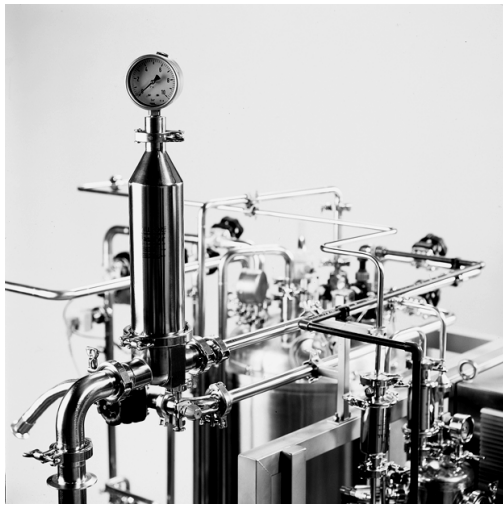
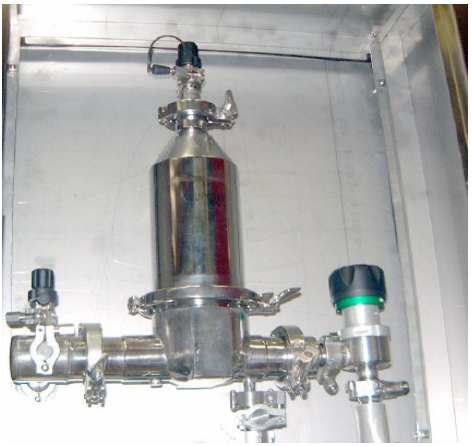


Operator Certification Course
Integrity Testing Methodology



Hydrophobic filter Integrity Testing

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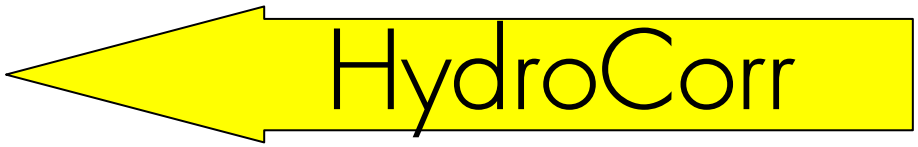
Integrity testing overview

- **Particle based**
  - Microorganism
  - Aerosols
- **Liquid property based**
  - Alcohols
  - Water



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Particle Based Integrity Testing

Microorganism - Destructive Test

- Aerosol microorganisms or liquid bacterial challenge
- Phage (T1, T3, phiX)
- Bacteria (B. diminuta)

Aerosol Based - Non-destructive Test

- "Smoke": D.O.P.(Di-Octyl Phthalate), Glycerol, Corn oil (**Dispersed Oil Particulate**) etc
- Methylene Blue, Sodium Flame
- Issues
  - Particle Distribution must be uniform
  - Must have correlation of particles vs microorganisms
  - High equipment cost
  - Difficult to perform in-situ (particle counter downstream of filter)

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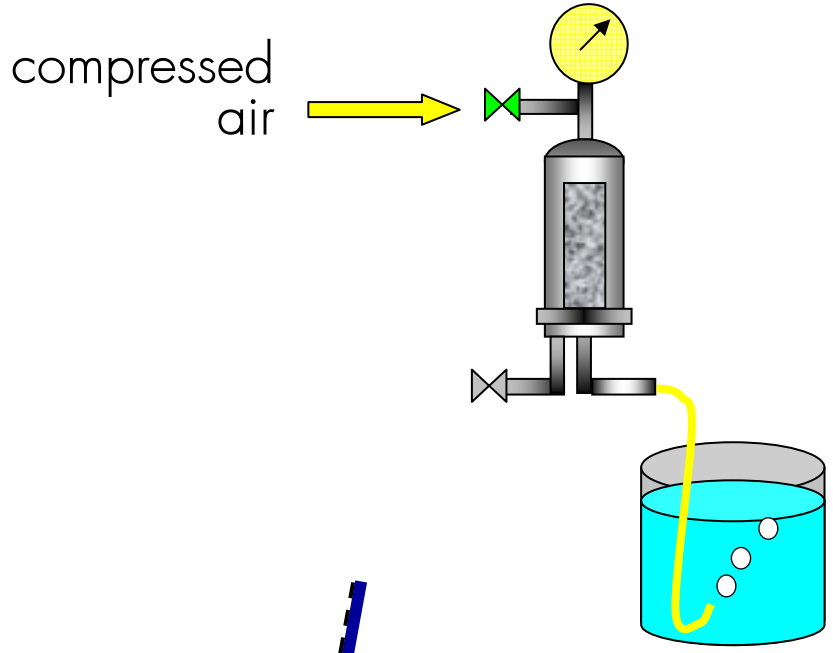
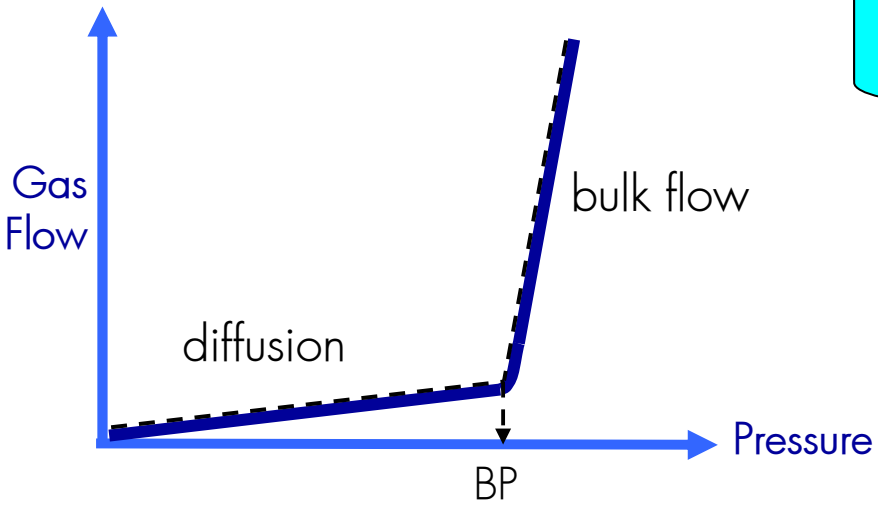
Alcohol test
Traditional Testing Principles

- **Typical wetting liquids are Isopropyl Alcohol (I.P.A. or Propanol-2), Methanol, Tert-butyl Alcohol, or a mixture of one of these and water**

- **Uses same principles as a hydrophilic test**

Diffusion & Bubble point





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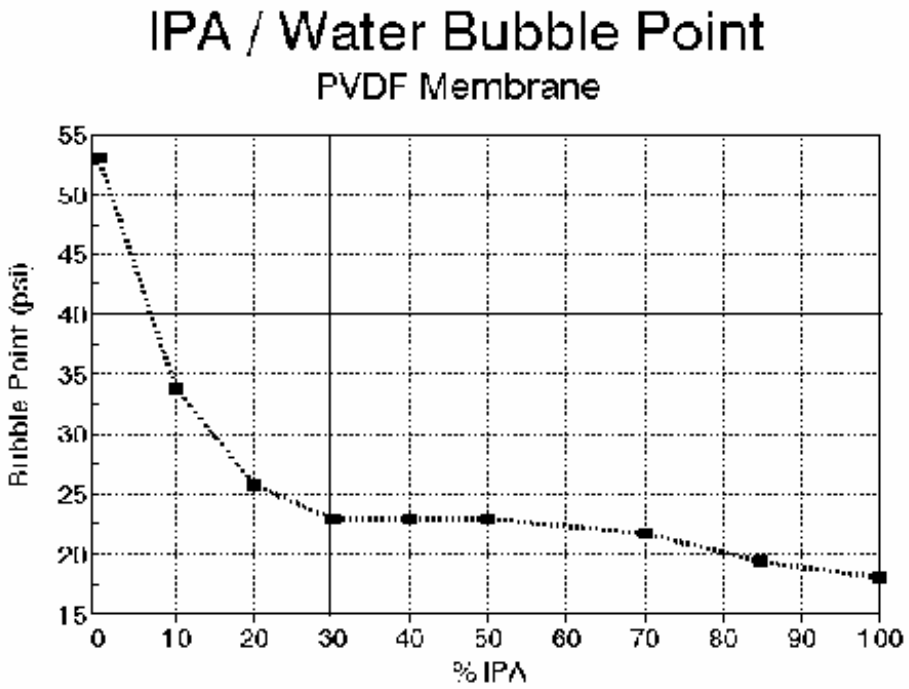
Alcohol test
Solvent Effects on Bubble Point



- Changing solvent changes wetting & contact angle
- Check alcohol concentration & quality

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Alcohol test
Advantages

- No special equipment required
- Follows similar procedures to hydrophilic membranes. Operator training time is reduced
- Traditional
- Reduced temperature influence
- Widely accepted
- Well understood
- Correlated to bacterial challenge
- Can be performed easily & quickly

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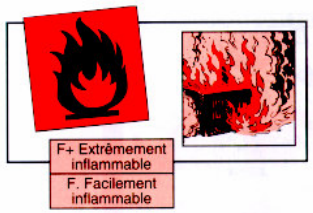
Alcohol test
Issues

- **Alcohol / Water mixtures are often used due to:**
  - cost
  - flammability
  - high diffusion
  - possibility of evaporation



- **Secure areas and equipment needed**
- **Can be difficult to perform in-situ**

- **Some concerns with residual test solution remaining in filter holder / pipework after testing**
- **Residual solution should be removed before filter sterilization**

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Alternatives to Alcohol Integrity Testing

Needed primarily due to:

- Issues with alcohol contamination of processes
  - residues
- Risks inherent with the use of solvents

Water-Based Integrity Tests have been developed to overcome these issues

- Ease of use

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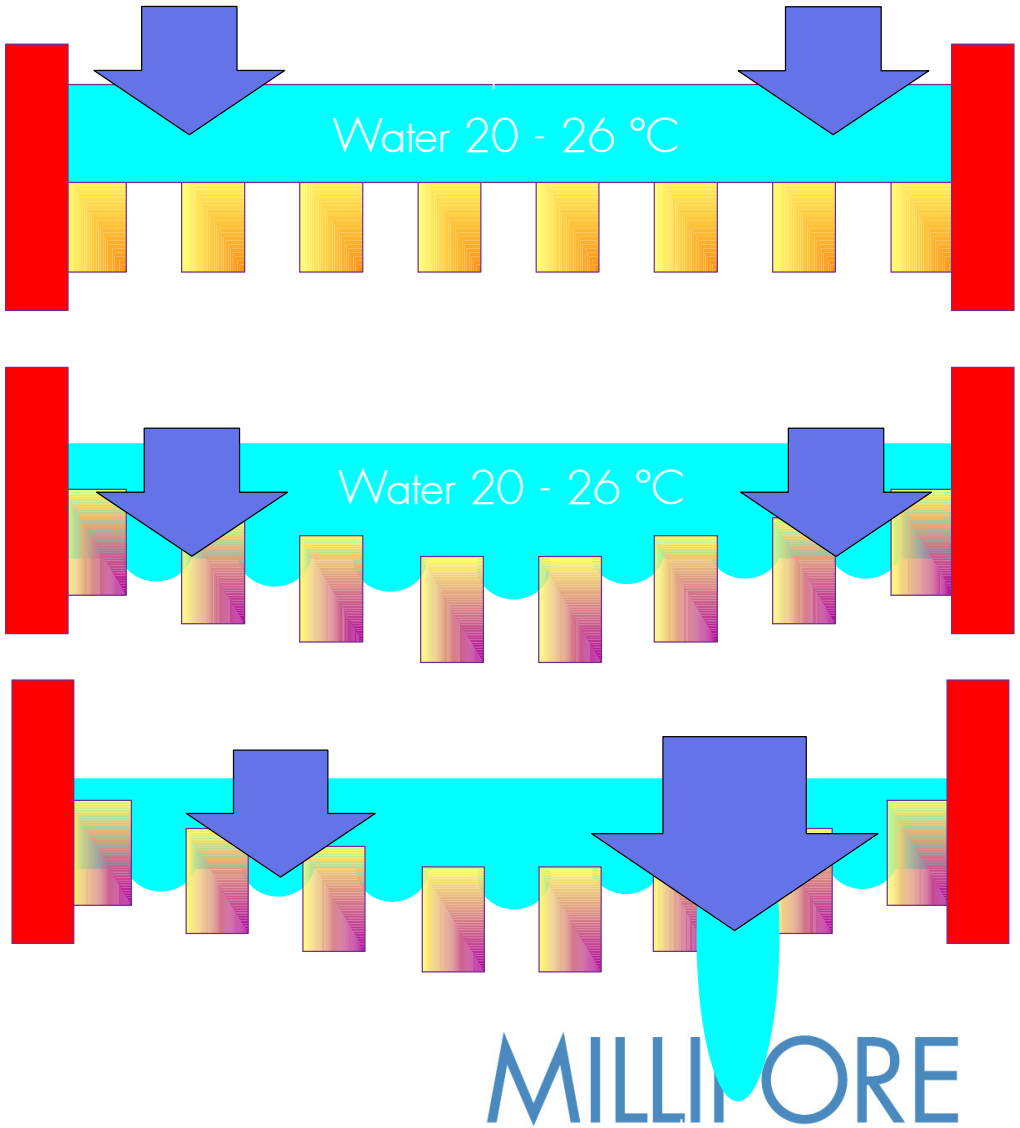
Advantages of HydroCorr Test

- HydroCorr test only involves water
  - no downstream operation
  - minimal water flow
  - does not compromise sterility
- Easy to automate
- Test can be performed
  - in-line
  - after SIP
  - before and after lyophilization



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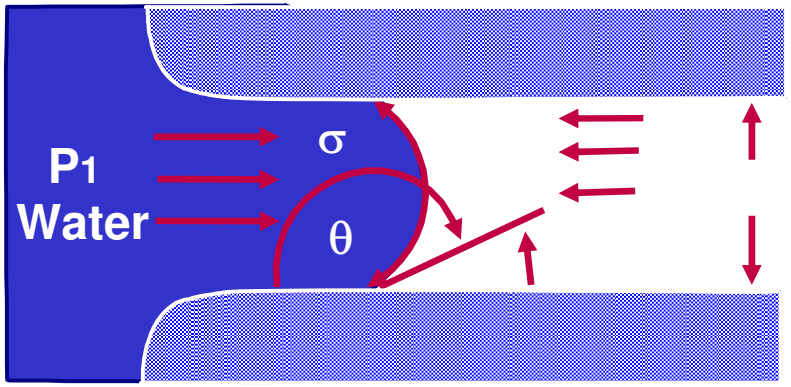
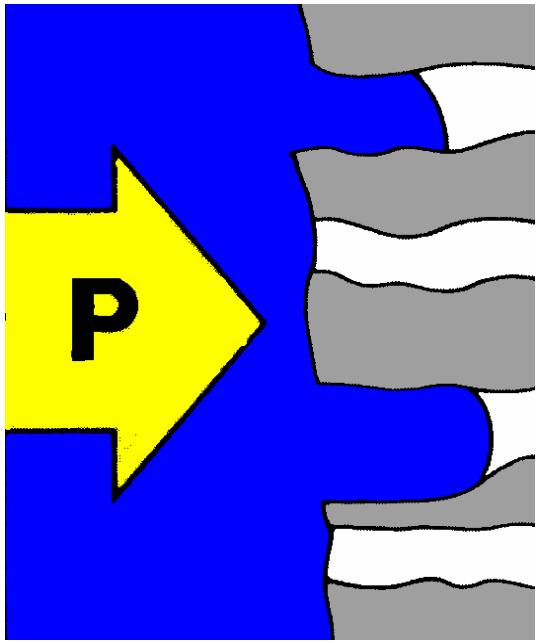
Water test
Water-Based Integrity Test Basis

- Hydrophobic polymers repel water

- Water **Intrusion Pressure** The minimum pressure necessary to force water into the largest pores of a ***hydrophobic*** membrane.

$$IP = -\frac{4k\sigma Cos(\theta)}{d}$$





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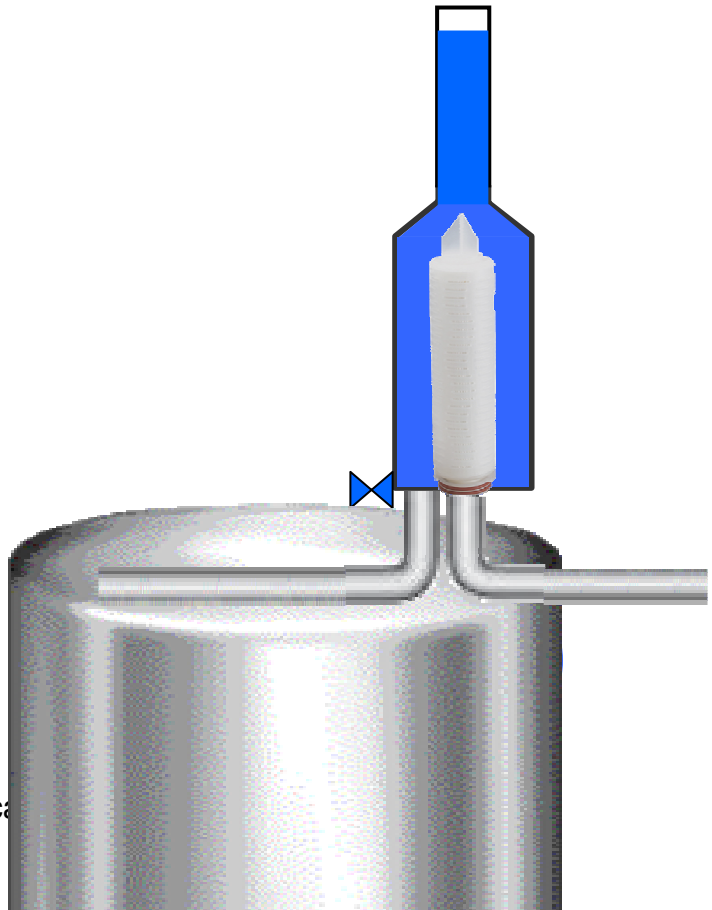
Water test
Resistance to water intrusion



- Force water under pressure onto the surface of the filter.
- Applied pressure is < integral filter intrusion pressure
- The water pressure is maintained but not increased.
- Pleated structures compact under pressure
- If integral, the upstream pressure will not drop below a preset value.

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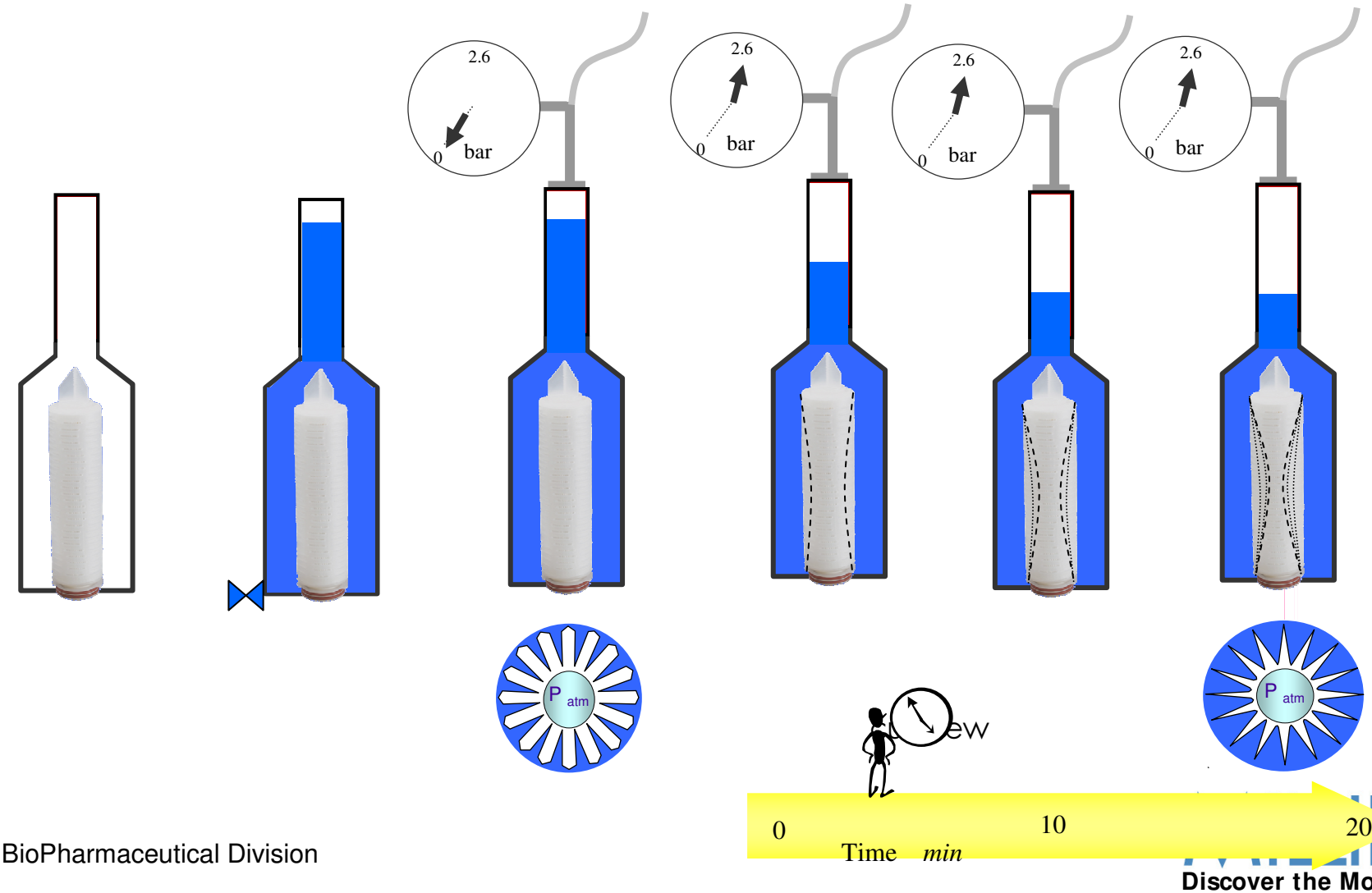
Water test
Resistance to water intrusion



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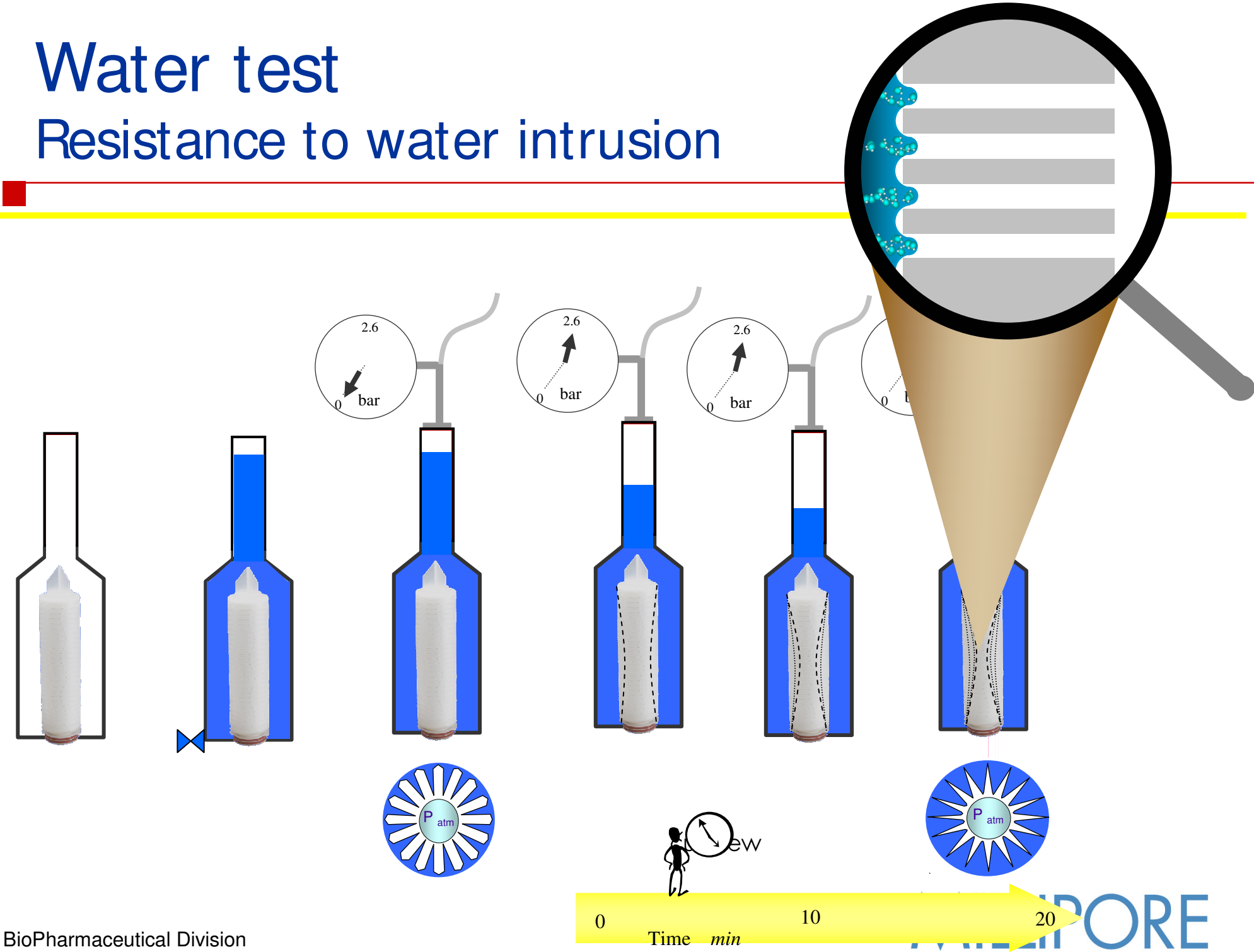
Water test

Resistance to water intrusion



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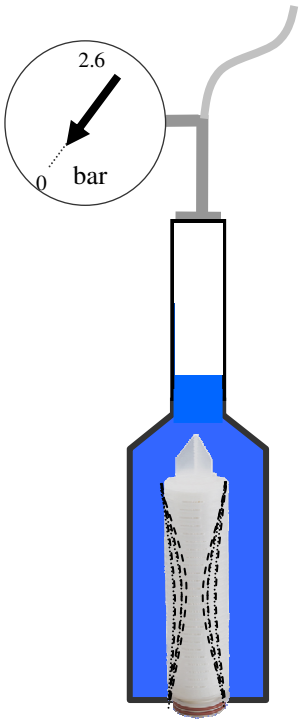
Water test
Resistance to water intrusion



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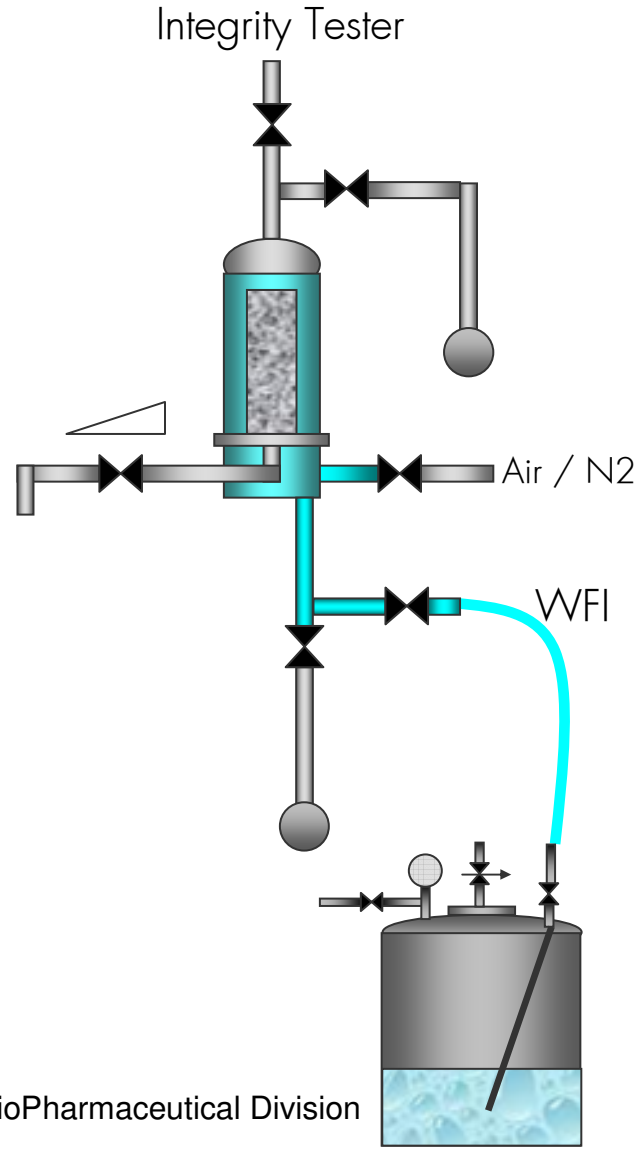
HydroCorr Test



- HydroCorr test requires
  - Filling of the filter with WFI
    - stored in a pressure vessel
    - direct supply line
  - Evaluation of the air upstream volume
  - Measurement of the pressure drop
  - Conversion in HydroCorr rate (ml/min)
    - Hydrocorr = ($\Delta P \times V$) / $Pt \times t$

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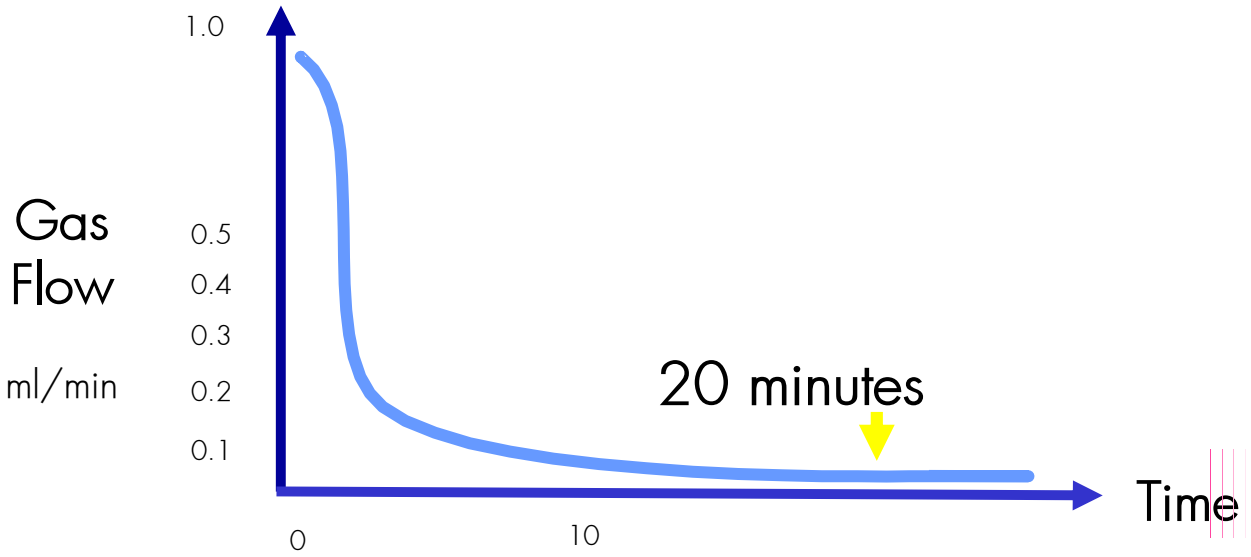
HydroCorr test

- Applicable for all types of hydrophobic testable membranes
- Correlated to bacterial Challenge
- To be conducted on a perfectly dry membrane



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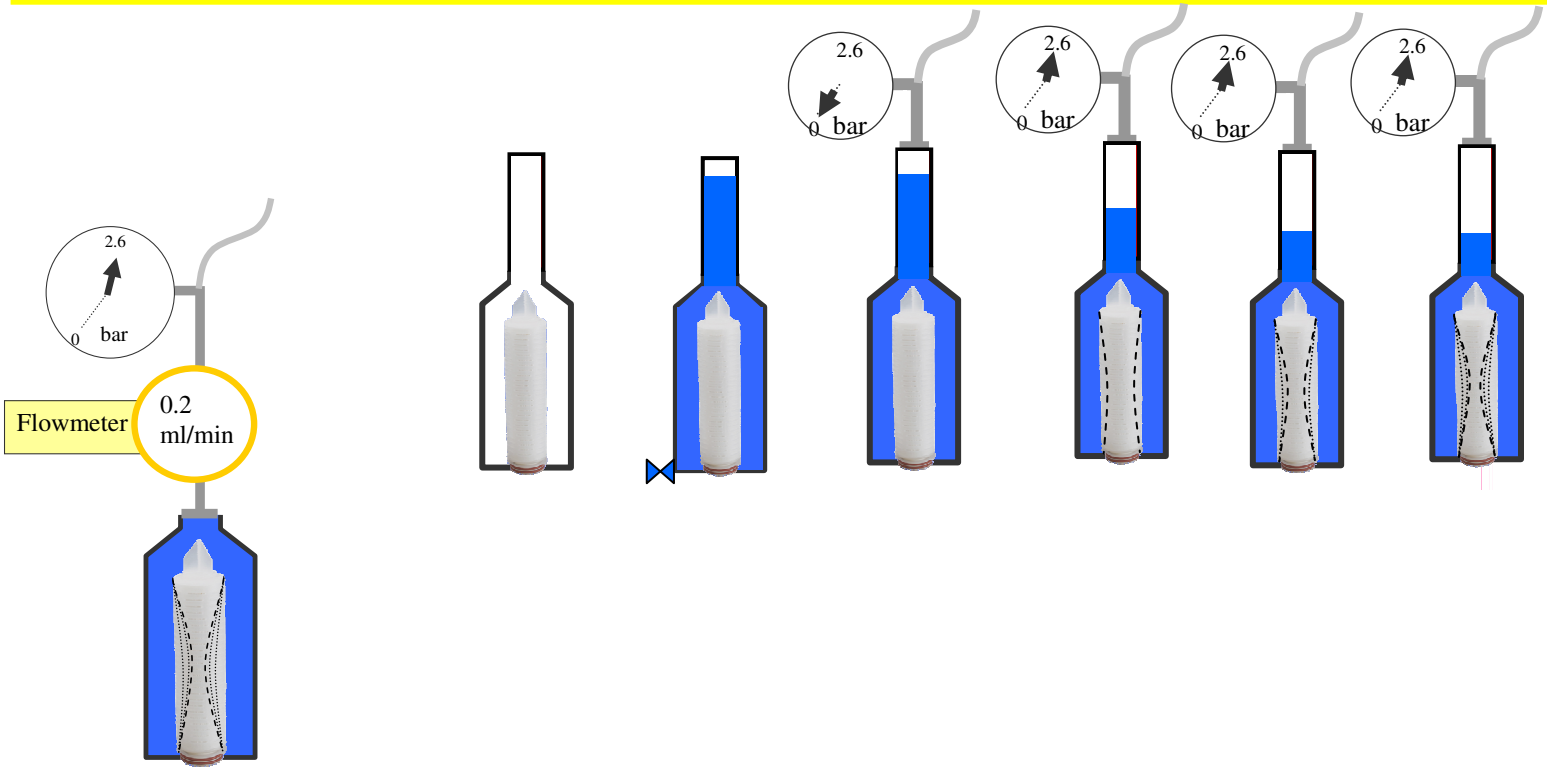
Water test
Performing Water-Based Tests



Manually

Use a flow meter to measure actual upstream water displacement

Automatically

Use a pressure transducer to measure upstream gas pressure loss

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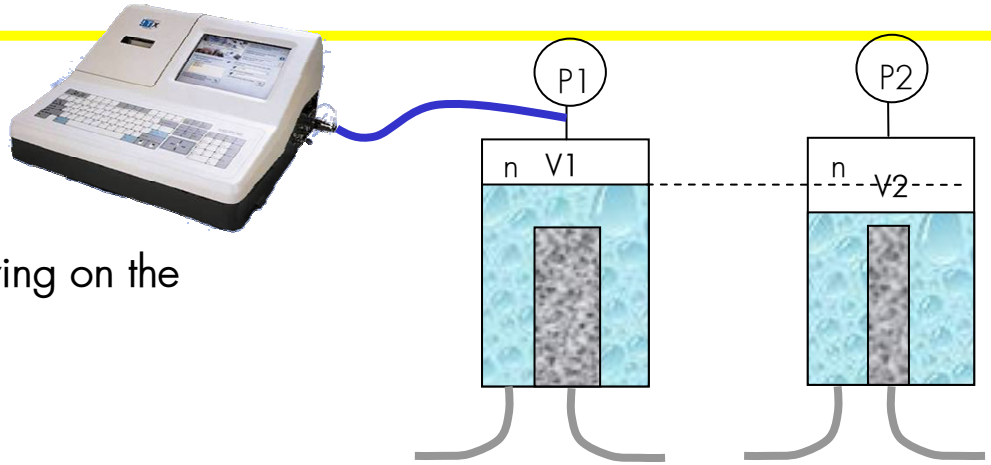
Water test

Automated water based testing



As pleats compress water level drops,

Upstream air volume increases

Principle based on pressure decay monitoring on the upstream side of the filter

Instrument determines volume (V2-V1) change by measuring the corresponding pressure drop (P2-P1)

The gas volume is an isolated system (there is no gas exchange = diffusion is negligible)
The temperature is constant

The ideal gas law written for the system is : $P1 \cdot V1 = P2 \cdot V2 = n R T$

$$\text{HydroCorr}_{ml/min} = (V2-V1) / t$$

$$= V1 \cdot (P1 - P2) / P2 \cdot t$$

$$= V1 \cdot \Delta P / t \cdot P2$$ Absolute !

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Water test
Water-Based Test Considerations

- Must have a leak-free system
- Filters must be dry and clean
- Temperature changes should be minimized
- Reference testing is important
- Must have a complete validation package
- Values must be comprehensively correlated to microorganism challenge

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