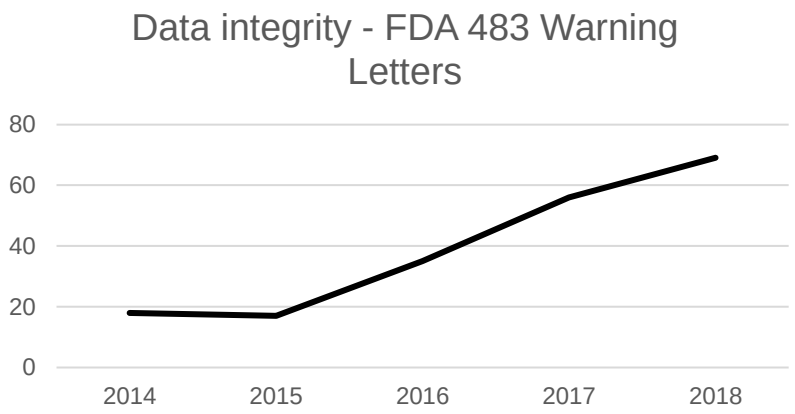
- There is a high focus on data integrity from regulatory bodies (cf. frequency of regulatory texts hare below)
- The number of FDA warning letters related to data integrity has greatly increased over the last years
- The vulnerability of computerized companies have been understood by recent ransomware attacks (cf. “WannCry” and “NotPetya” malware outbreak 2017 - $10 billion total damages
  (https://www.apextechservices.com/topics/articles/435235-notpetya-worlds-first-10-billion-malware.htm#)

US FDA – Dec 2018
Data Integrity and Compliance with Drug CGMP Questions and Answers:
Guidance for Industry

MHRA – March 2018
‘GXP’ Data Integrity Guidance and Definitions

ISPE – March 2017
GAMP Guide: Records & Data Integrity

US FDA – April 2016
Data Integrity and Compliance with CGMP: Guidance for Industry



https://govzilla.com/blog/2019/05/pharma-medical-devices-data-integrity-breaking-down-keywords-and-citation-trends-from-the-fda/

ALCOA / ALCOA+ Principle

FDA: *"For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (**ALCOA**)."*

Attributable
- Who did it?

Legible
- Can I read it?

Contemporaneous
- When is it recorded?

Original
- Has it been modified?

Accurate
- Is it contextually correct?

Complete
- Is it a full set?

Consistent
- Is it contextually consistent?

Enduring
- Is it durable?

Available
- Is it easily accessible for review?

Integrity Tester– Data Integrity

- Internal Double Data Backup
  - All generated data is instantly backed up on the internal inaccessible memory
- Encrypted Data
  - Efficient protection against misuse
- Audit Trail and NTP
  - Reliable time stamps in the audit trail of all events
  - Export as digitally signed write-protected PDF
- User Matrix to generate individual user roles
  - Freely define user roles according to the matrix of all existing features for a maximum of flexibility
- Four eyes principle with electronic signature
  - Enhance test result reliability and data validation
  - Combined with automatic detection of faulty setups it enhances the reliability of the operator's evaluation

I-Testing with Alcohols
HSE / OSH – Explosion proof

- The only filter integrity tester device on the market to be explosion proof
- This allows safe re-testing of alcohol wetted filters according to recommended procedures (cf. PDA Technical Report 26 and Points To Consider part 2).

IECEx, ATEX Zone 2 Groupe II-B
FM (USA) Class 1 Zone 2 Group II-B

HSE / OSH – External Cleanability – Contamination Control Strategy

- External cleaning can be made with most of the commonly used chemical agents thus allowing rotating use of disinfectants e.g.
  - Spor-Klenz® Ready-To-Use Cold Sterilant
  - 3% Hydrogen Peroxide WFI Sterile Solution
  - Septihol® Sterile Alcohol Solution 70% IPA
  - Water for injection
  - Sodium hydroxide (NaOH) 10%
  - Quaternary ammonium compounds 0.2%

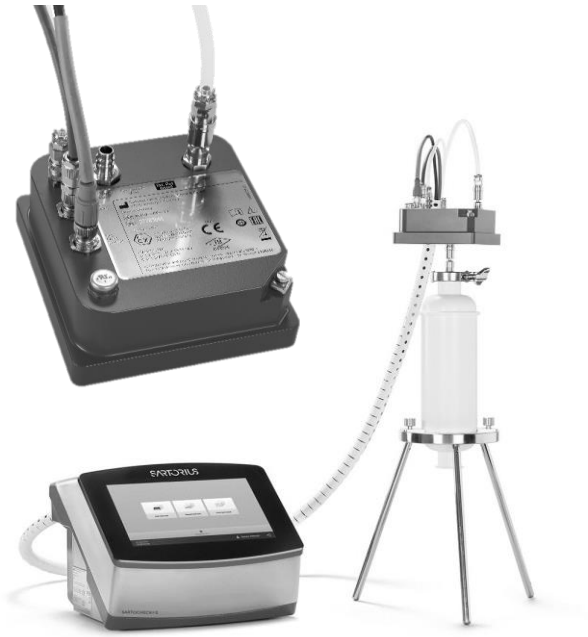
- The Sartocheck® 5 / 5 Plus is designed to be compatible to **VHP** and can therefore be left in the cleanroom during fumigation

HSE / OSH – Internal Cleaning – Contamination Control Strategy

- The internal pneumatics of the Sartocheck® 5 / 5 Plus can be cleaned with up to 0.5M NaOH @ 50 °C
  - 0.1M NaOH at room temperature is mostly enough (c.f. cleaning study)
  - Fully automated cleaning, rinsing and drying – plug and play without intermediate steps or disconnection during the process (fully risk assessed)

HSE / OSH – Backflow protection and protection against cross cont.

- The optional Accessory Kit for External Venting Prevents Unwanted siphoning of liquid
  - Prevents cross contamination between product-soaked filters being post-use tested and new filters being pre-use tested (e.g. PUPSIT)
  - Is complementary to the cleaning kit to reach the highest level of CCS
  - A specific CCS datasheet is available



The ATEX classification of the AKEV

- IECEx, ATEX Zone 1 Group II-B
- FM (USA) Class 1, Div. 1, Zone 1 Group II-B

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Trouble Shooting of Integrity Tests

Failure Analysis / Troubleshooting (from PDA Technical Report No. 26)

If a sterilizing filter fails an integrity test, it could be damaged, but there may be other causes for the failure that include incorrect assembly (incomplete sealing) and incomplete wetting. Any investigation of filter failure or retesting should be described in the operating procedure.

Filter Damage or Test Problems?

- To distinguish between filter damage and possible test problems or artifacts, the following verification steps may be taken —
  - The appropriate integrity test has been selected.
  - The correct test parameters have been used.
  - The correct wetting fluid and wetting procedure have been used.
  - There are no leaks in the test system.
  - Filter assembly temperature has remained stable and within specification during testing.
  - Equipment has been properly calibrated.
  - Test setup has been properly assembled and functions properly.
  - Correct filter has been installed.

Retesting Protocol

To confirm corrective action has been effective, the following retesting step may be taken —

- Rewet the filter according to the specifications and repeat the test

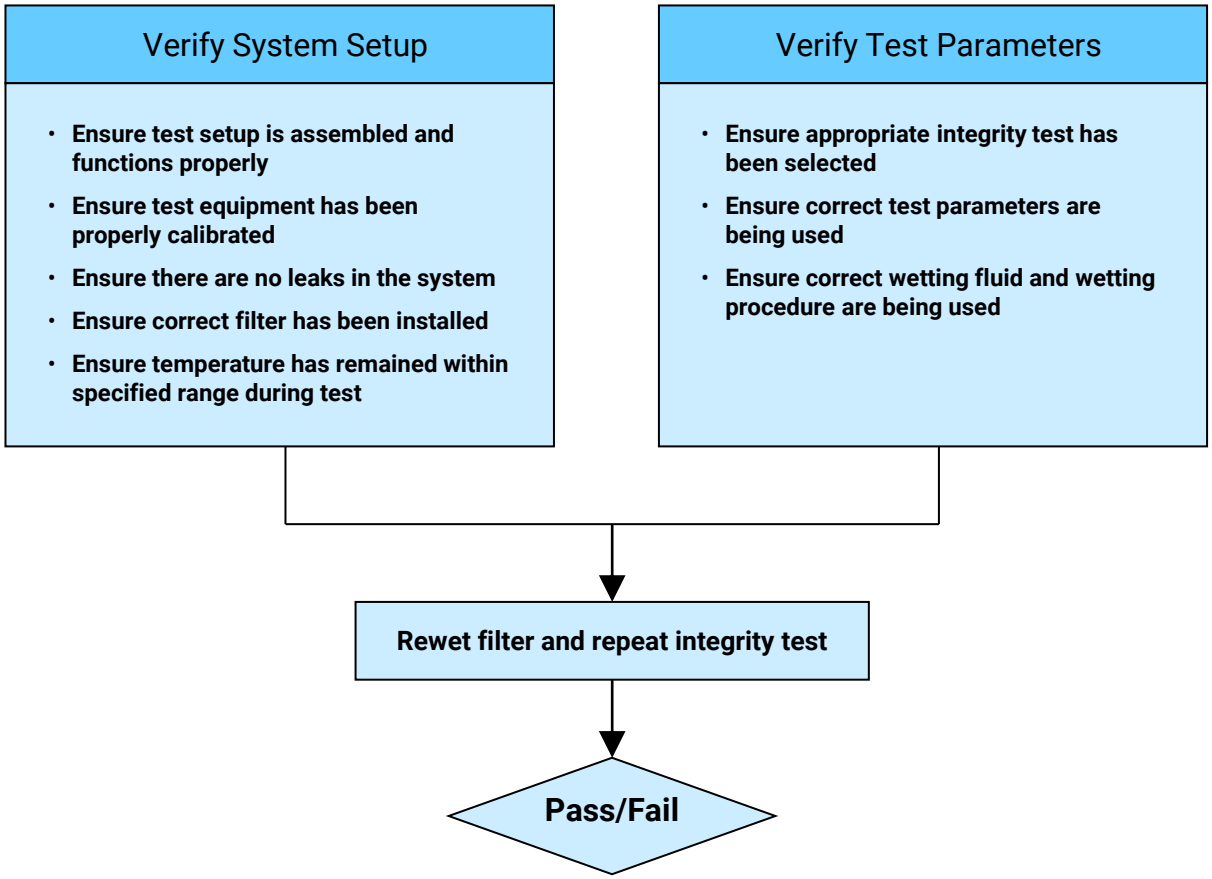
If the filter integrity test fails again, the following step may be employed —

- Apply more aggressive wetting conditions by increasing flush volume / time, increasing pressure differential and / or applying back pressure

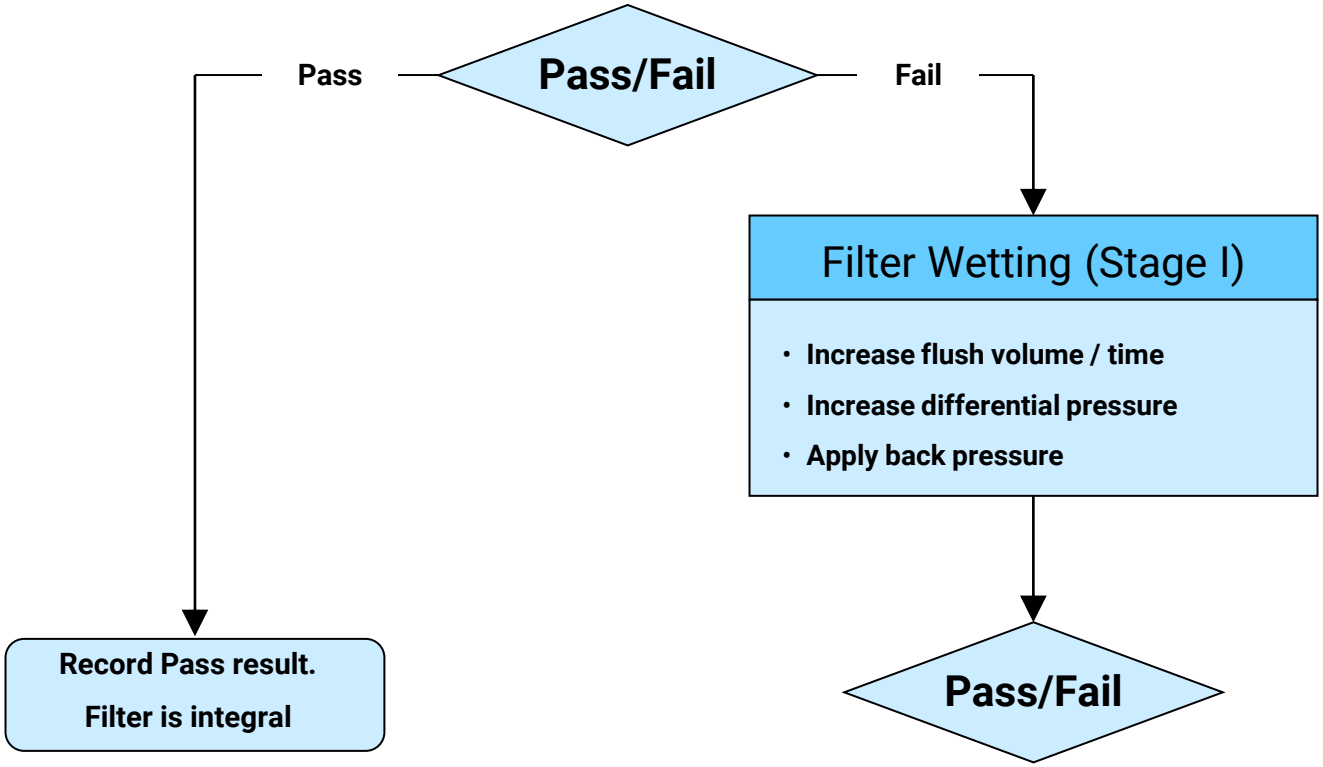
If the filter integrity test fails yet again, the following step may be employed —

- Perform the integrity test in a lower surface tension reference fluid to assess filter wettability changes independent of filter integrity
- If the filter fails using the reference fluid, the filter fails the test

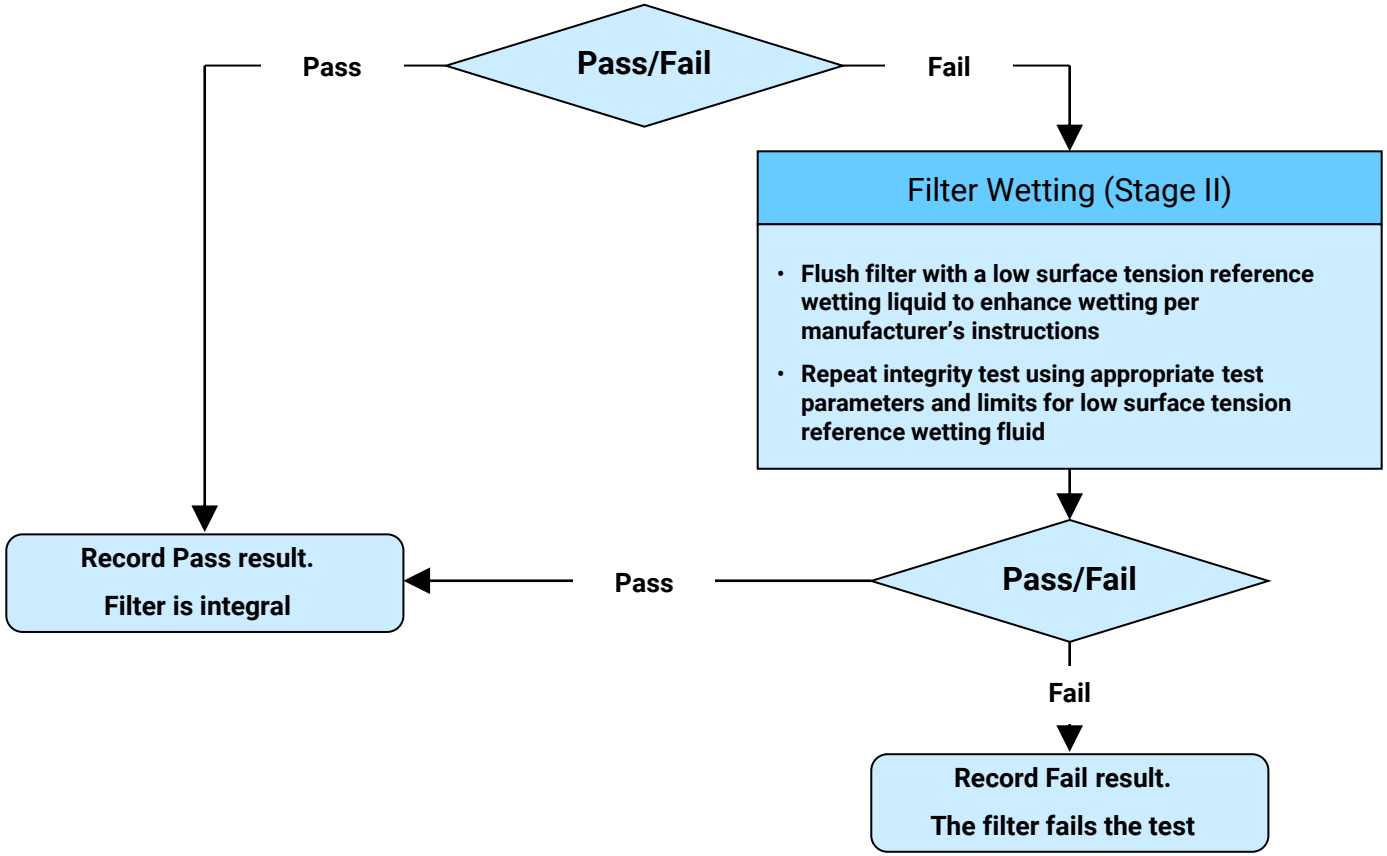
Failure Analysis Decision Tree (Step 1)



Failure Analysis Decision Tree (Step 2)



Failure Analysis Decision Tree (Step 3)



Membrane Wetting

- **Membrane polymer:** Some polymers are easier to wet than others, depending on the critical surface tension of the membrane material.
- **Pore size:** The smaller the pore size, the more difficult the pores are to wet.
- **Wetting fluid:** Some wetting fluids may interact unfavorably with the polymeric matrix.
- **Product residues or contaminants:** Product residues or contaminants can alter the hydrophilicity of the membrane polymer and repel the wetting fluid or lower the surface tension.
- **Pressure conditions:** Manufacturer's pressure recommendations should be followed to completely wet the membrane.
- **Temperature conditions:** Temperature influences the surface tension of the wetting fluid.

Key Factors Affecting Diffusion Tests

Wetting liquid:

- Complete wetting / thickness of the wetting layer
- Temperature consistency / range throughout test

Test gas:

- Solubility coefficient of the test gas in the wetting liquid
- Diffusivity of the test gas through the wetting liquid
- Applied differential pressure
- Temperature consistency / range throughout test

Membrane:

- Porosity

System:

- Stabilization and test time
- Leak tightness
- Temperature equilibrium

Key Factors Affecting Bubble Point Tests

Wetting liquid:

- Surface tension
- Wetting angle
- Temperature consistency / range

Test gas:

- Applied differential pressure (incremental)
- Temperature consistency / range during any pressure decay increment

Membrane:

- Complete wetting
- Diameter of largest pores

System:

- Leak tightness

Key Factors Affecting Water Intrusion Tests

Wetting liquid:

- Fill level / headspace
- Wetting angle
- Temperature consistency / range during entire test

Test gas:

- Applied differential pressure
- Temperature consistency / range during entire test

Membrane:

- Contamination (e.g. hydrophilic spots / hydrophobic interaction)
- Porosity

System:

- Leak tightness
- Stabilization time
- Test time
- Thermal equilibrium

Automated Integrity Test Musts

- Use calibrated integrity tester
- Maintain constant temperature throughout entire test

$$T_{system} = T_{air} = T_{fluid} = T_{filter} = T_{housing}$$

- Thoroughly wet membranes
- Ensure system leak tightness
- Use proper integrity test parameters for filter being tested

Integrity Test Troubleshooting Guide (from TR26, Appendix D, Table D-2)

No Test Pressure Buildup	• Filter system leakage (i.e., damaged sealing, valve open, clamps improperly closed, damaged filter) • Improperly wetted filter • Inappropriate wetting medium (e.g., solvent instead of water) • Filter contains traces of product solution or extraneous material from wetting fluid • Incorrect filter pore size rating • Gas supply to the unit blocked • Inlet tubing to the housing improperly installed • Excessive temperature drifts • Improper valve function within unit • Internal pneumatic leaks
Continuous Venting of the Unit	• Internal valve contamination and improper function
Abortion of Test During Stabilization Phase	• Filter system leakage (i.e., damaged sealing, valve open, clamps improperly closed, damaged filter) • Insufficiently wetted filter • Contaminated filter • Incorrect filter pore size rating • Excessive temperature drifts • Internal pneumatic leaks
Measured Volume is Wrong	• Incorrect input of the reference volume • Internal pneumatic leaks

Integrity Test Troubleshooting Guide (cont.)

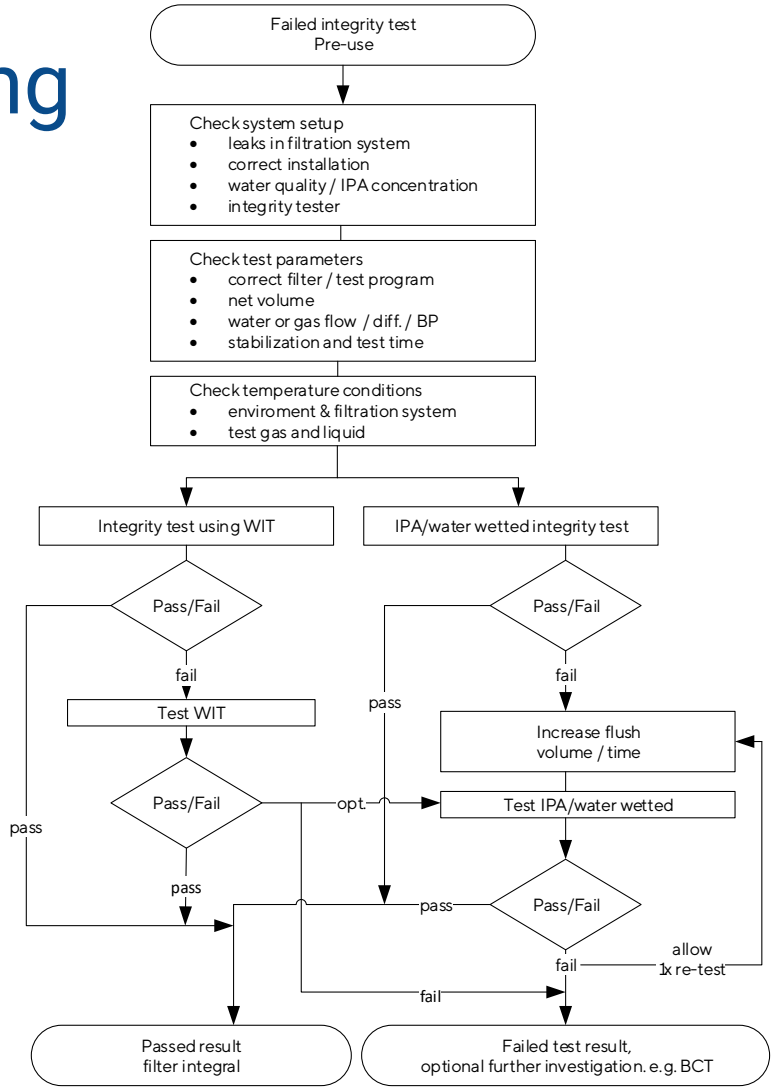
Failure of Bubble Point	• Damaged filter • Insufficiently wetted filter • Inappropriate wetting medium (e.g., solvent instead of water) • Incorrect filter pore size rating • Filter contains traces of product solution or extraneous material from wetting fluid • Internal pneumatic works improperly • Inlet tubing to the housing improperly installed • Incorrect test gas • Incorrect test parameter setting • Incorrect test code • Large multiple-cartridge assembly
Failure of Diffusive Flow	• Damaged filter • Insufficiently wetted filter • Inappropriate wetting medium (e.g., solvent instead of water) • Incorrect filter pore size rating • Filter contains traces of product solution or extraneous material from wetting fluid • Internal pneumatic works improperly • Inlet tubing to the housing improperly installed • Incorrect test gas • Incorrect test parameter setting • Temperature shifts during the test time • Insufficient stabilization time
No Pressure Decay	• Inlet tubing to the housing improperly installed • Downstream valve closed • Blocked connector • Blocked internal pneumatic • High temperature during test time

Integrity Test Troubleshooting Guide (cont.)

Failure of Pressure Decay	• Filter system leakage (i.e., damaged sealing, valve open, clamps improperly closed, damaged filter) • Insufficiently wetted filter • Inappropriate wetting medium (e.g., solvent instead of water) • Incorrect filter pore size rating • Filter contains traces of product solution or extraneous material from wetting fluid • Internal pneumatic works improperly • Inlet tubing to the housing improperly installed • Incorrect test gas • Temperature shifts during the test time • Insufficient stabilization time or incorrect test time
Inappropriate Diffusion Test Result	• Damaged filter • Insufficiently wetted filter • Inappropriate wetting medium (e.g., solvent instead of water) • Incorrect filter pore size rating • Internal pneumatic works improperly • Inlet tubing to the housing improperly installed • Incorrect test gas • Incorrect test parameter setting • Temperature shifts during the test time • Insufficient stabilization time or incorrect test time

From Appendix D, Table D-2. PDA Technical Report No. 26, Sterilizing Filtration of Liquids, Revised 2008

WIT Trouble Shooting (Pre-use)



WIT Trouble Shooting (Post-use)