完整性测试

密理博中国有限公司
生物制药工艺部

MILLIPORE

讲座主要内容

- Millipore公司简介
- 完整性测试原理
- 自动完整性测试仪
- 过滤器的验证

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Who is Millipore ?密理博简介

•创建于1954年,总部位于美国麻省波士顿，世界最早的膜生产商之一。

•雇员超过5800人

•专注于生物/制药及生命科学领域

•分离纯化设备的领先者

•拥有超过6500种产品

•2006年销售额达到15亿美元

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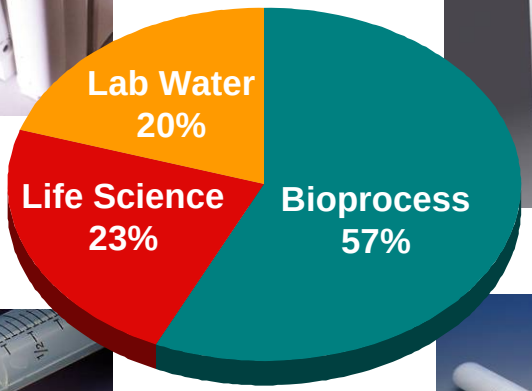
Millipore全球有7个符合ISO9000标准的制造工厂

Millipore Product Range: from a $2.00 pipette tips to $5 million custom-engineered systems

密理博产品范围: 从2美金的移液管至500万美金专为客户定制的系统



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无菌工艺:已经有超过800亿支无菌产品使用我公司的Durapore产品（2005）

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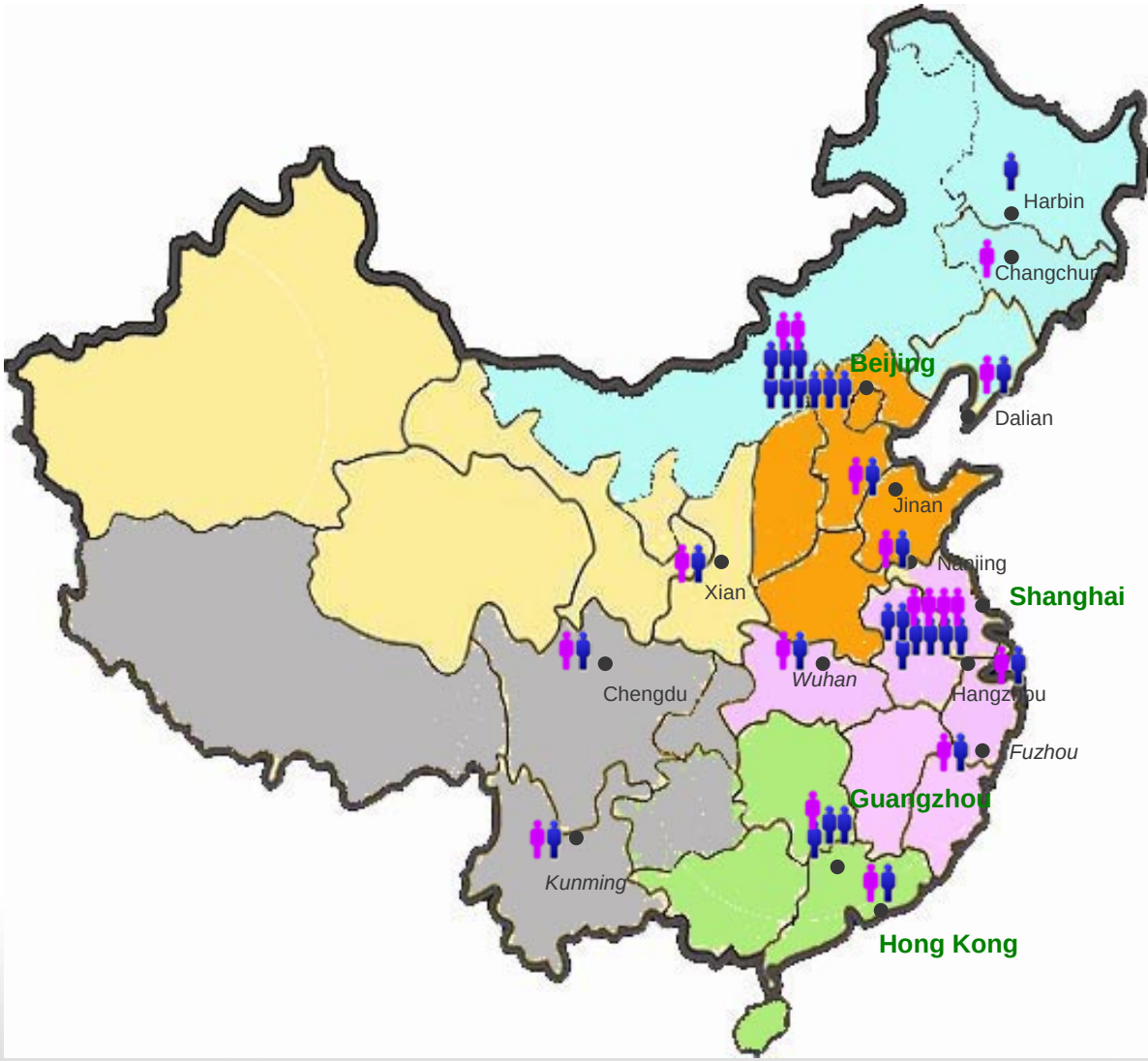
密理博中国

- 1982年在中国开始设立办事处
- 2000年在上海设立贸易有限公司
- 在香港, 上海, 北京, 广州, 成都, 沈阳等地都有办事处



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Millipore 将成为您忠实的战略合作伙伴

- **专业的销售人员**
  产品，应用，商务
- **技术应用专员**
  验证专员
  为客户提供技术解决方案
- **服务工程师**
  售后服务
- **实验室支持**
  验证实验室
  应用开发实验室
- **现场验证**
  欧洲总部支持
  本地服务

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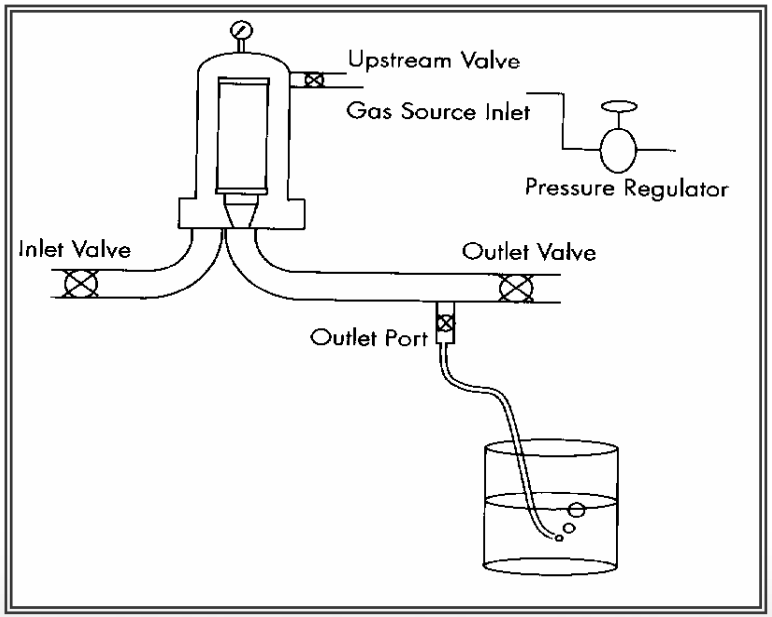
Integrity Testing Theory
完整性测试理论



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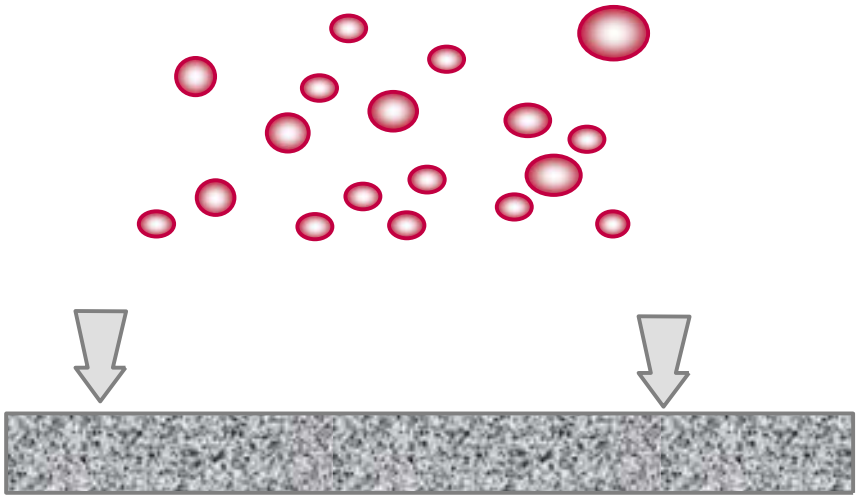
讲座目录

- 为什么要对除菌滤器进行完整性测试？
- 完整性测试的方法有哪些？
- 为什么可以用起泡点的方法代替细菌挑战试验？
- 什么时候进行完整性检测？
- 起泡点测试原理是什么？
- 扩散流测试原理是什么？
- 自动完整性测试仪

什么是滤膜完整性?

完整滤膜

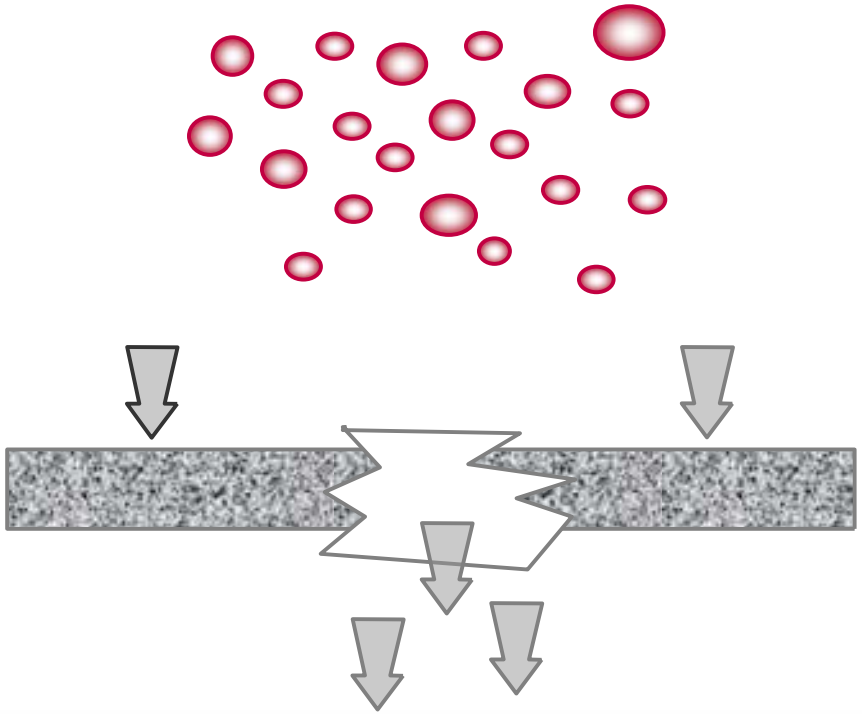
比膜孔大的污染物



下游没有污染物

非完整滤膜

比膜孔大的污染物



下游污染

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Why Integrity Test?
为什么做完整性测试?

Common Sense通常理解

- Filtration is often the most critical step in an operation
- 过滤通常是操作的关键步骤
- Confirmation of manufacturers specifications
- 确认制造规格
- Detecting leaks due to o-rings, gaskets, seals
- 检测0形环, 垫圈, 密封垫的泄漏
- Assuring the correct pore size filter
- 确认正确的过滤孔经
- Assuring integrity before sterilization
- 确认灭菌前完整性
- Assuring integrity after steaming or autoclaving
- 确认蒸汽和消毒锅灭菌后完整性

Business Practice 商业惯例

- Government Guidelines & Regulations法规要求
- Part of corporate standard operating procedure公司标准操作规程
- Auditing requirement审计需要

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法规中对完整性测试的规定

- **FDA Guideline指南 (2003)**
  - *Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst-case production conditions…"对于由一个或多个滤器组成的过滤系统，对它的验证都应该包括在最差条件下进行的微生物挑战试验。*

Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory affairs (ORA)

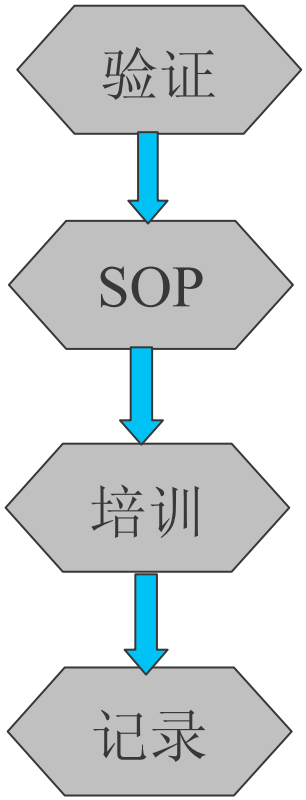
September 2004
Pharmaceutical CGMPs

法规中对完整性测试的规定

- **Revision of annex 1 to EC Guide to GMP for sterile medicinal products (1997)**
- 欧盟对于无菌药品GMP指南的附件一(1997版)
  - **“The integrity of the sterilized 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”**
  - 除菌过滤膜应该在使用前及使用后立即采取合适的方法确认其完整性,可以采用泡点,扩散流或压力保持的方法.
- FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (1987)
- FDA对于无菌操作生产的无菌药品的要求(1987版)
  - “Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilized prior to use.”
  - 完整性测试通常在过滤器安装,灭菌后使用前进行
- PDA Technical Report # 26
- **PDA技术报告26版**
  - “It generally is regarded as a cGMP requirement that filters or filter systems routinely be integrity tested both prior to and after use.”
  - 现行的GMP要求过滤器及过滤系统在使用前及使用后均需要进行完整性测试

SFDA在GMP检查中对过滤工艺的要求：

- 灭菌与非灭菌：
- 过滤时间与压力：
- 空气过滤器的维护：
- 完整性测试方法与书面报告：
- 验证：



Where & When Do We Integrity Test?
何时和何地做完整性测试?

- **WHEN TO DO IT?**
- 什么时候做?

- **Before sterilization**
- 灭菌前

- **Before use**
- 使用前

- **After use**
- 使用后

DETECTS WHAT?
检查什么?

- **Faulty housings**
- 外壳的问题

- **Out-of-the box failures**
包装以外的问题

- **Sterilization induced failures**
- 灭菌的影响

- **Stress induced failures**
压力的影响

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→What Are The Integrity Testing Choices?

→完整性测试的选择?

分类	测试名称	测试实施者
破坏性	细菌挑战测试	制造商以及客户进行验证时进行
非破坏性	起泡点测试，扩散测试	制造商出厂时及使用者现场进行

金标准

Regulatory & quality organizations need data from both to assure reliable and predictable filter performance法规和质量管理需要数据确保可靠和预知过滤器性能

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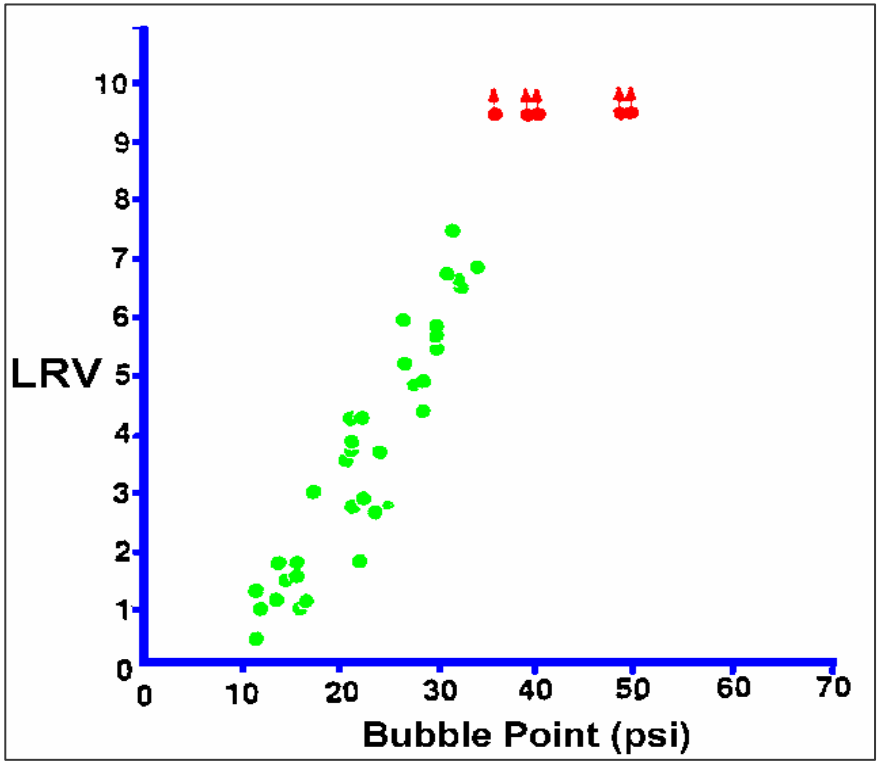
Destructive vs. Non-destructive Testing破坏性和非破坏性测试

There must be a correlation between a destructive and a non-destructive integrity test

破坏性和非破坏性测试两者必须有关联

- Regulatory requirement
- 法规需要
  - FDA Aseptic Guidelines
  - FDA无菌指南
- Validation justification for the use of a test
- 测试应用的验证理由



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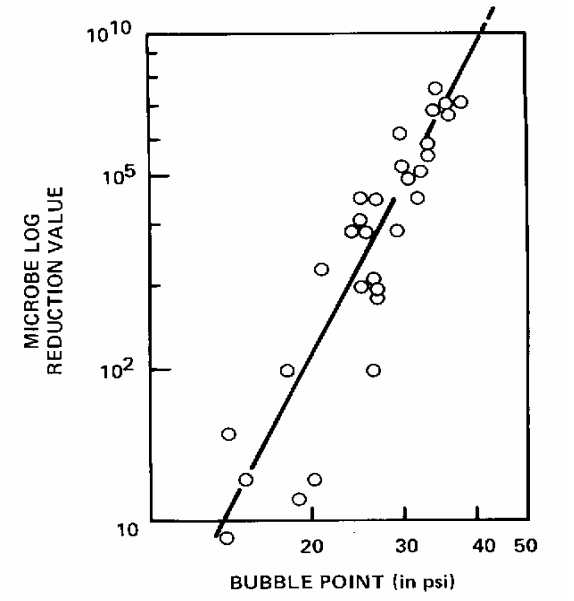
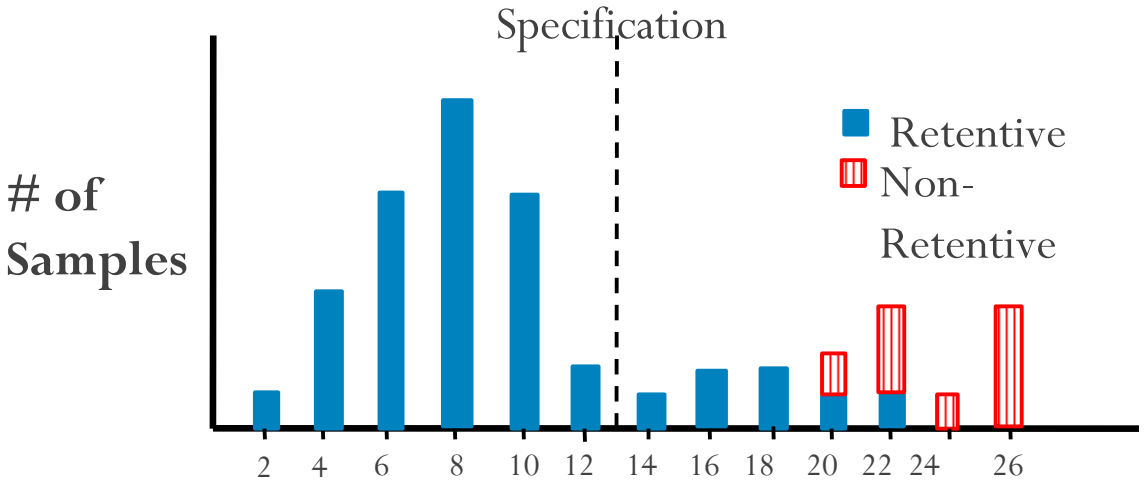
Integrity Testing Correlations
完整性测试关联





Bubble point can have a direct correlation

起泡点有直接的关联

Diffusion & other tests can have an "go - no go" correlation

扩散和其它测试有”通过, 不通过”关连

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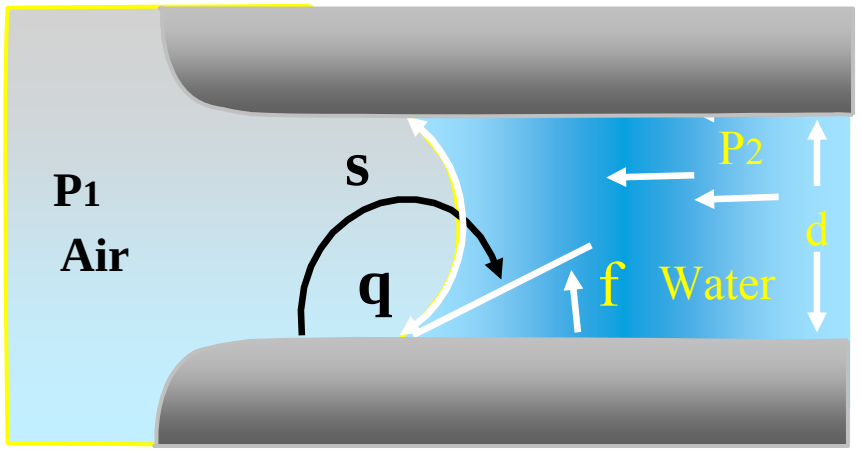
What Non-Destructive Integrity Tests are Available?

何种非破坏性测试合适?

Capillary based tests

基于毛细管测试

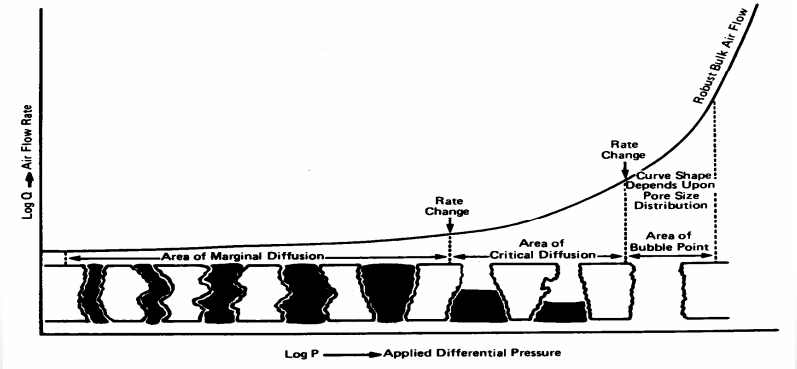
- Bubble Point起泡点
- HydroCorr 挤水法
- Corrtest水压法



Diffusive based tests

基于扩散测试

- Diffusion扩散
- Forward Flow前向流
- Pressure hold / decay压力保持/衰减



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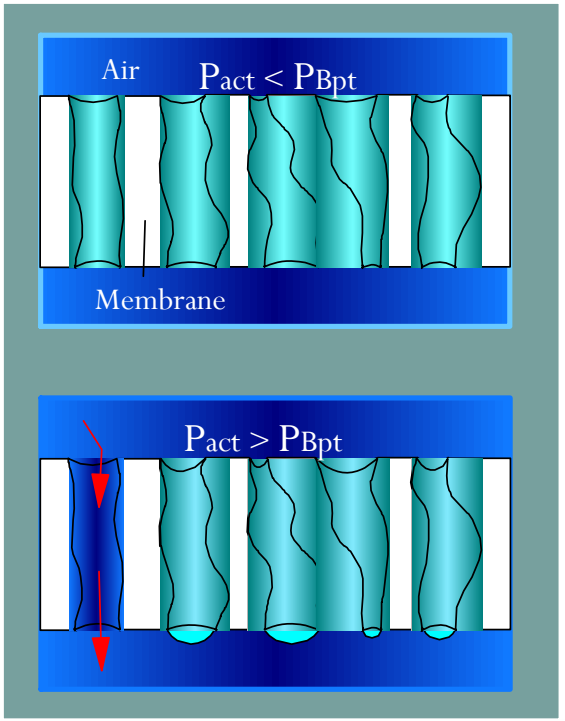
Bubble Point Introduction 起泡点介绍

Bubble point is the pressure at which gas displaces liquid from the largest set of filter pores and flows rapidly through the filter
→起泡点是气体从湿润的最大膜孔挤出液体快速流出时的压力

→ Bubble point indicates the magnitude of the forces holding liquid in the filter structure
→起泡点显示过滤结构内保持液体的力的大小

→ The oldest non-destructive integrity test
→最传统的非破坏性测试



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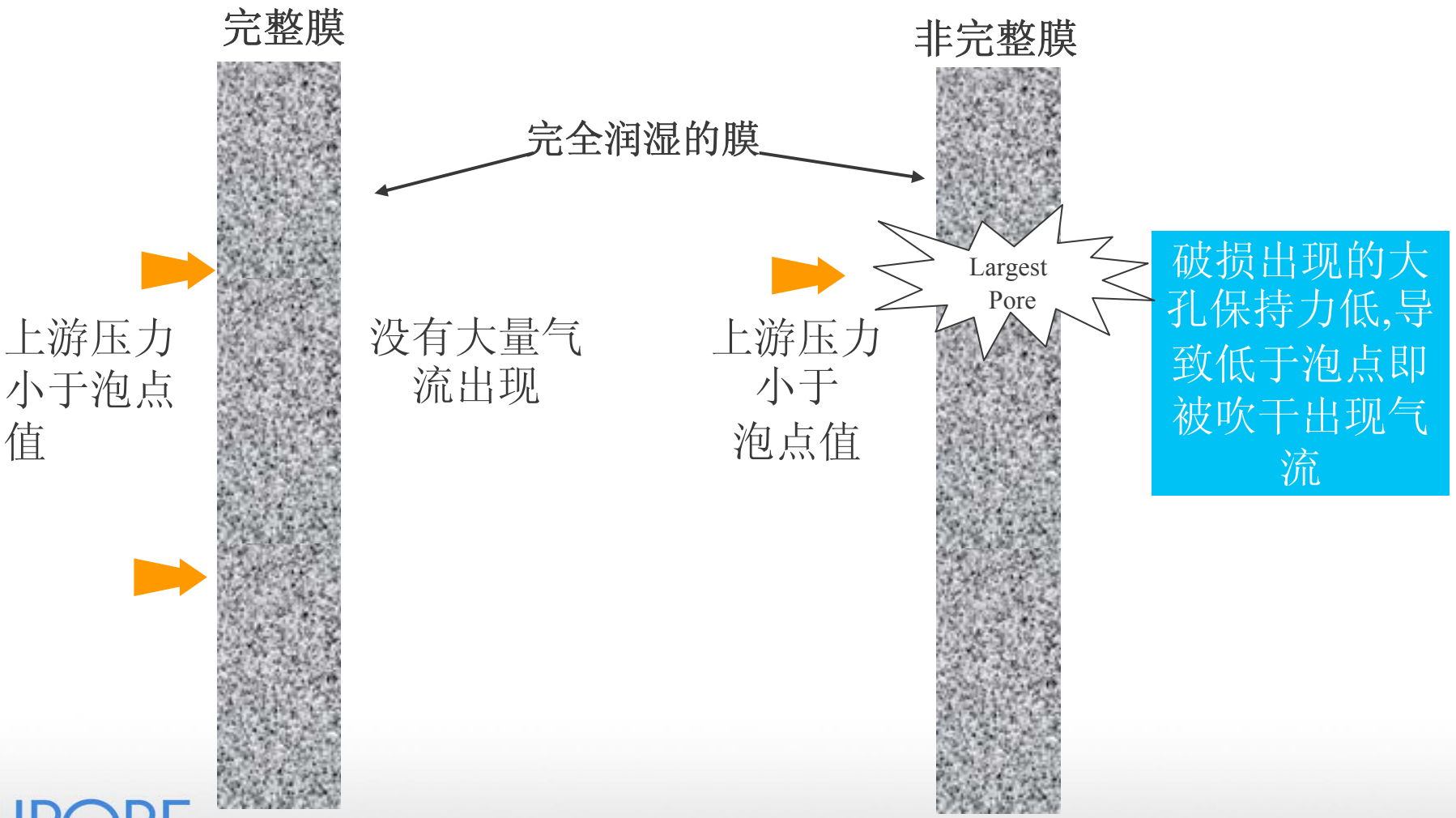
泡点测试



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Bubble Point Test Applicability
起泡点测试适用性

Useful for qualified manual testing of filters less than approximately 2000 cm^2 (~2 sq.ft.)
手动测试通常适用于过滤器面积小于2000平方厘米

Useful for automatic integrity testers for filters with gas flow rates of up to 100 ml/min or limit of the automatic testers qualifications
自动完整性测试仪适用于气体流速超过100毫升/分钟或自动测试仪的限定

Bubble Point Equation起泡点等式

The bubble point is expressed as:泡点可表达为

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

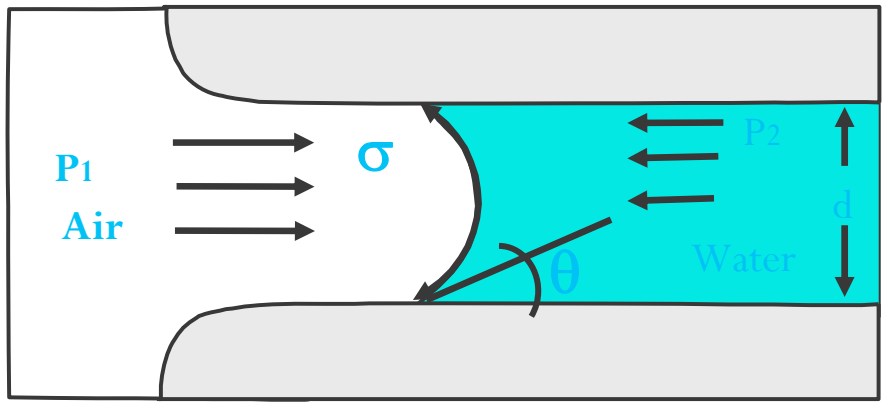
where 这里

k = shape correction factor 形状校正因子

γ = surface tension 表面张力

θ = contact angle 接触角

d = pore diameter 孔径



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泡点的影响因素

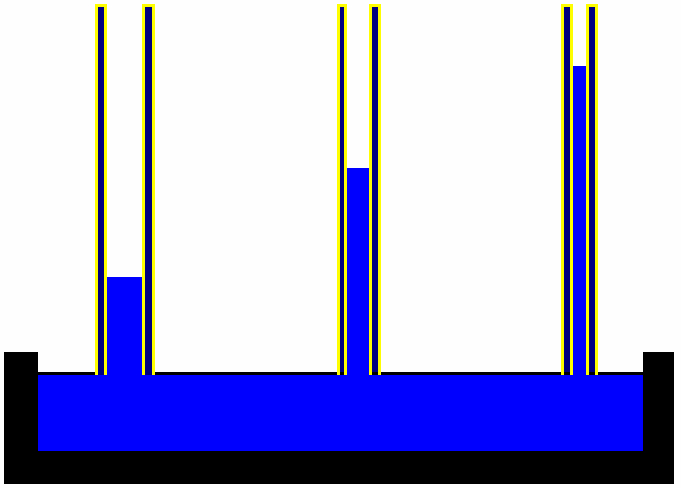
Depends on capillary forces;
依赖毛细管力

- membrane material, surface tension, contact angle, effective diameter,

膜材料, 表面张力, 接触角, 有效孔径

起泡点说明(包括SOP)应当包括

- filter type过滤器类型
- wetting liquid湿润液体
- Temperature温度
- minimum pressure最小压力



接触角的影响

Solid / liquid interaction

固/液相互作用

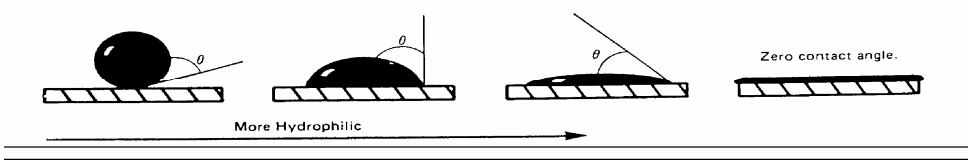
- Changing the wetting fluid changes the bubble point
- 改变湿润液体会改变起泡点

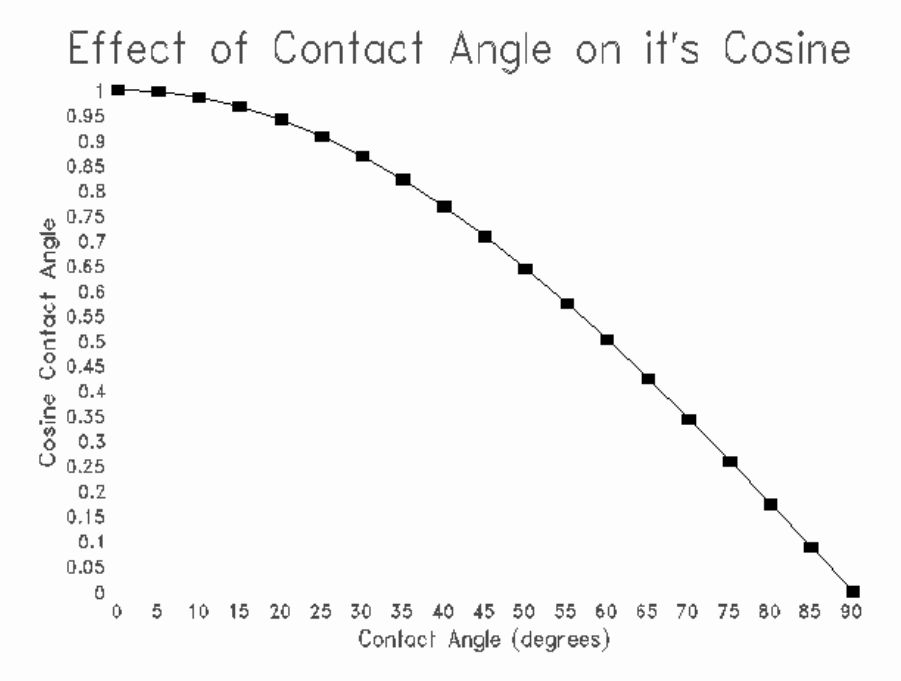
Applies to

- different wetting fluid不同的湿润液体
- different surface chemistries不同的表面化学性
- pre-use vs. post-use comparison使用前和使用后比较

Must know the effects of the changes, perform flushing or conduct product bubble point qualification

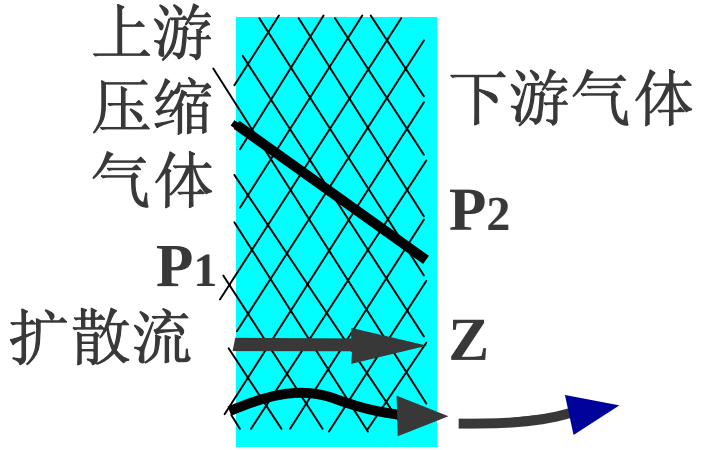
必须知道变化的影响，进行冲洗或用产品泡点确认

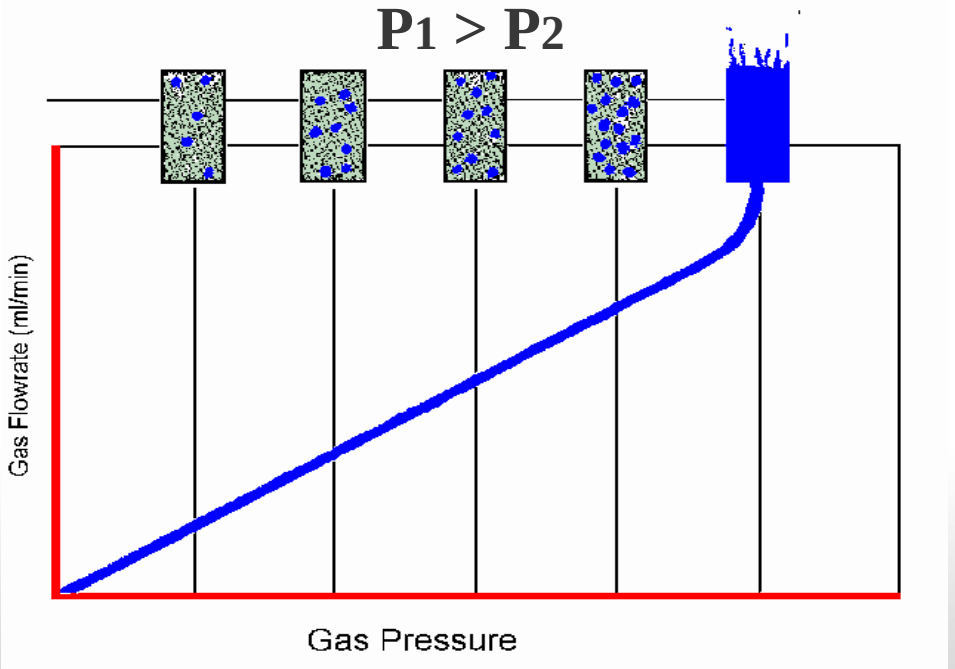




Diffusion Testing Introduction
扩散流测试介绍

- Gas dissolves in liquid held in the pores of a fully wetted membrane filter.气体溶解在完全湿润的滤器膜孔内的液体中
- A pressure differential will give a different gas concentration across the filter.膜压差造成跨膜气体浓度差
- Results in gas flow through the liquid dissolved in the filter pores.结果使膜孔溶解的气体流出





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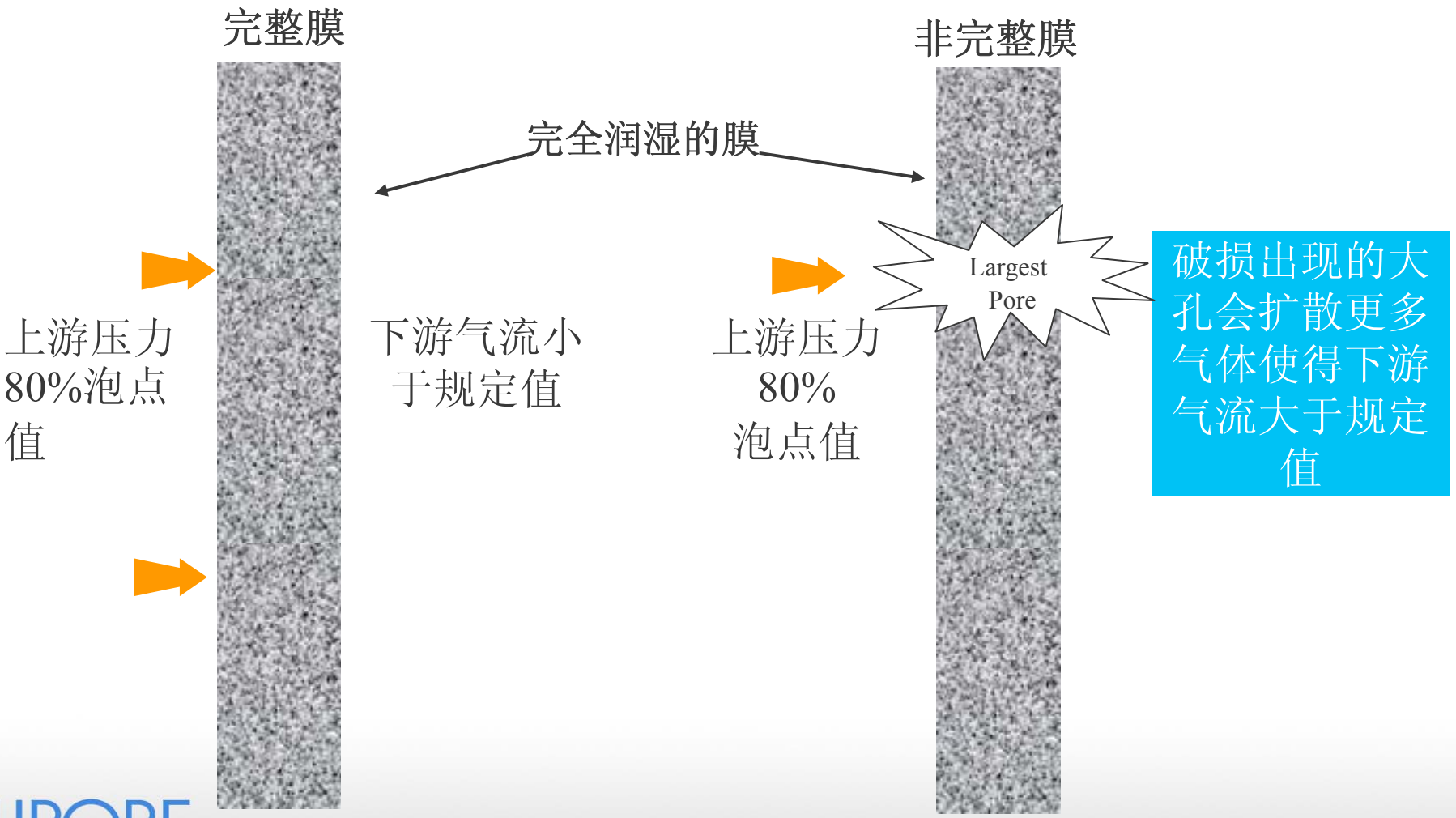
扩散流测试



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Diffusion Testing Equation扩散测试方程

$$\text{Diffusion} = \frac{K \cdot (P1 - P2) \cdot A \cdot \rho}{L}$$

where:

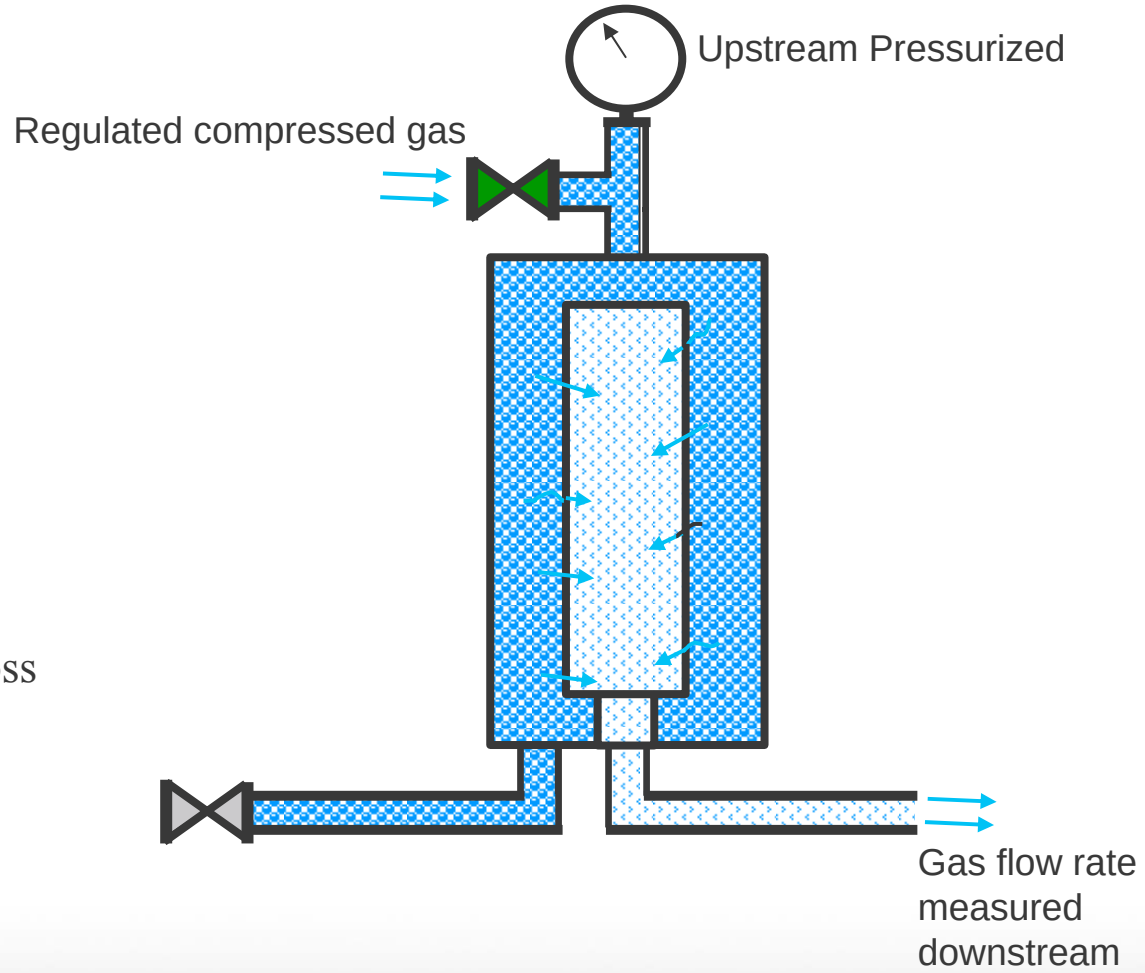
K = Diffusivity / Solubility coefficient扩散因子

P1, P2 = Pressure difference across the system系统两边的压力

ρ = Membrane porosity膜开孔率

L = Effective path length有效膜孔长度

A = Membrane area膜面积



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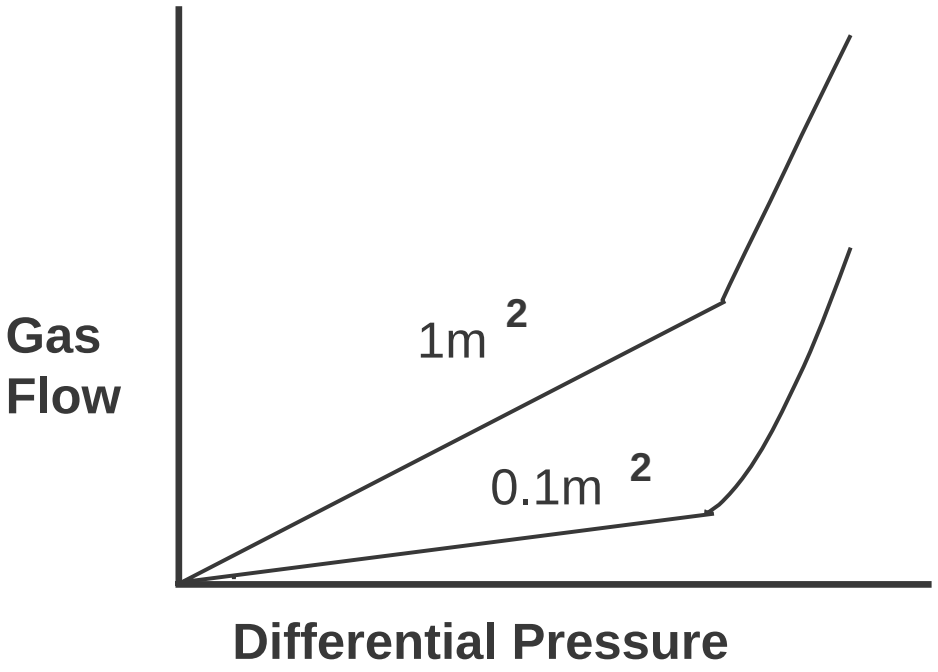
A Reason for Diffusion Testing
什么情况下采用扩散测试

Bubble Point detection becomes harder as membrane area increases
随着膜面积增加起泡点检测变得困难
Need as much information about the filter as possible
需要尽可能多关于膜的信息

- Use diffusion testing in combination with bubble point testing使用起泡点与扩散测试相结合



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Diffusion Test Applicability
扩散测试适用性

For filters with gas flowrate of >100 ml/min
过滤器扩散流速大于100ml/min

- high surface area filters大表面积过滤器
- thin membranes薄的膜
- organic solvent wetted filters有机溶剂湿润的过滤器

Diffusional flow specifications (and the S.O.P.) should include;扩散速率说明(包括SOP)应当包括

- filter type过滤器类型
- wetting liquid湿润液体
- test gas测试气体
- Temperature温度
- maximum acceptable flow rate最大接受流速

Factors Affecting Diffusion Tests
扩散测试的影响因素

Wetting湿润度

- Lower or inconsistent film thickness increases diffusion
- 低的和不均匀的薄厚会增加扩散

Fluid流体

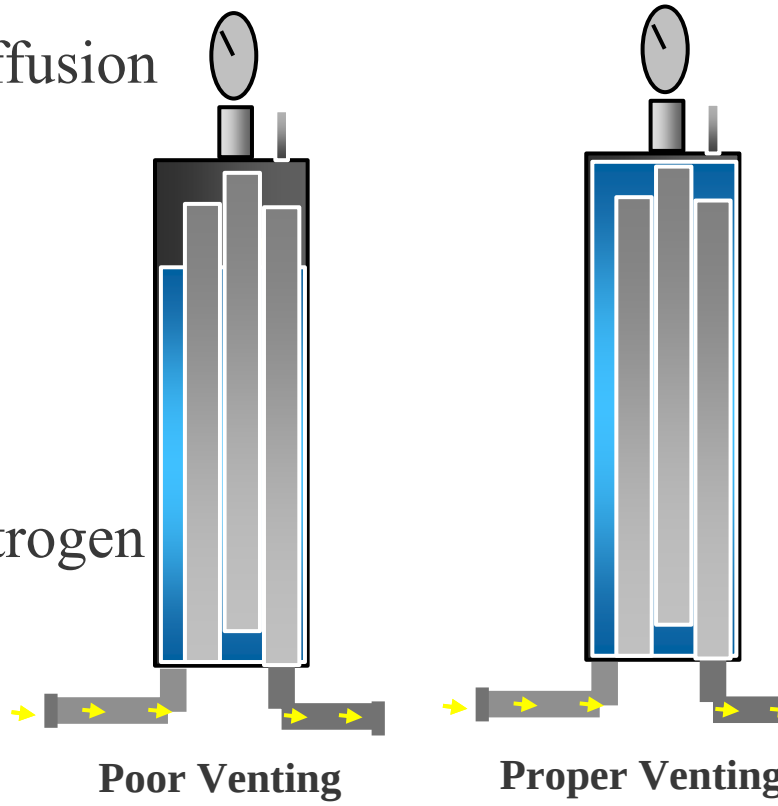
- Organic solvents have high diffusion flowrates
- 有机溶剂有较高的扩散流速

Gas气体

- Carbon dioxide has higher gas flow than air or nitrogen
  - 二氧化碳比空气或氮气有较高的扩散流速

Temperature温度

- 80% higher flowrate at 60 degrees
- 在６０摄氏度流速高80%



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“Diffusion Testing” Summary
扩散测试总结

Diffusion testing measures gas flow扩散测试测量气体流速

At bubble point, gas flows rapidly through the largest pore(s)
在起泡点，气体则快速通过最大的孔

Downstream gas flow (or upstream pressure loss) can come from both diffusion through the wetted pores PLUS the gas flow through the “dry” pores which have reached their bubble point

下游气流（或上游压力损失）可以由扩散流和达到起泡点时流出“干”孔的气流两者引起

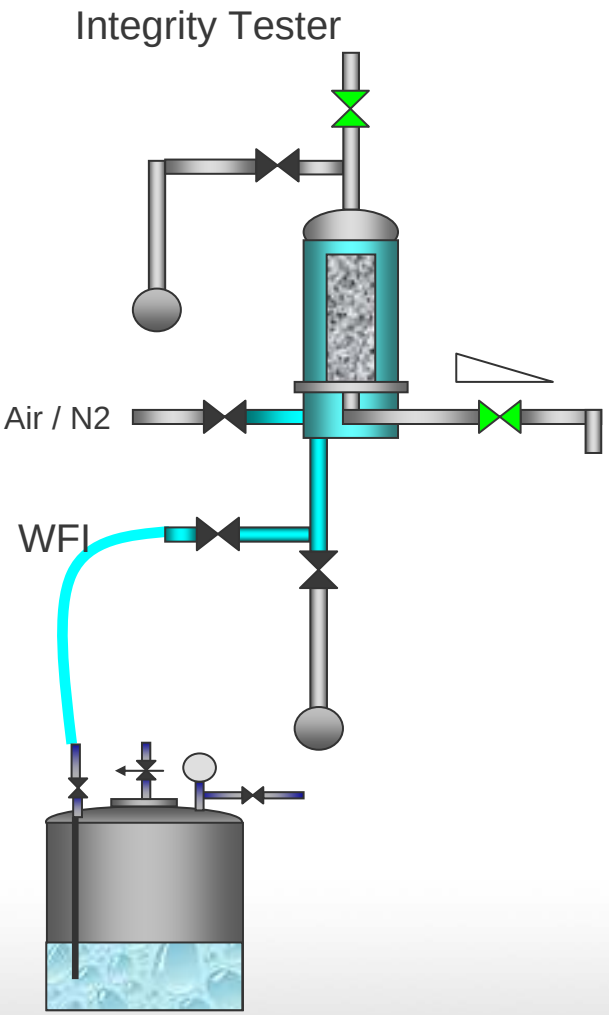
疏水滤膜采用有机溶剂进行完整性测试的问题

- **Alcohol / Water mixtures are often used due to:**
- 酒精/水的混合物使用经常会导致
  - Cost成本高
  - Flammability有燃烧的危险
  - high diffusion高的扩散流

- **Secure areas and equipment needed需要可靠的区域及设备**
- **Can be difficult to perform in-situ很难在线操作**
  - **Some concerns with residual test solution remaining in filter holder / pipework after testing**
  - 在测试后,测试液体会残存在过滤器/管路中
  - **Residual solution should be removed before filter sterilization**
  - 灭菌前需要去除残存的液体

HydroCorr Testing
Hydrocorr测试

- Force water under pressure onto the surface of the filter.
- 把水灌在膜表面
- Applied pressure is < integral filter intrusion pressure
- 加压至小于膜的水浸入压
- The water pressure is maintained but not increased.
- 压力维持但不再加压
- Pleated structure compacts
- 折叠式结构进一步压缩
- If integral, the upstream pressure will not drop below a preset value.
  膜如果是完整的,上游的压力不会太快下降



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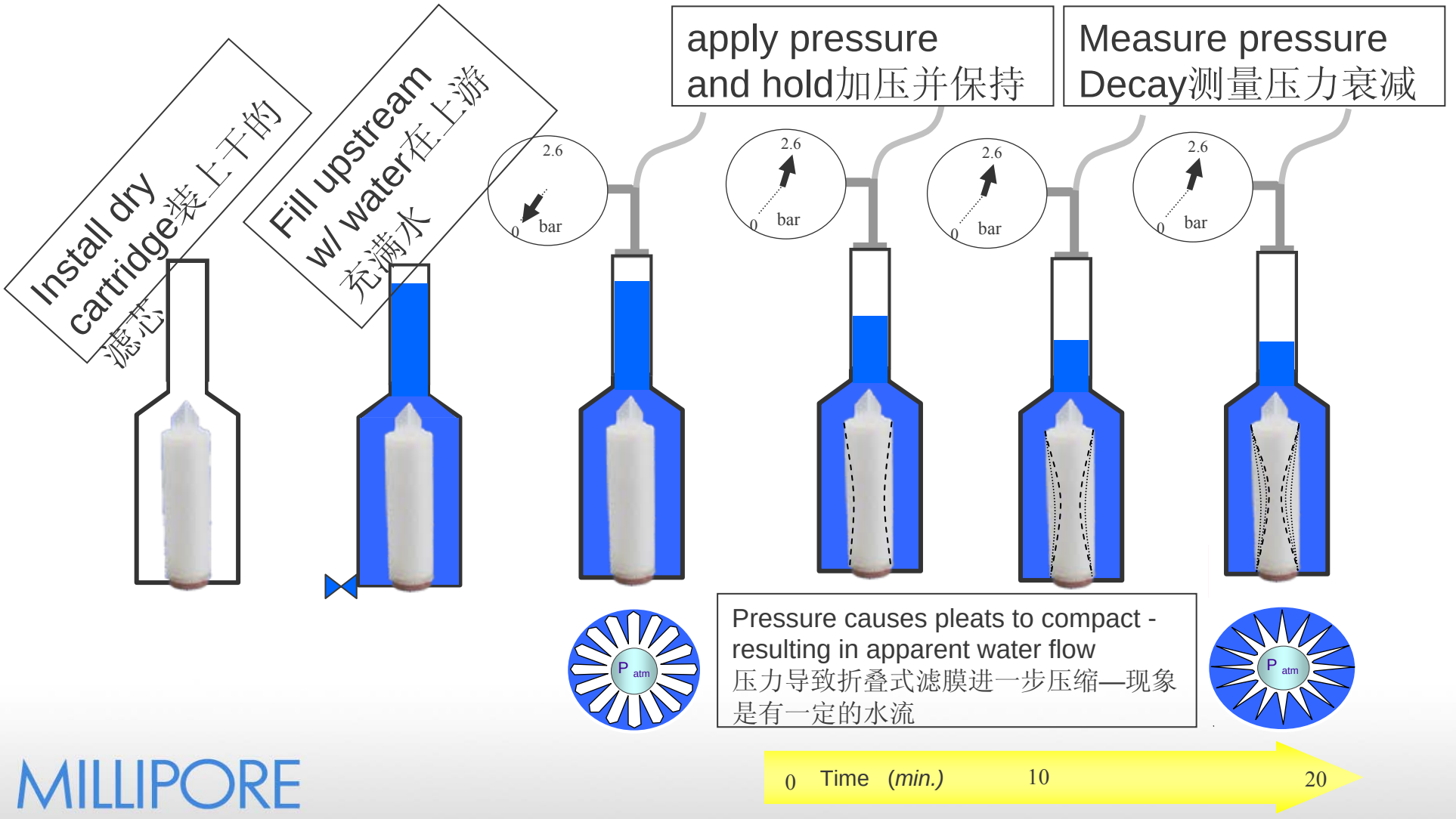
HydroCorr Test
Resistance to water intrusion水浸入法测试



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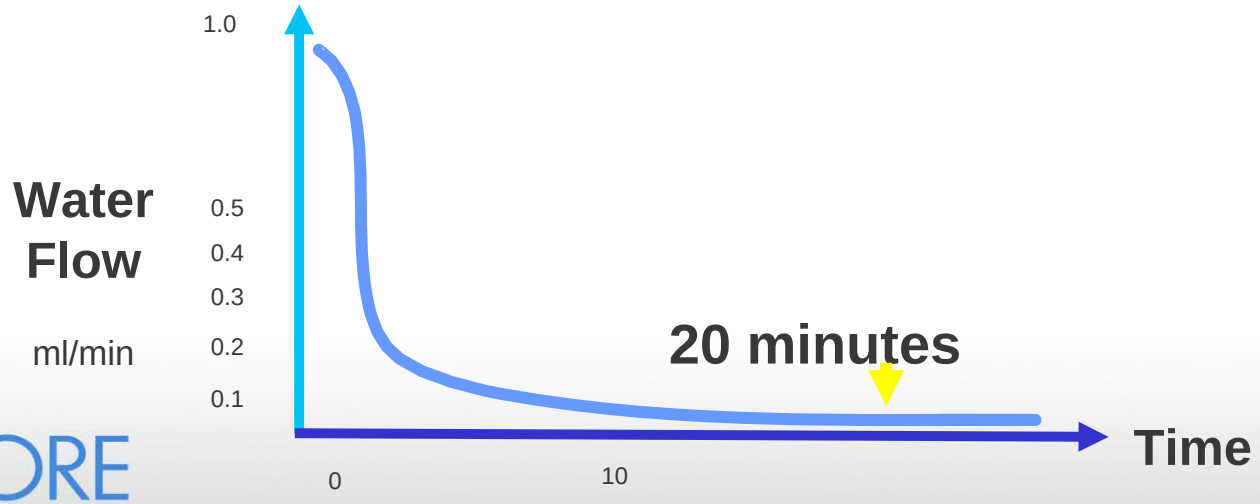
HydroCorr Test Results测试结果

- After initial stabilization, “apparent” water flow for an integral filter is very low
- 在最初的稳定后,对于完整膜来说,水流是非常小的
- Specifications are correlated to bacterial challenge
- 水流指标是与细菌挑战有关
- For integral filter there is no “actual” water flow
- 实际上完整膜,没有实际的水流
  - Filter remains dry and does not require drying between testing and use
  - 在测试与使用中,过滤膜维持干燥也不需要干燥



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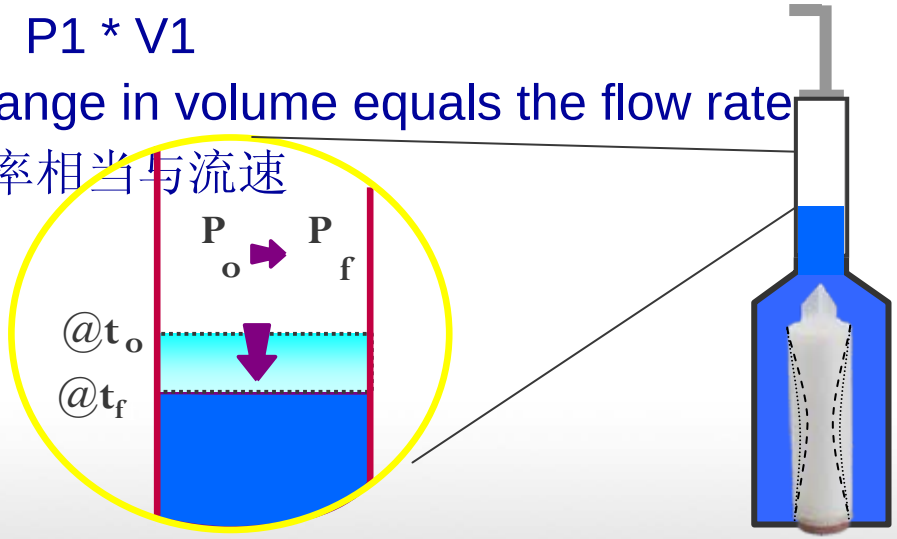
Performing HydroCorr Tests
进行疏水性测试

- Manually手动操作
  - Use a flow meter to measure actual upstream water displacement
  - 使用流量计来测量上游水面的下降速度
- Automatically自动操作
  - Use a pressure transducer to measure upstream gas pressure loss
    使用压力传感器来测量上游气体压力的损失
- Both need long stabilization & test time
- 都需要长时间的稳定及测试时间
  - Typically 10 minute stabilization & 10 minute test
  - 一般需要10分种的稳定时间及10分钟的测试时间

Automated HydroCorr Test自动化测试

- As pleats compress water level drops
- 由于折叠式结构压缩,水平面下降
- Upstream air volume increases
- 上游气体流增加
- Instrument determines volume change by measuring the corresponding pressure drop
- 通过测量相应的压力降来得出体积变化
  - Po * Vo = P1 * V1
- The rate of change in volume equals the flow rate
- 体积改变的速率相当与流速



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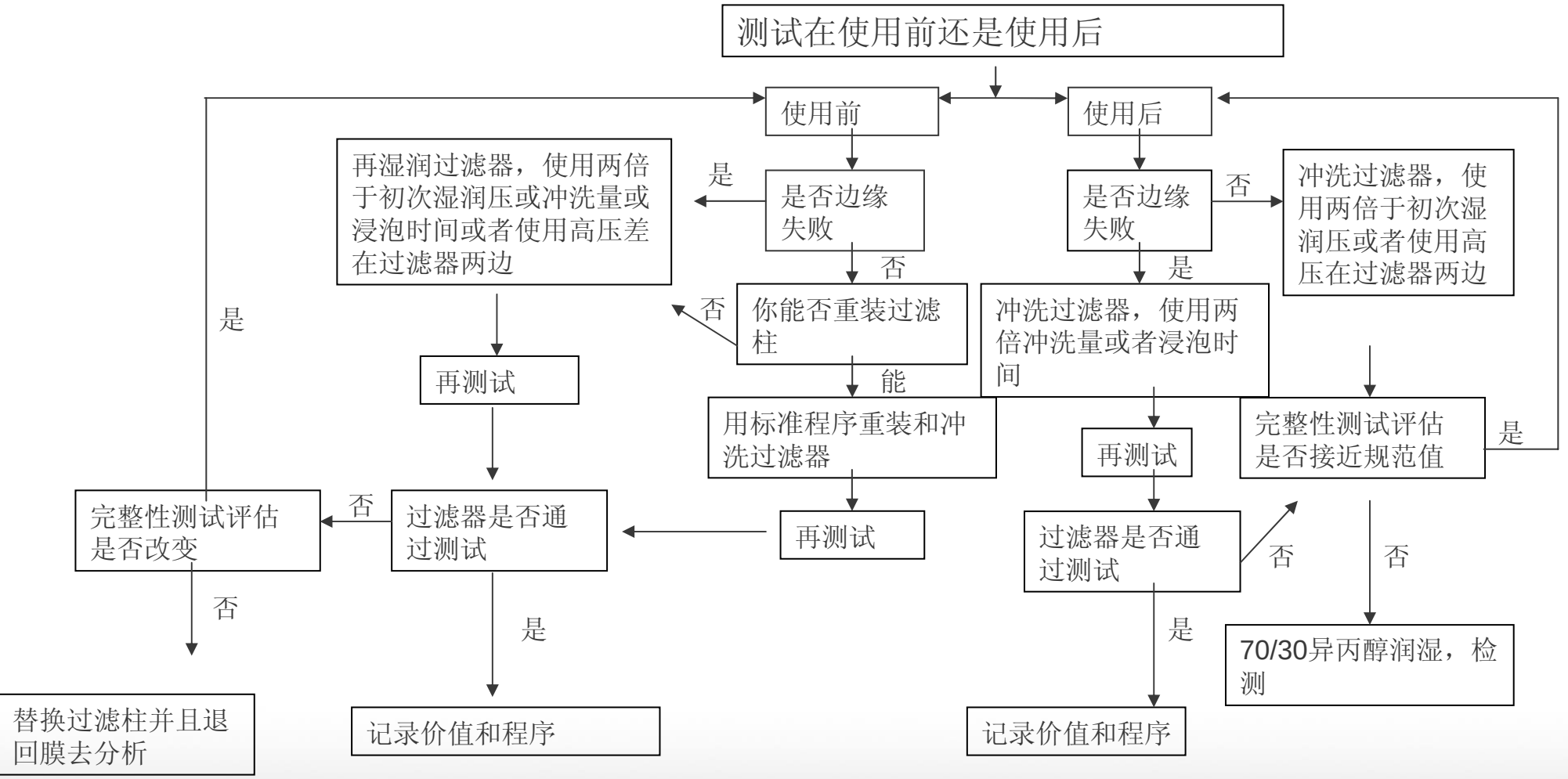
HydroCorr Test Considerations测试的注意点

- Must have a leak-free system必须在一密闭系统内进行
- Filters must be dry and clean过滤芯必须干燥且干净
  - It is relatively easy to Hydrocorr test “very hydrophobic” membranes such as PTFE
  - 对于疏水性很强的滤芯,例**PTFE**材质的膜,水浸入法是相当容易
  - Successfully testing “less hydrophobic” membranes such as PVDF requires ideal conditions that can be difficult to achieve in actual biopharmaceutical processes
  - 在实际的生物制药工艺中,测试一些疏水性不强的滤膜,例**PVDF**膜是比较困难的
- Temperature changes should be minimized
- 尽量减少温度的变化
- Reference testing is important
- 相关的参考比较重要
- Must have a complete validation package
- 必须有一完整的验证文本
- Values must be comprehensively correlated to microorganism challenge
- 数据必须与细菌挑战相关

完整性测试失败处理措施



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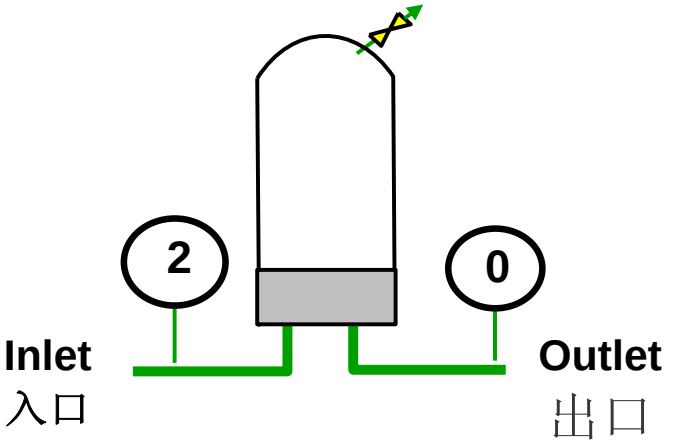
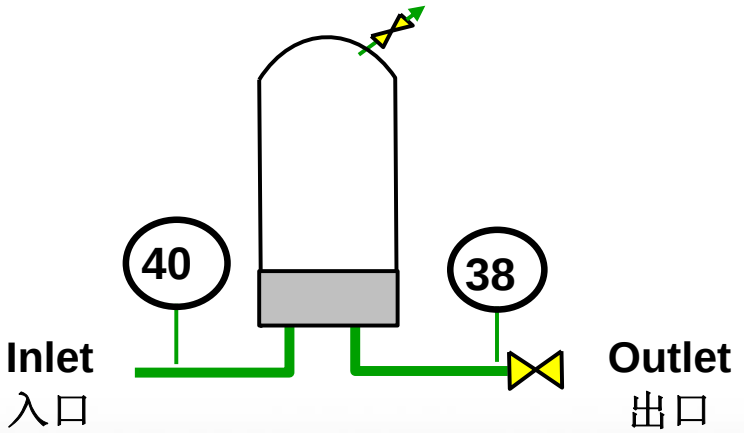
润湿建议

再润湿

- 使用更长的时间润湿
- 使用更高的压力润湿
- 使用更高的温度润湿
- 用酒精润湿
- 用动态的冲洗取代静态的浸透





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Summary总结

- Bubble point and Diffusion (or “Forward flow”) are BOTH valid integrity tests as per regulatory agencies.
起泡点, 扩散流（或前向流）和HydroCorr是法规认可的完整性测试方法
- The choice of an integrity test depends on the testing equipment, the filter manufacturer, the company‘s philosophy and the testing environment
完整性测试的选择倚赖测试装置，过滤器制造商，公司体系和测试环境
- Bubble point provides a direct correlation to bacterial retention, the critical performance characteristic
起泡点提供与细菌截留的直接关联，重要的性能特性
- Diffusion testing provides a sensitive way to determine integrity for larger area filters扩散测试提供一个敏感方法来测试大面积过滤器

Automated Integrity Testers
自动完整性测试仪

MILLIPORE

Why Do People Use Automatic Testers
为何用户会选用自动测试仪

- Ability to perform test without risk to downstream sterility
- 可以在排除下游无菌状态受到影响的情况下操作
  - Post SIP testing
  - 可以在蒸气灭菌后操作
- Hard copy printout
- 有打印文本
- Eliminate operator subjectivity
- 排除操作人员的主观因素
- Validatable
- 可验证的

Post SIP Integrity Testing
SIP后的完整性测试

- **Revision of annex 1 to EC Guide to GMP for sterile medicinal products (1997)**
- 欧盟对于无菌药品GMP指南的附件一(1997版)
  - **"The integrity of the sterilized 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"**
  - 除菌过滤膜应该在使用前及使用后立即采取合适的方法确认其完整性,可以采用泡点,扩散流或压力保持的方法.
- FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (1987)
- FDA对于无菌操作生产的无菌药品的要求(1987版)
  - "Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilized prior to use."
  - 完整性测试通常在过滤器安装,灭菌后使用前进行
- PDA Technical Report # 26
- **PDA技术报告26版**
  - "It generally is regarded as a cGMP requirement that filters or filter systems routinely be integrity tested both prior to and after use."
  - 现行的GMP要求过滤器及过滤系统在使用前及使用后均需要进行完整性测试

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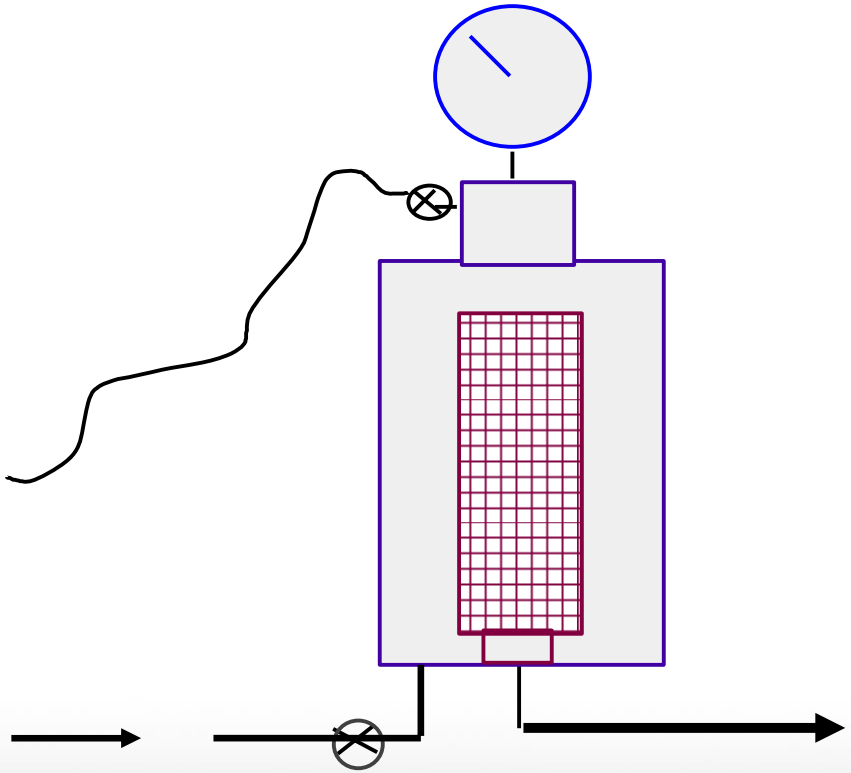
Automated Integrity Testing
自动完整性测试



A. During integrity testing gas molecules leave the system due to diffusion or bulk flow
在完整性测试中,气体流失的原因是扩散及穿孔后的流失

B. Fewer gas molecules upstream results in lower pressure.
上游气体分子越少压力越低

C. All else being constant, the change in pressure can be used to determine the gas flow rate
在其它参数保持稳定的状况下,压力的改变可以确定气体的流速

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Ideal Gas Law
理想气体定律

- PV = nRT
  - Where其中:
    - P = pressure 压力
    - V = volume 体积
    - n = number of gas molecules气体分子数
    - R = gas constant 气体常数
    - T = temperature温度

- Key Point - The pressure in a closed system is directly related to the number of gas molecules in the system.
- 关键点:在密闭系统内,压力直接与气体的分子数有关

Relating Pressure Decay to Gas Flow Rate
压力衰减与气体流速的关系

- Gas flow rate calculation 气体流速计算

$$N = \frac{\Delta P \times V_u}{t_{test} \times P_{atm}}$$

- Where其中

N = Gas flow rate 气体流速

ΔP = Pressure decay压力衰减

t_{test} = time (min)时间

P_{atm} = atmospheric pressure大气压

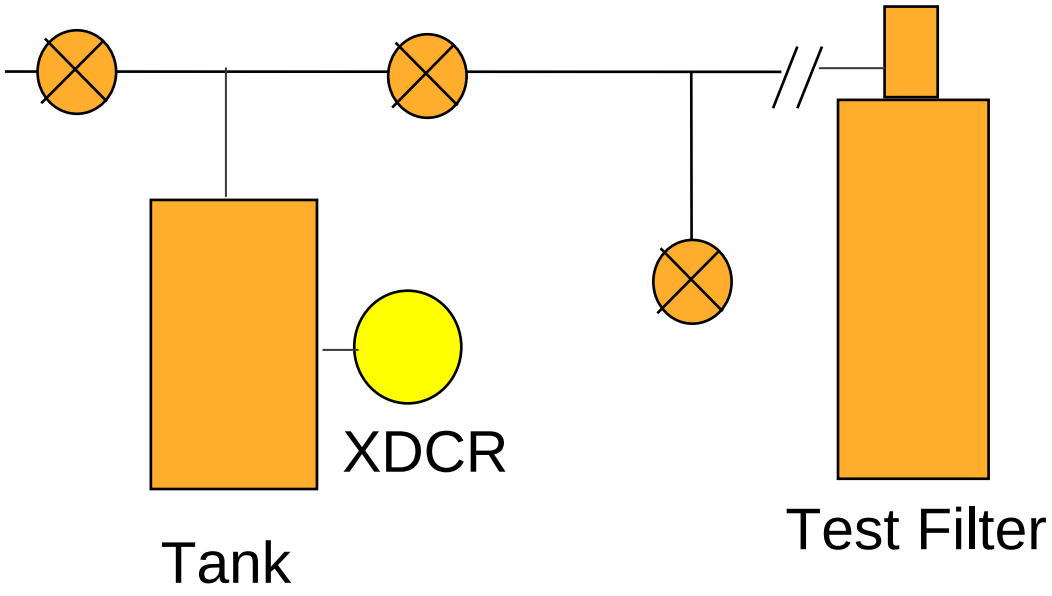
V_u = housing volume (cc)外壳体积

How Automatic Testers Determine Integrity
完整性测试仪如何工作

- Dependent on upstream volume
- 依据上游体积
- Dependent on gas flow curve properties of the filter
- 依据过滤器的气体流量曲线
  - Diffusion is gas flow measurement at a single pressure
  - 扩散是在单一压力下测量的气体流
  - Bubble point is a determined by measuring gas flow multiple times at increasing pressures
  - 泡点是在不断加压的情况下多次测量气体流的情况下而得的.

Upstream Volume Measurement
上游体积的测量

- P1V1 = P2V2
  - Internal tank is V1
  - 内部储罐是V1
  - P1 is measured
  - P1是测量而得
  - Valve between internal tank and housing opens
  - 在内部储罐及外壳之间的阀门是开的
  - P2 is measured
  - P2是测量而得
  - V2 is calculated
  - V2是计算而得



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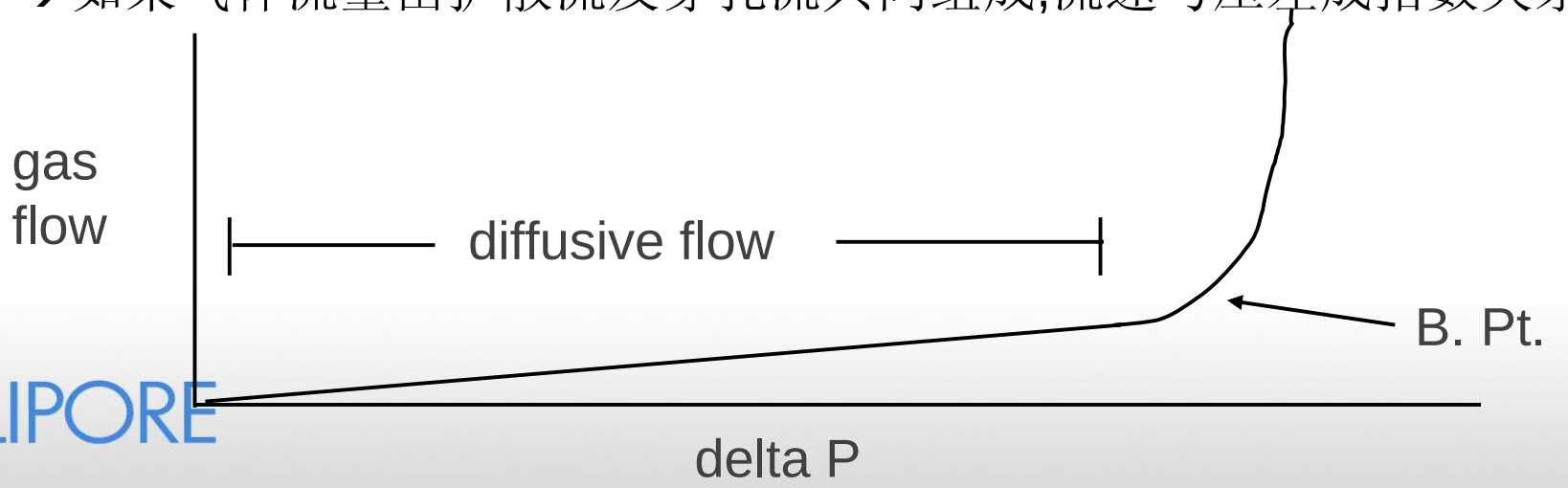
Gas Flow Curve气体流量曲线

- Diffusion and Bubble point together make up a "gas flow curve“
- 扩散及泡点共同组成了一个”气体流量曲线”
  - If flow is due to diffusion, it will increase linearly vs. delta P
  - 如果气体流量是由扩散而造成,流速与压降成正比
  - If flow is a combination of diffusion and bulk flow, it will increase exponentially vs. delta P
  - 如果气体流量由扩散流及穿孔流共同组成,流速与压差成指数关系



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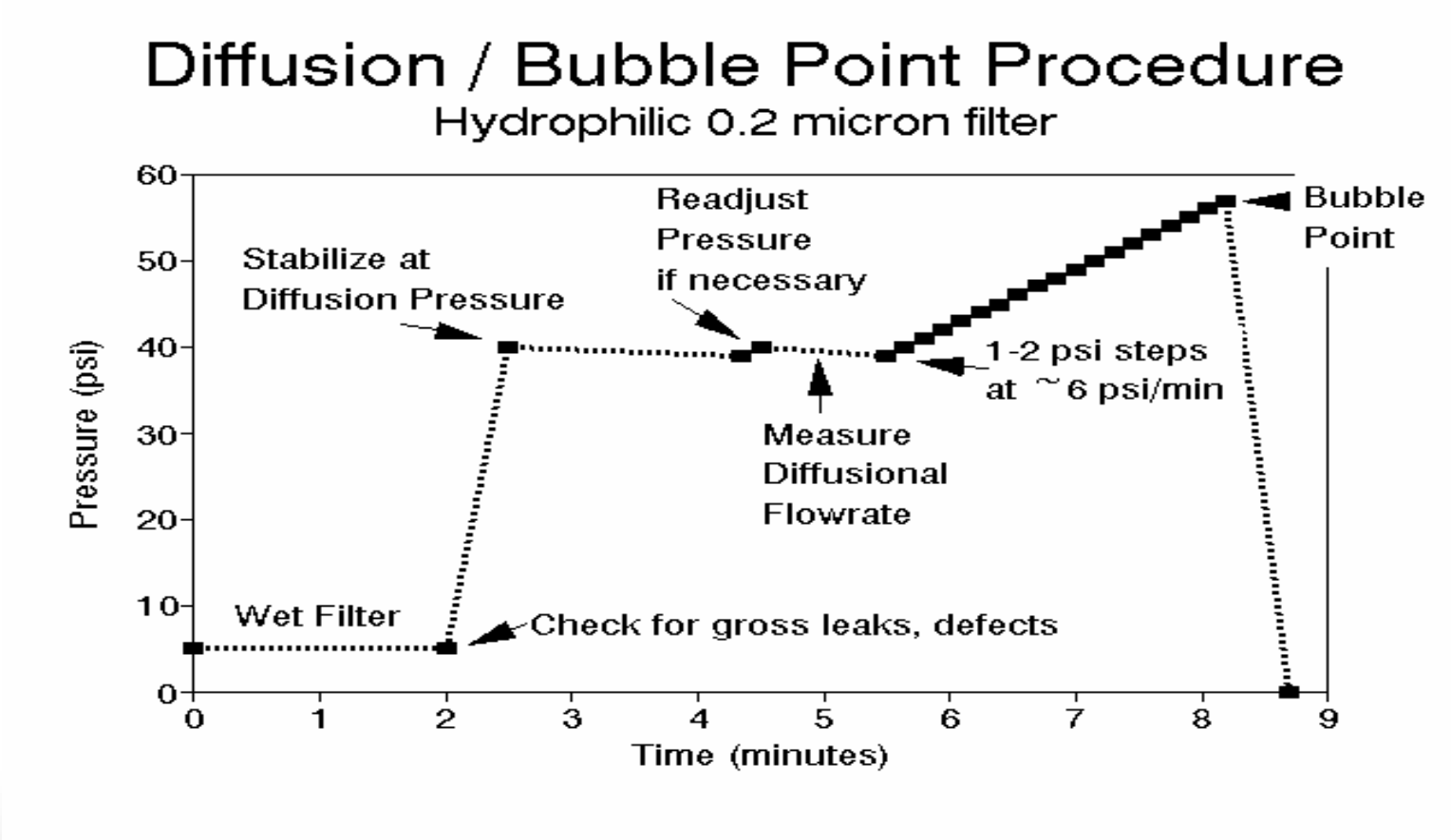
自动测试压力曲线



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Effect of Temperature on Automated Testing
温度对自动测试的影响

- Temperature CHANGES during a pressure decay test will have MAJOR impact on test results.
- 在压力衰减测试中,温度变化对结果的影响是非常大的.
  - Ideal Gas Law - PV = nRT 理想气体定律
    - As Temperature increases Pressure increases
    - 温度上升时压力上升
    - As Temperature decreases Pressure decreases
      温度下降时压力下降
- If the temperature changes even 1^{o}C. during the test, the pressure change WILL NOT be solely due to gas flow
- 在测试中,温度变化哪怕仅1度,压力的变化将不在仅归于气流
  - Additional pressure loss or pressure gain are test error
  - 额外的压力损失或增加会发生测试错误

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Temperature Changes温度变化因素

- Temperature changes can be due to:
- 温度变化是由以下因素引起
  - Inadequate stabilization after steaming
  - 灭菌后,冷却时间不够
  - Touching the housing碰到了外壳
  - Heating the automated tester加热了自动完整性测试仪
  - Environmental changes during testing在测试中,环境温度变化
  - Expansion and contraction膨胀及压缩

Interpreting the Printout分析打印输出的结果

- Important to look at the whole printout, not just the words “PASSED” or FAILED”
- 流览整个打印报告是非常重要的,而非仅看结果”通过”或”失败”
- Check for:核实
  - Changes is gas flow rate气体流速的改变
    - Temperature changes during the test测试中温度的变化
  - Very low gas flow rates气体流速非常低
    - Increasing temperature温度的提高
    - Improperly closed valves不正确的关闭阀门
  - Marginally high gas flow rates非常高的气体流速
    - Leaks泄露
  - Product specifications产品的规格
    - Does the test program match the type of filter?测试程序是否能适用于此种滤芯?

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Summary总结

- Main advantage of automatic integrity testers is ability to easily test sterilized systems
- 自动完整性测试仪的优点是能够容易的测试灭菌后的系统
- Upstream pressure decay measurements are related to actual downstream gas flow
- 上游压力衰减与下游气体的流速相关
- Automated integrity test systems are VERY sensitive to temperature changes
- 自动完整性测试仪对于温度的变化非常敏感
- Interpreting the test result is more than just looking for “PASSED” or “FAILED”
- 看结果时不应只看”通过”或”失败”

IT4完整性测试仪简介

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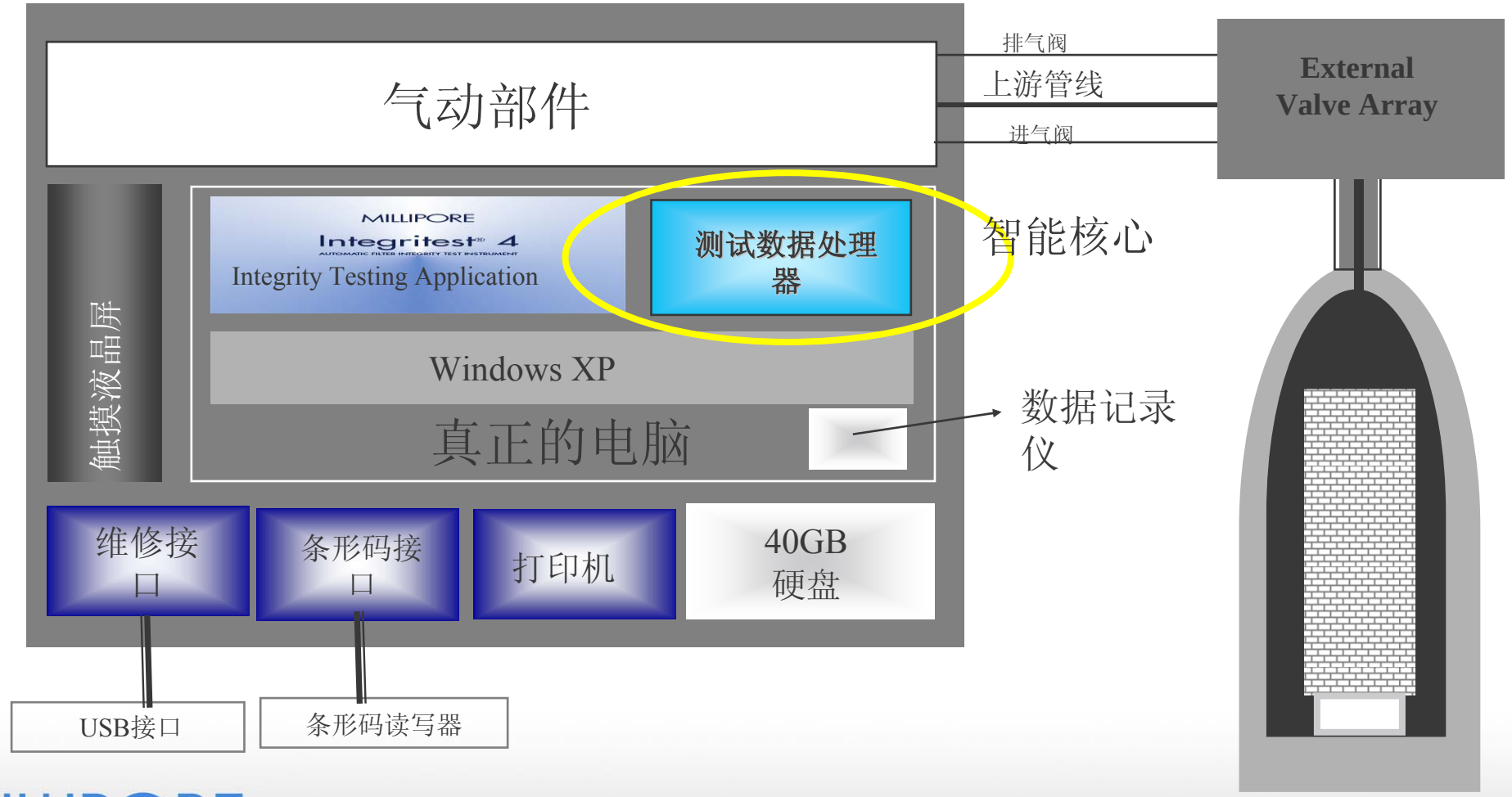
测试仪组成



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友好的用户界面

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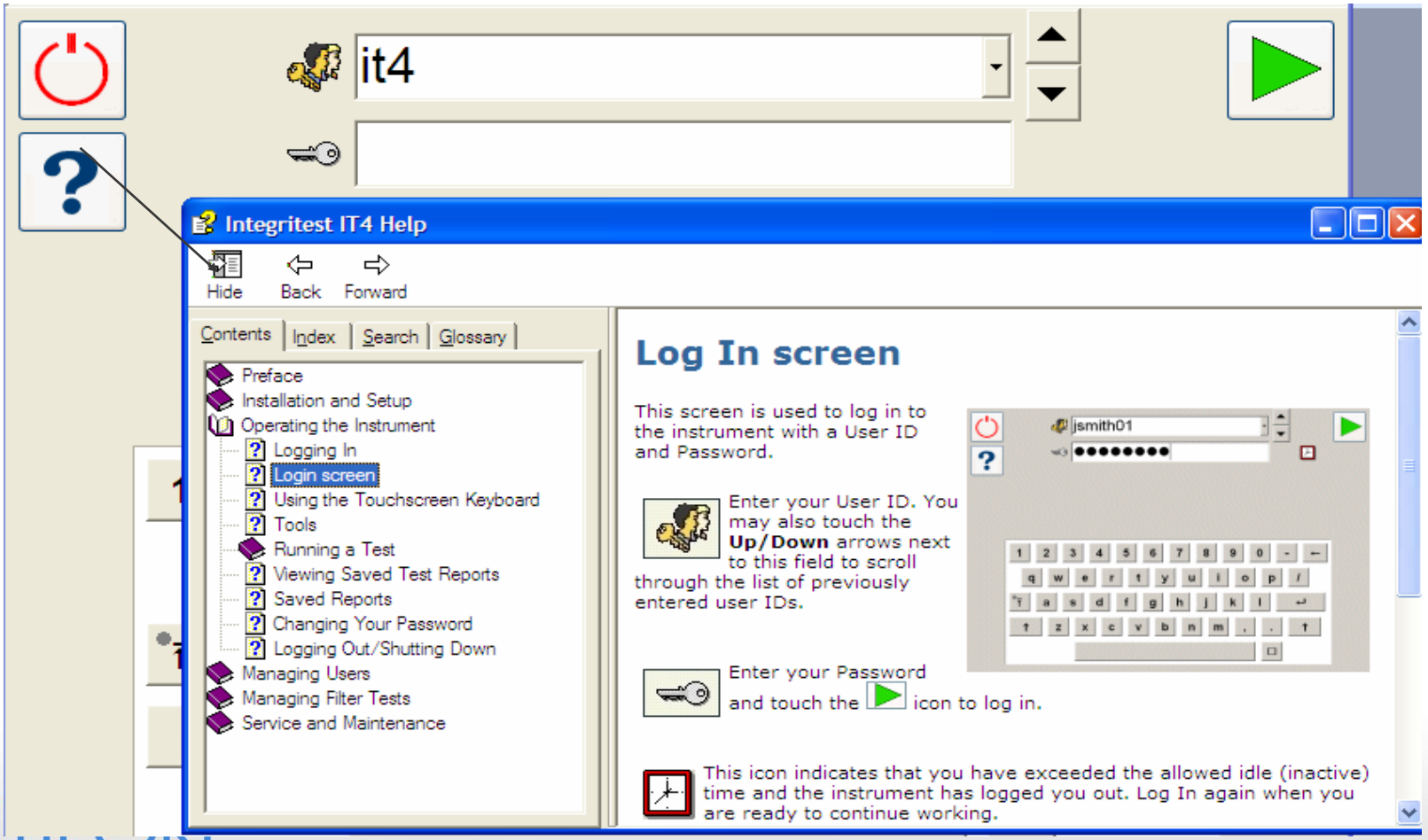
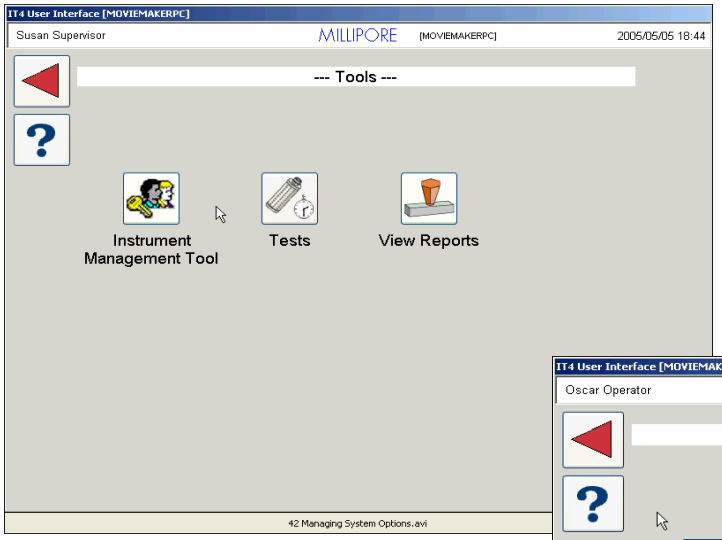
在线帮助

根据使用帮助

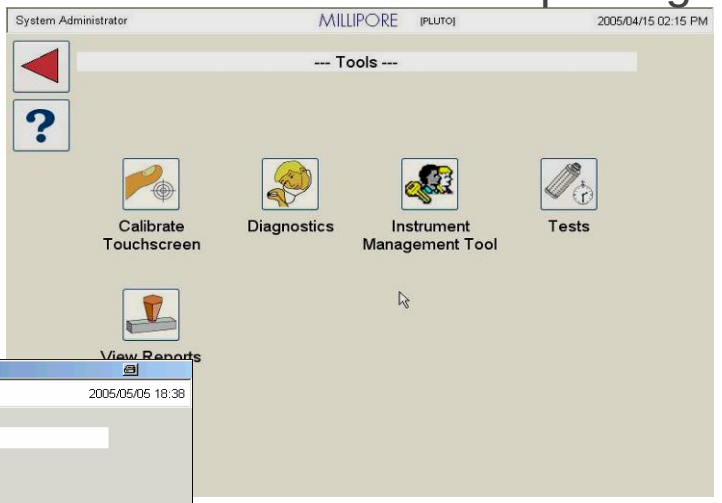

it4
Integritest IT4 Help
Hide
Back
Forward
Contents
Index
Search
Glossary
Preface
Installation and Setup
Operating the Instrument
Logging In
Login screen
Using the Touchscreen Keyboard
Tools
Running a Test
Viewing Saved Test Reports
Saved Reports
Changing Your Password
Logging Out/Shutting Down
Managing Users
Managing Filter Tests
Service and Maintenance
Log In screen
This screen is used to log in to the instrument with a User ID and Password.
jsmith01
Enter your User ID. You may also touch the Up/Down arrows next to this field to scroll through the list of previously entered user IDs.
Enter your Password and touch the icon to log in.
This icon indicates that you have exceeded the allowed idle (inactive) time and the instrument has logged you out. Log In again when you are ready to continue working.

适于不同操作者的菜单

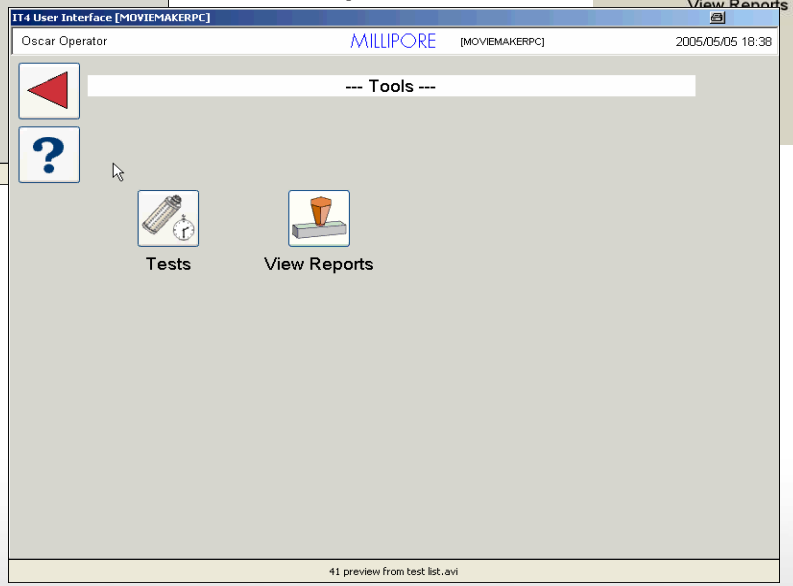
Administrator



Administrator w/ Service privilege



Operator



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IT4 – the SMART ONE

- **S** imple to use使用方便
- **M** ulti-test capability多种测试方法
- **A** ccurate algorithms计算准确
- **R** eliable components部件质量可靠
- **T** raining and services included
  完善的培训及服务体系
- **O** n-site calibration现场校验
- **N** ew generation of testers新型探头
- **E** xcellent interface & design友好的界面及精致的外观设计

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过滤工艺的验证

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为什么要进行过滤器的验证？

- 确保无菌工艺的稳定性及可重现性
- 各国法规要求

法规机构对过滤器的验证有哪些要求？

- US GMP 21 CFR Parts 210 & 211美国GMP
- Appropriate written procedures…shall be established and followed. Such procedures shall include **validation of any sterilization process**
- 适当的书面规程**…**应当被建立和遵循。这些规程应当包括任何无菌工艺的验证。
- EU GMP Annex 1 Sterile Medicinal Products 欧盟 GMP
- All **sterilization processes** should be **validated**
- 所有的无菌工艺都应当被验证
- Australian TGA GMP 澳大利亚TGA GMP
- **Filtration processes** used as the sterilizing step for products should be **validated**
- 作为产品除菌步骤的过滤工艺应当被验证
- Health Canada GMP 加拿大GMP
- Documented evidence is available establishing **validation** and validity **of each sterilization** process
- 每个无菌工艺的验证及其有效性都应当建立书面化的证据

法规及工业指南中的过滤器验证

- FDA Aseptic Processing Guidelines (1987 replaced by new 2004 - www.fda.gov)
- FDA无菌工艺指南（2004新版）
- Correlate filter performance with filter integrity testing
- Include microbiological challenges to simulate 'worst case' production conditions
- 过滤器性能与完整性测试的关联应当包括微生物挑战以模拟"最差"的工艺条件"。
- PDA Technical Report 26 (1998, www.pda.org) PDA技术报告26
- "Early, careful screening of potential filter types and configuration can result in fewer technical and regulatory problems, fewer delays, more efficient product processing, and greater sterility assurance"
- 尽早的，仔细的选择过滤器类型及配置可以有效的减少技术及法规方面的问题，减少延迟，使生产工艺更为有效，提供更高的无菌保障。
- ISO/DIS 13408-2 Aseptic Processing (2003, www.iso.ch) ISO/DIS 13408-2无菌工艺
- Filter Pre-selection shall take into account chemical and physical characteristics of the filter, as established by the filter manufacturer.
- Bacterial retention performance of filters shall be validated in a fluid-specific manner or for fluid groups under worst case conditions in production.
- 过滤器的预选应当考虑到过滤器生产商所确定的滤器的化学物理特性。过滤器的细菌截流特性应当通过生产中特定的料液或者最差条件下的料液进行验证。

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过滤器供应商和使用者各自应承担哪些责任？

- **滤器供应商的责任：**
- Filter Design Qualification
- 过滤器设计确认
- Filter Fabrication Qualification
- 过滤器制造确认
- Filter Quality & Testing
- 过滤器质量检验
- **过滤器使用者的责任：**
- Filter Selection (w/manufacturer’s assistance)
- 过滤器的选型（在滤器生产商的指导下进行）
- Filter/Product Specific Validation Studies
- 过滤器/产品特定的验证研究
- Process Validation
- 工艺验证

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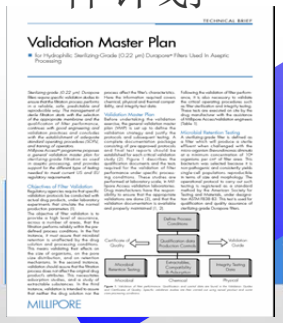
过滤器使用者应当做到：

- 确定过滤器与产物的兼容性---通过适当的过滤器筛选，化学兼容性表及产物测试进行。
- 审计过滤器供应商---生产设施及质量管理系统
- 确认操作员资质
- 验证过滤器灭菌次数
- 验证清洁次数
- 在过滤器的参数范围内进行操作
- 验证每一个过滤工艺
- 过滤器生产商应当以过滤器验证指南的形式提供产品的验证信息。而过滤器使用者则应当从根本上负责过滤器的验证。利用外部有测试资质的实验室进行过滤器验证测试是可以被接受的。

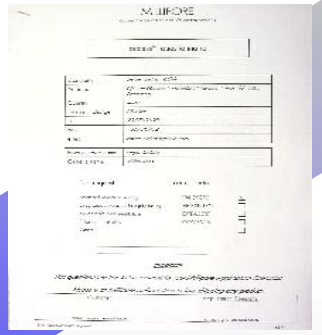
验证指南中的过滤器测试通常采用标准化的测试方法，因此，密理博可以通过**Access**伙伴服务协助您进行产品和工艺特定的过滤器验证。

验证总方案

VMP验证总体计划

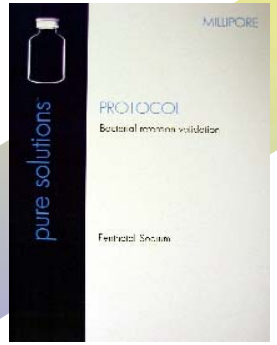


Access Questionnaire调查表



Protocol

方案



Report

报告

Validation Master file

验证总文件


Sampling
Equipment
取样设备
IQ OQ
安装确认,运行确认
Microbiological
method validation
微生物方法验证
PQ性能确认
surfaces
air
fluids
Filter
integrity test
operator certification
滤器操作者资格证书
Steritest school
项目
Design, SOP
validation for
filter sterilisation灭菌过
程设计,标准操作程序的
制定,
Filterability
studies
过滤性研究
Engineering
加工
SIP
validation
在线灭菌验证
Tester
IQ OQ检测仪的安装
运行确认
Product
specific
parameters
产品规格参数
Adsorption吸附性
Compatibility
兼容性
Extractables
析出物
Bacteria
retention细菌截留
Bioburden
Sterility
生物负荷的降低
Filter
performance过滤
器性能
Training
Education培训
Regulatory
Compliance法规
Sterility Assurance无
菌保证
Process
design
过滤设计
Filter
Sterilisation
过滤器的灭菌
Filter
integrity
Test过滤器的完整
性检测

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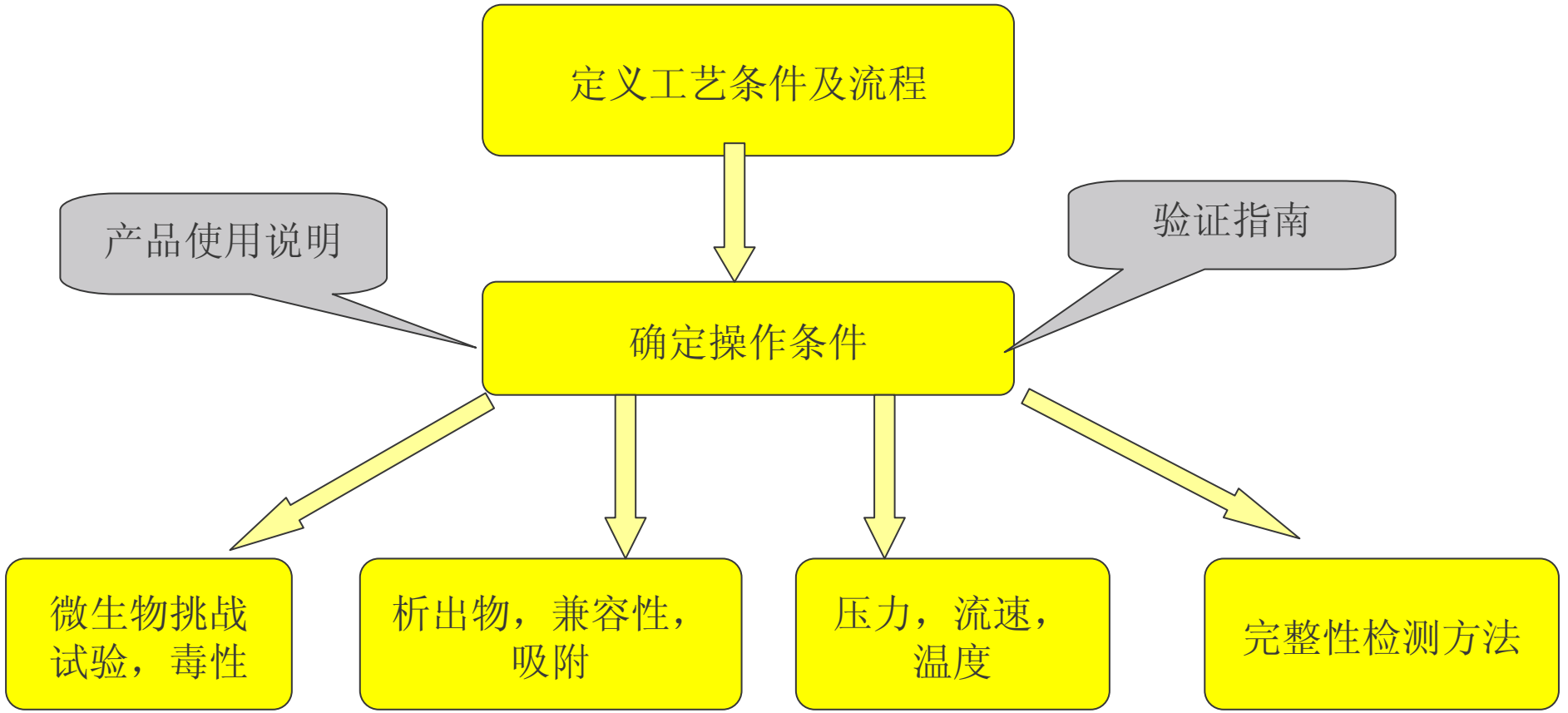
除菌过滤器验证流程



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Validation Guide

验证指南

VALIDATION GUIDE

Durapore® Cartridge Filter

CVGL 0.22 µm

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Contents

无菌级过滤器需要验证的项目

- 生物性质
  - 微生物截留试验
  - 毒性试验
- 物理性质
  - 压力
  - 流速
  - 温度
- 化学性质
  - 析出物
  - 兼容性，吸附
- 产品完整性测试方法

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细菌截流验证

- 菌种，安全性
- 浓度，
  - 体积，
  - 流速（2-4L/min，cm^2）
  - 压力（0.2mpa-30Psi）
- 产品细菌截流验证
  - 抑菌反应，裂菌反应
  - 阴性对照

细菌挑战试验流程

- 灭菌
- 润湿：生理盐水，
- 完整性
- 阴性对照
- 挑战
- 培养

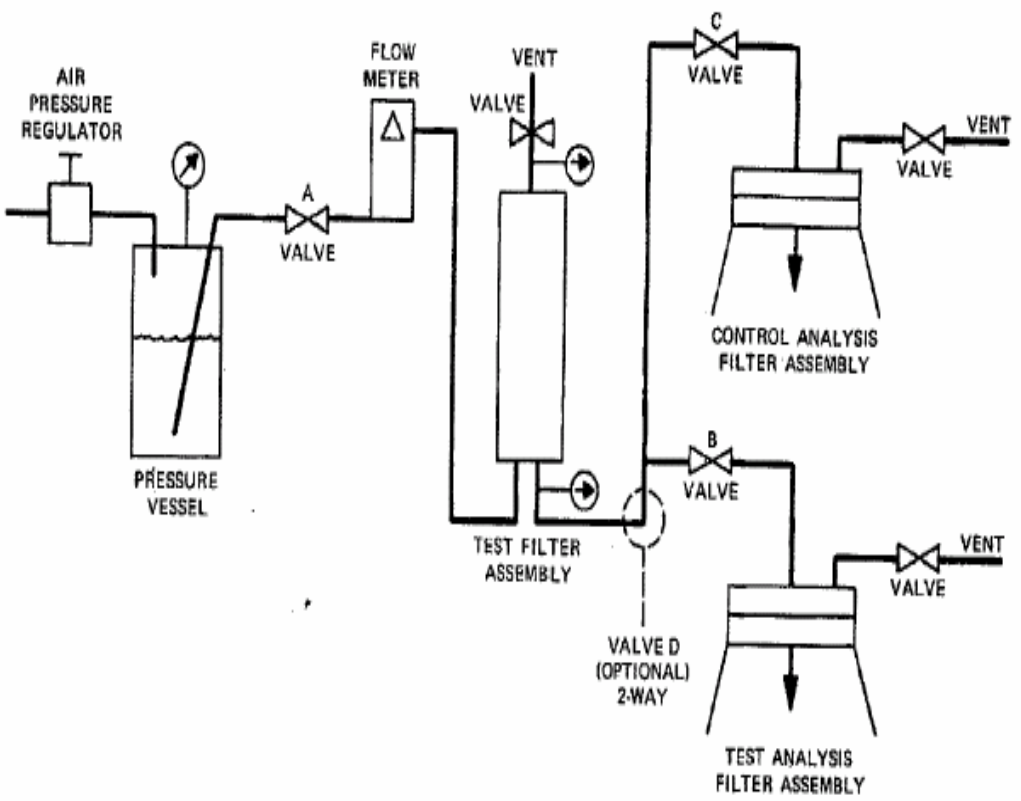

FIG. 1 Test Set-Up for Bacteria Retention Testing

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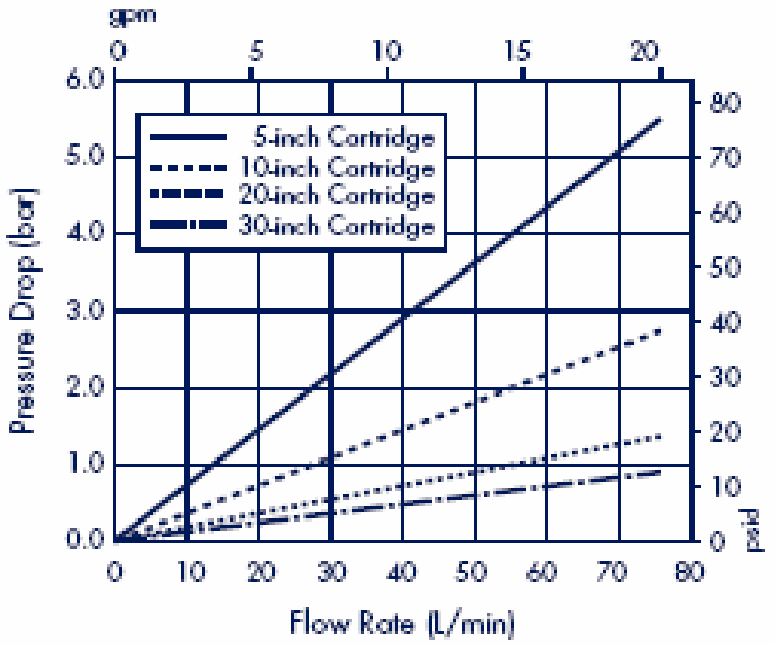
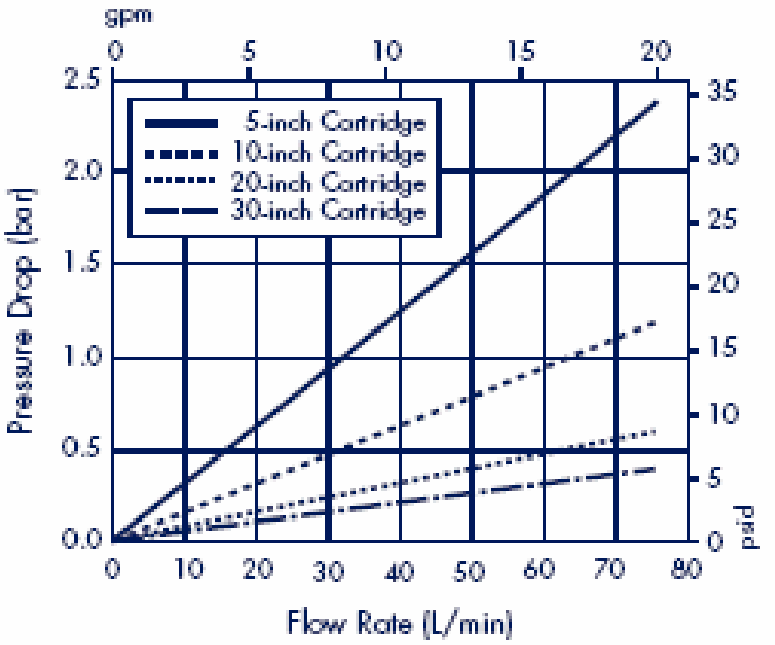
物理性质验证：压力速度曲线

Cartridge Filters —
0.1 µm Hydrophilic Durapore Membrane



Cartridge Filters —
0.22 µm Hydrophilic Durapore Membrane



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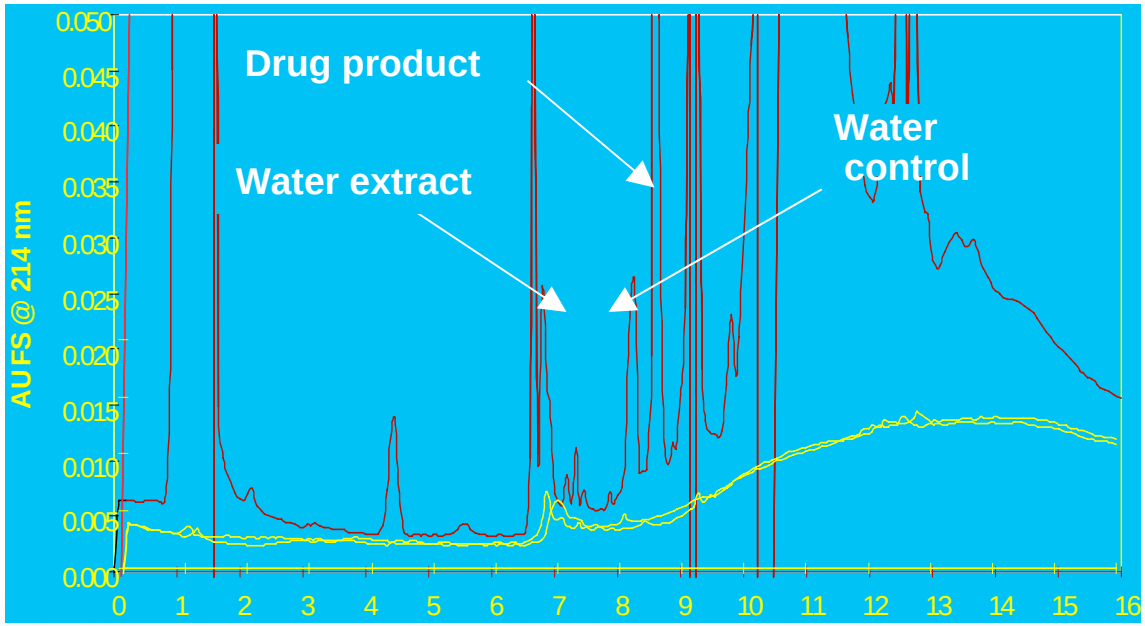
析出物检测

- 滤器析出物验证:

  NVR, TOC, HPLC, FTIR

  - 可能影响药品纯度



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化学兼容性验证

ＣＶＧＬ化学兼容性

	A	B	C		A	B	C
酸和碱				汽油	L	N	R
乙酸 (5%)	R	R	R	甘油	R	R	R
硼酸	R	R	R	己烷	L	N	R
浓盐酸	R	R	R	双氧水(3%)	R	R	R
氢氟酸	R	N	N	异丁醇	R	R	R
浓硝酸	N	N	N	异丙酸乙酯	R	N	R
浓硫酸	N	N	R	异丙醇	R	R	R
氨水 (6N)	N	R	R	煤油	L	N	R
浓氢氧化钠	N	R	R	甲醇	R	R	R
溶剂				二氯甲烷	L	N	R
丙酮	N	N	R	甲乙酮	L	N	R

A-Durapore CVGL滤柱
B-硅胶O形圈
C-不锈钢过滤器外壳

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产品起泡点测试

- 原理及必要性:
- 方法:
- 成功标准
  CV<5%

- 案例:

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谢谢!