sartorius stedim biotech

DESIGN AWARD 2018

Designed, developed and made in Germany

Integrity test principle and regulatory introduction

完整性测试原理及法规

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1. Integrity Test 完整性测试

- Standards and regulations/标准与法规
- Bacteria Challenge Test / 细菌挑战实验
- Correlate to BCT/BCT关联

2. IT Method and principle 原理与方法

- Diffusion Test/扩散流
- Bubble Point Test/泡点
- Pressure Decay Test/压力降
- WIT & WFT /水侵入
- Multicount Housing IT /多芯系统测试

Why is Integrity Testing so Important? 为什么进行完整性测试

- To prevent damage to the product by the use of defective filters

  避免使用有缺陷的滤器对产品造成损害

- To determine the presence of oversized pores within the membrane

  确保选择正确的过滤器孔径

- To detect system leaks (housings, O-rings, etc.)

  检测是否存在系统泄漏

- To fulfill the regulatory requirement

  满足法规要求

To get reliable sterility assurance !

获得可靠的无菌保障 !

What, Why, When, How

Standards and regulations 标准与法规

EU GMP

- 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.无菌的滤器应该在使用前以及使用后用合适的方法进行测试，像泡点，扩散流或者压力保持

WHO

- 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.无菌的滤器应该在使用前以及使用后用合适的方法进行测试，像泡点，扩散流或者压力保持

USA FDA

- 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.滤器的完整性可以在使用前测试，并应该在使用后测试，使用后的完整性测试很重要可以检测滤器泄漏或者使用过程中的损坏

CFDA

- The integrity of the sterilizing grade filter should be verified by proper method after use. An appropriate method includes bubble point, diffusive flow and pressure drop.除菌级滤器应该在使用前后确定完整性，适当的方法如泡点，扩散流，压力降

Standards and regulations 标准与法规

PMDA

- PIC/S GMP Guide Line Annex 1：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.无菌的滤器应该在使用前以及使用后用合适的方法进行测试像泡点，扩散流或者压力保持

Korean FDA

- Filters for sterilizing grade filtration should be tested before use and after use with appropriate methods (such as bubble point, diffusive flow, pressure hold test)用于除菌过滤的滤器应该在使用前后采用适当的方法进行完整性测试（像泡点法，扩散流，压力保持法）

India FDA

- For membrane filters used for filtration, appropriate filter integrity tests that ensure sterilization shall be carried out before and after filtration对于过滤用的膜过滤器，确保无菌工艺的完整性测试应该在过滤前后进行

Standards and regulations 标准与法规

国家/地域	文件	使用前完整性测试		使用后完整性测试
		灭菌前	灭菌后	
欧盟	法规	不需要	强制要求	强制要求
WHO	法规	不需要	强制要求	强制要求
日本	法规	不需要	强制要求	强制要求
美国	法规	可选（基于风险控制）		强制要求
	指导原则	可选（基于风险控制）		强制要求
中国	法规	未提及		强制要求
	指导原则	可选（基于风险控制）		强制要求
韩国	法规	强制要求		强制要求
印度	法规	强制要求		强制要求

Filter Integrity Test Method 过滤器完整性测试方法

Integrity Test Method 完整性测试方法

Destructive Test破坏性方法

BCT 细菌挑战性试验

Non-destructive非破坏性方法

BPT 泡点法

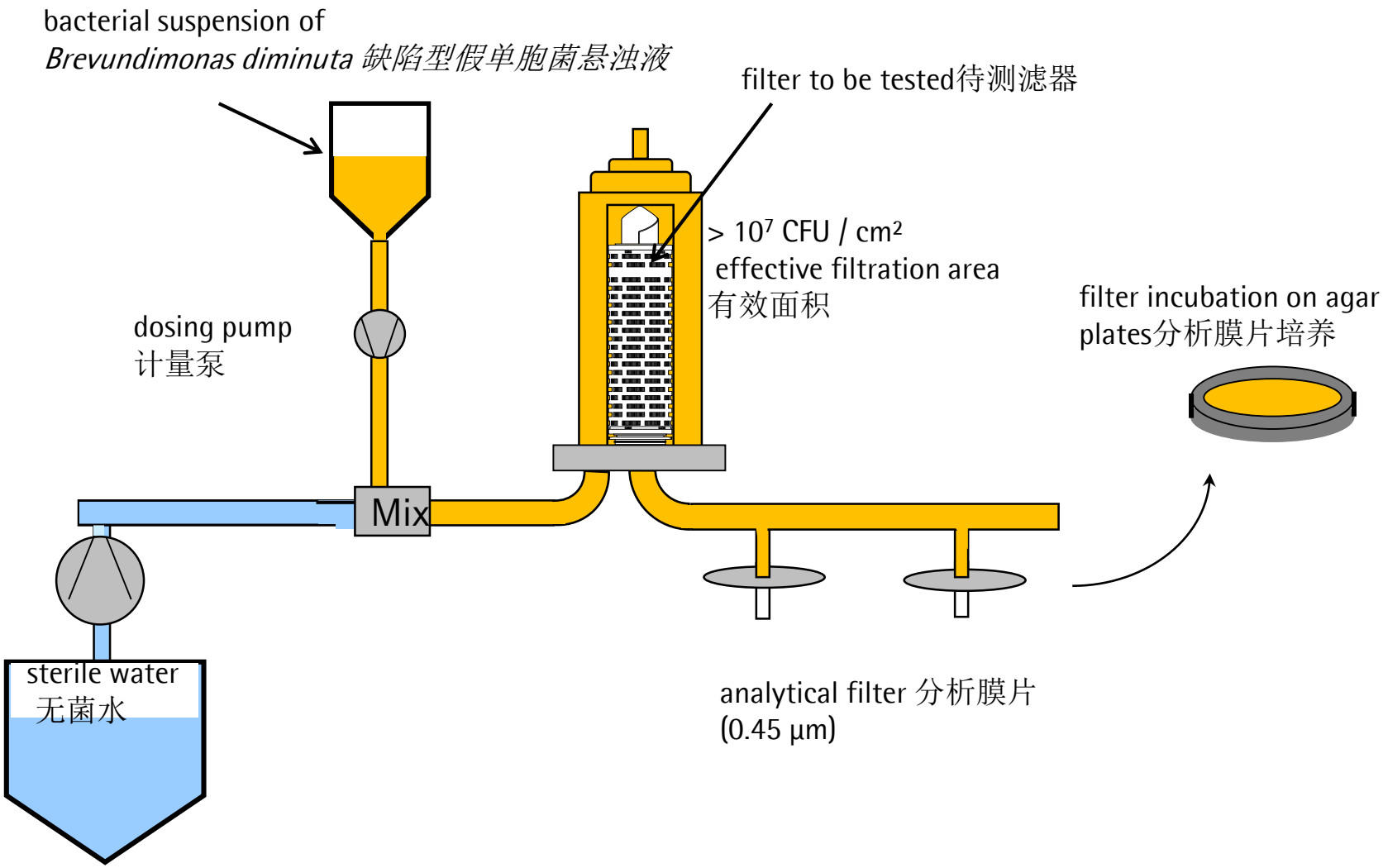
DIF 扩散流法((Forward Flow前进流)

Pressure Decay Test 压力降法

WIT水侵入

Non-destructive integrity test should be correlated to the bacterial challenge test.
非破坏性完整性测试的结果需要和过滤器细菌挑战实验数据相关联。

Bacteria Challenge Test | Destructive Test 细菌挑战实验|破坏性测试



Non-destructive Integrity Testing 非破坏性完整性测试

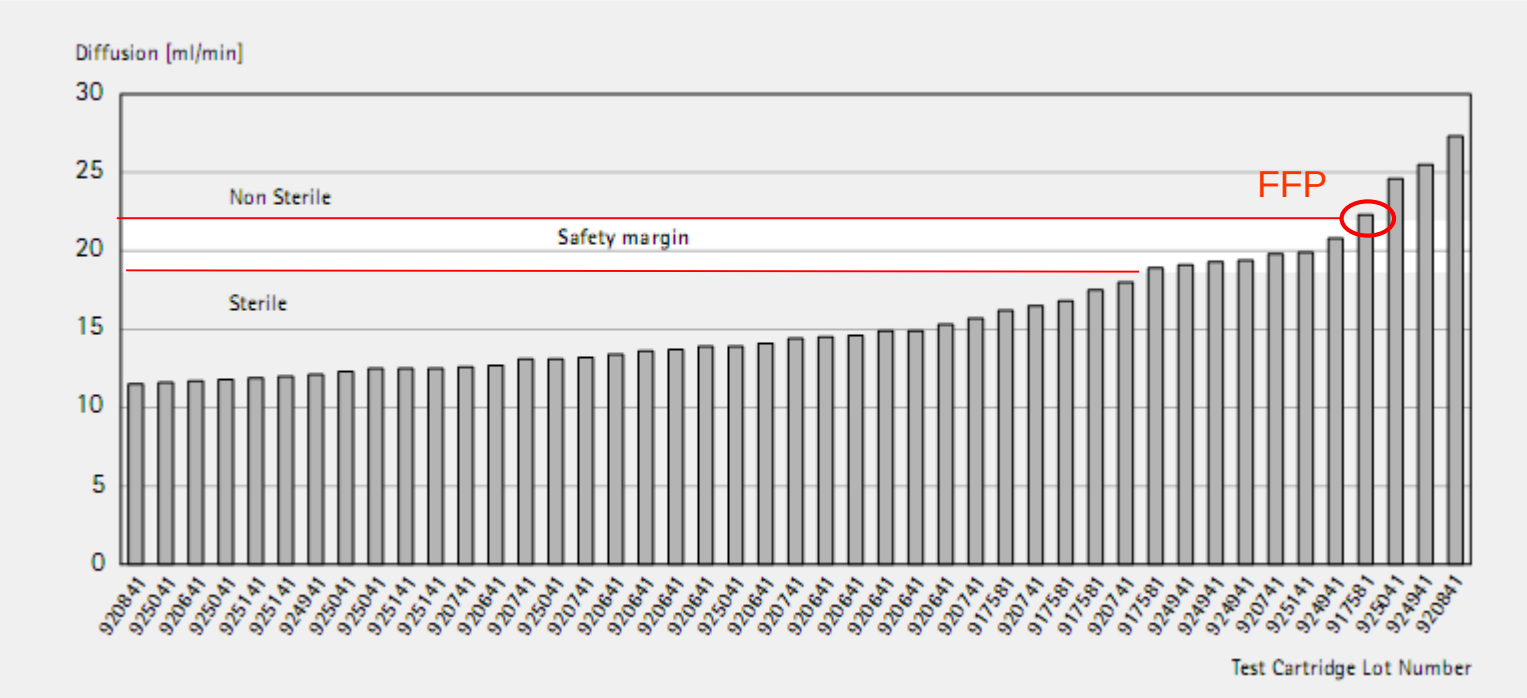
Non- destructive integrity Testing is performed by manufacturers for batch release and by operators for in-process control and batch release.滤器制造商以及制药企业采用非破坏性方法测试，作为生产工艺控制以及药品放行

Correlation:

To be able to use a non-destructive integrity test, physical tests were developed that correlate to the bacterial challenge test. 为了能采用非破坏性方法测试完整性，特殊的物理测试方法需要跟细菌挑战性试验关联

Once this correlation is established, it is determined that a cartridge passing the physical test is an integral sterilizing filter. 这种关联一旦建立，并且滤器通过了这种物理测试方法，这个滤器就是完整的除菌滤器 （FDA, Sep. 2004）

Correlate to BCT 扩散流与BCT相关联



1.Take sample from different lots of filter 挑选很多不同批号的滤芯

2.Detect the filter's diffusion values 测出它们各自的扩散流值

3. Rank from small to large 按照扩散流值大小形成坐标

4. BCT for every element 将它们分别做细菌挑战性实验

5. Find the First Failure Point 找出首支细菌挑战失败的滤芯

6. Defind a safety margin 设定一定的安全余量

e.g.: 10" Sartopore 2

Diffusion values 扩散流< 20.8 ml/min

Safety margin安全余量2.8 mL/min

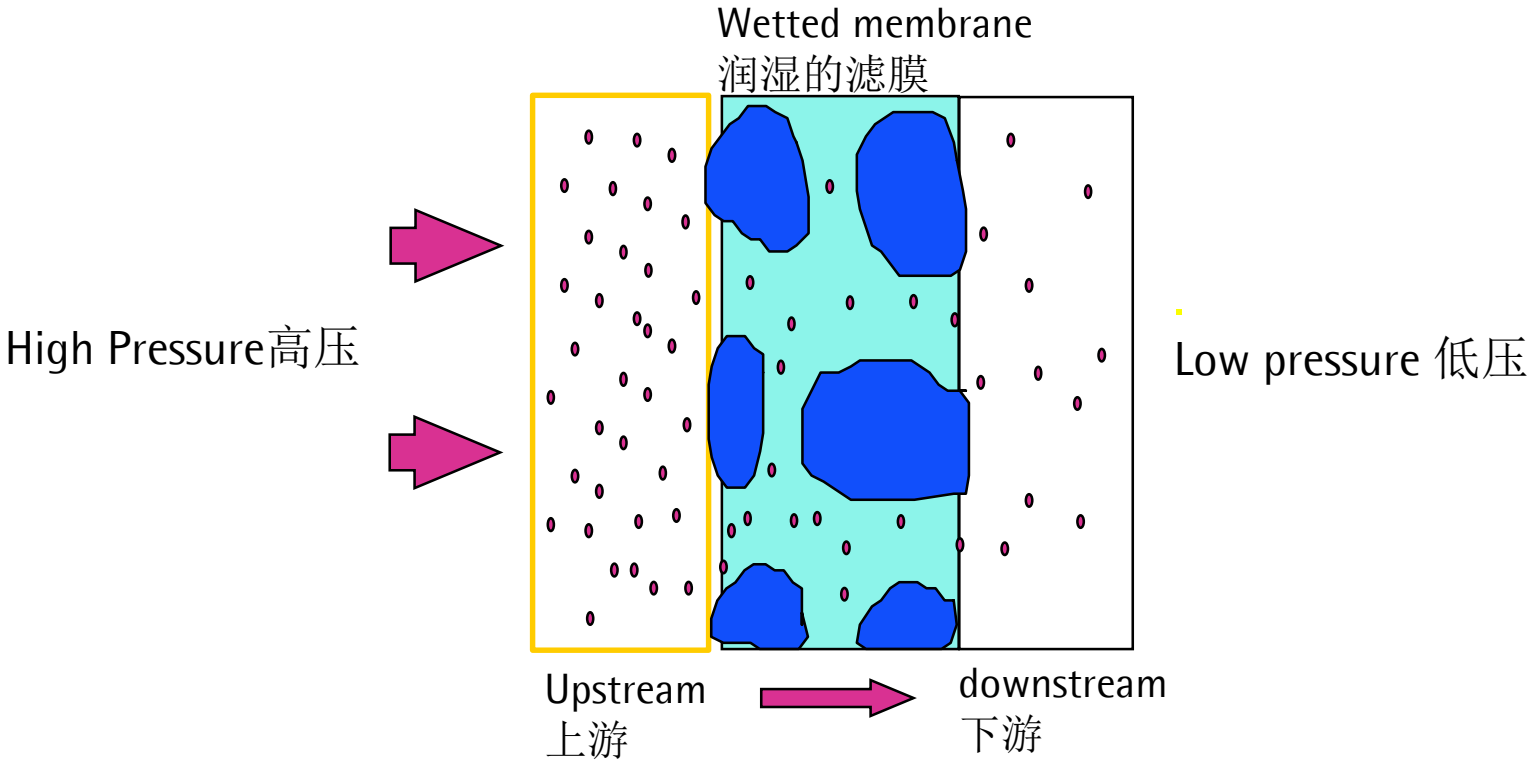
Maximum diffusion value at 2.5 bar at 20 °C is： 18ml/min

Correlate to BCT 完整性与BCT相关联

Lot Number	Diffusion Rate* [ml/min]	Bubble Point [bar|psi]	Results B.C.T.**	LRV***
579/01	5.4	≥ 1|14.5	sterile	≥ 11
577/01	5.4	≥ 1|14.5	sterile	≥ 11
576/01	8.0	≥ 1|14.5	sterile	≥ 11
576/01	8.2	≥ 1|14.5	sterile	≥ 11
576/01	8.2	≥ 1|14.5	sterile	≥ 11
576/01	8.3	≥ 1|14.5	sterile	≥ 11
579/01	8.4	≥ 1|14.5	sterile	≥ 11
579/01	8.4	≥ 1|14.5	sterile	≥ 11
576/01	8.4	≥ 1|14.5	sterile	≥ 11
576/01	8.5	≥ 1|14.5	sterile	≥ 11
576/01	8.6	≥ 1|14.5	sterile	≥ 11
⋮	⋮	⋮	⋮	⋮
576/01	14.0	≥ 1|14.5	sterile	≥ 11
576/01	14.4	≤ 1|14.5	non sterile	≈ 8.4
576/01	16.8	≤ 1|14.5	non sterile	≈ 7.5
579/01	39.0	< 1|14.5	non sterile	< 7
576/01	66.0	< 1|14.5	non sterile	< 7
576/01	66.0	< 1|14.5	non sterile	< 7

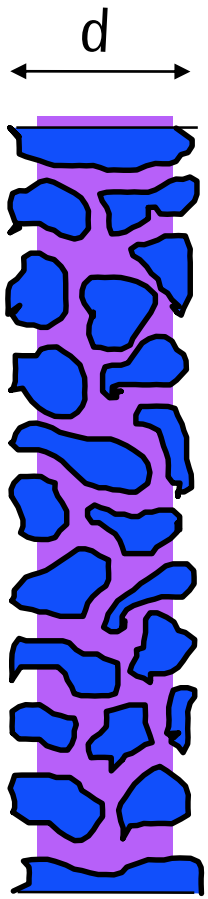
Diffusion Test | Principle 扩散流测试原理

Disolve溶解—Diffusion 扩散模型



The diffusion is the gas flow through a wetted membrane every minutes
扩散流是气体每分钟通过膜孔液体的分子流

Diffusion Test | Important parameters 扩散流的重要参数



$$\frac{N}{t} = \frac{D \cdot L \cdot \Delta p \cdot F}{d}$$

N/t: Gasflow per time单位时间内气体流速 [mol/s]

D: Diffusion coefficient 扩散系数 (liquid-gas-system)

L: Solubility coefficient 溶解度系数(liquid-gas-system)

Δp: Differential pressure 压差

F: Boundary surface gas / liquid 气/液接触面积(~ membrane area)

d: Thickness of the layer 膜厚度(membrane)

correction factor for nitrogene as test gas 采用氮气测试校正因子:

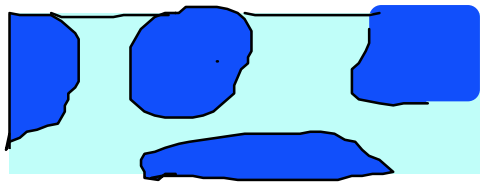
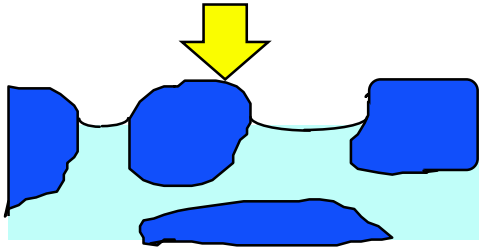
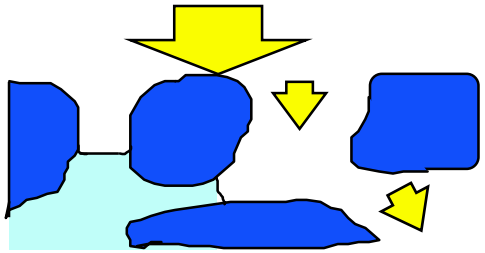
$$Diff_{N2} = Diff_{Luft} \times 0.82$$

Diffusion Test | Summary 扩散流总结

- The diffusion depending on the different solubility at atmospheric pressure and elevated test pressure.气体扩散与气体在大气压和测试压力下的溶解度有关
- The diffusion gas flow is proportional to the differential pressure, the filter area and its thickness.扩散流速度与压差、过滤面积、膜厚度相关
- Diffusion depends also from solubility and diffusivity of the test gas in the wetting liquid and from the temperature 扩散流与气体在相应润湿液体中的溶解度和测试温度有关
- Suitable for filters with ≥ 150 cm^2 EFA适用于有效过滤面积≥150cm^2的滤器
- The test is performed at one defined test pressure 在一个确定的压力下测试(70-80% of BP).
- Test criterion: max. diffusion rate (Diff.max.)测试标准：最大扩散流值
  → test is successful when the measured diffusion rate does not exceed the limit value.测试值不超过最大扩散流值即为测试通过

Solubility溶解度/ΔP压差/Area面积/Thickness厚度/Temperature 温度

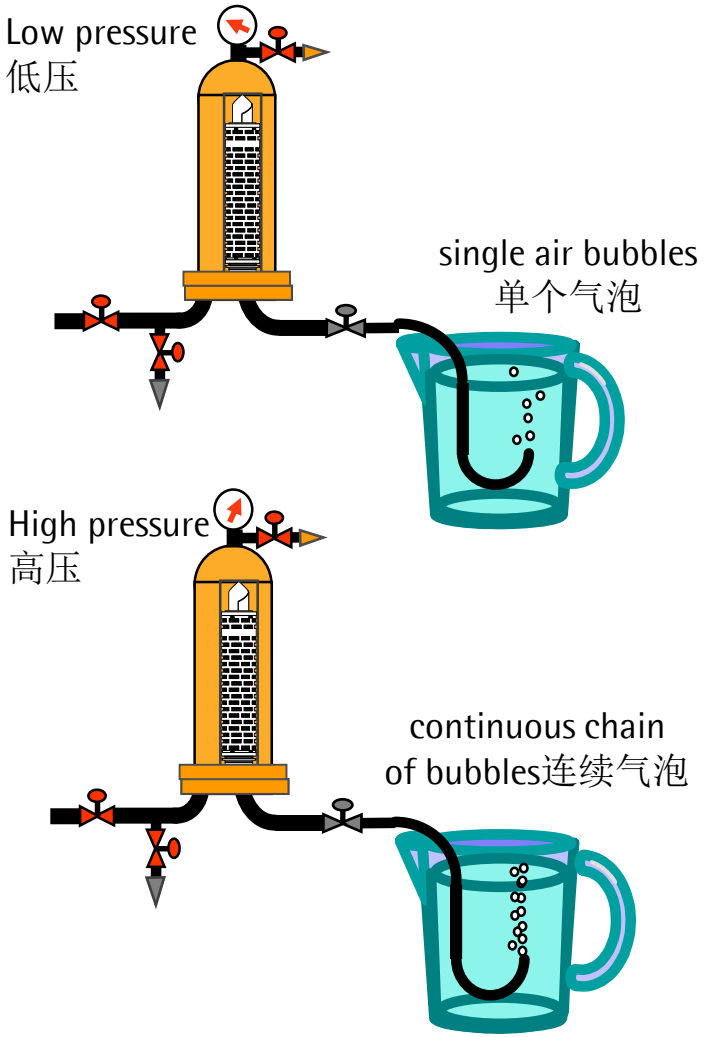
Bubble Point | Principle 泡点测试原理

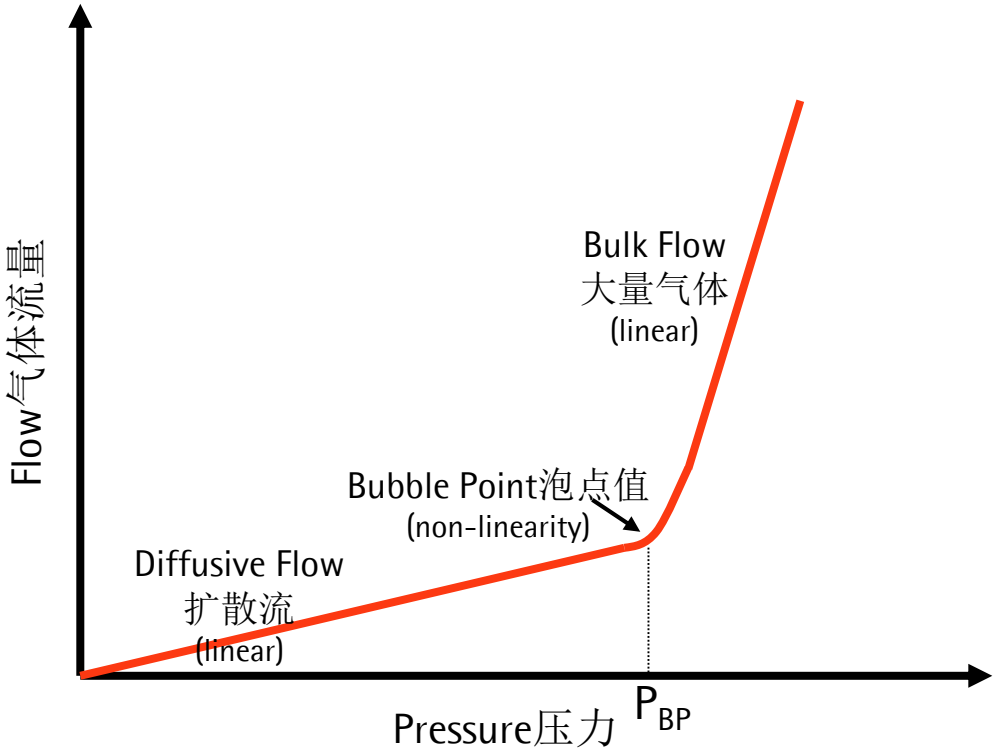
atmospheric pressure 大气压	compressed air 压缩空气(P < BP)	compressed air 压缩空气(P ≥ BP)
		
Pores are filled with water 液体充满膜孔	increase the pressure 上游增压	Direct flow through the largest pores of the membrane 最大的膜孔中的液膜被最先吹破

wetted membrane
湿润滤膜

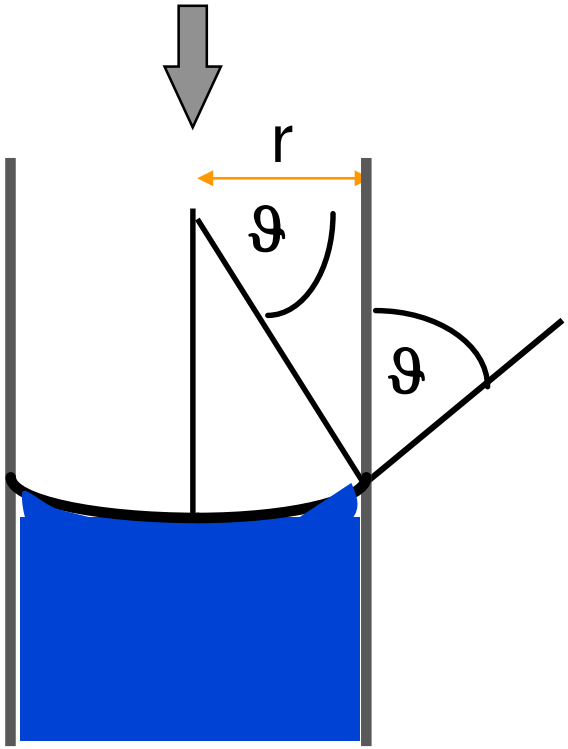
The Bubble Point is the pressure at which a given liquid in the wetted pores of a membrane is forcibly removed吹破湿润滤膜上最大膜孔的液膜所用的压力

Bubble Point | Principle 泡点测试原理





Bubble Point | Parameters 泡点测试重要参数



$$p_{BP} = \frac{2\,\sigma\,\cos\vartheta}{r} \cdot K$$

p_{BP} :	Bubble Point 泡点
σ:	Surface tension 表面张力
ϑ :	Wetting angle 润湿角
r:	Radius of the pore 孔道半径
K:	Correction factor 孔道系数 (required because pore is no ideal cylinder孔道非理想圆柱形）

Liquid润湿液体/Membrane膜材质/Pore size孔径/Temperature温度

Bubble Point | Summary 泡点测试总结

- The Bubble Point is the pressure at which a given liquid in the wetted pores of a membrane is forcibly removed 吹破湿润滤膜上最大膜孔的液膜所用的压力
- At the Bubble Point the acting force (pressure) exceeds the capillary forces which holds the liquid inside the pores. 泡点达到时，提供的压力超过液体与膜孔的表面张力
- The Bubble Point detects the largest pores of a fully wetted membrane 泡点值大小取决于滤膜最大孔的孔径大小
- Recommendable for "small area" up to large filter systems ,from filter discs to multi-round systems 从小膜片到多芯系统都可以采用泡点测试
- Appropriate integrity test for single layer or heterogeneous double layer membranes 适用于单层膜以及不均一双层膜
- No correlation of Bubble Point and Bacteria Retention with homogenous double layer membranes 不适用双层均一性膜
- Test criterion: minimal Bubble Point (BPmin) 测试标准：最小泡点
  A test is successful if the measured BP is ≥ Bpmin 实际泡点大于最小泡点，测试成功

Diffusion & Bubble Point 扩散流与泡点

Diffusion Test 扩散流

$$\frac{N}{t} = \frac{D \cdot L \cdot \Delta p \cdot F}{d}$$

N/t: Gasflow per time单位时间内流速 [mol/s]
D: Diffusion coefficient 扩散系数
L: Solubility coefficient 溶解度系数
Δp: Differential pressure 压差
F: Boundary surface gas / liquid 气/液接触面积(~ membrane area)
d: Thickness of the layer 膜厚度)

Bubble Point Test 泡点

$$P_{BP} = \frac{2\ \sigma \cos \vartheta}{r} \cdot K$$

p_{BP}: Bubble Point 泡点
σ: Surface tension表面张力
ϑ: Wetting angle润湿角
r: Radius of the pore 孔半径
K: correction factor校正因子

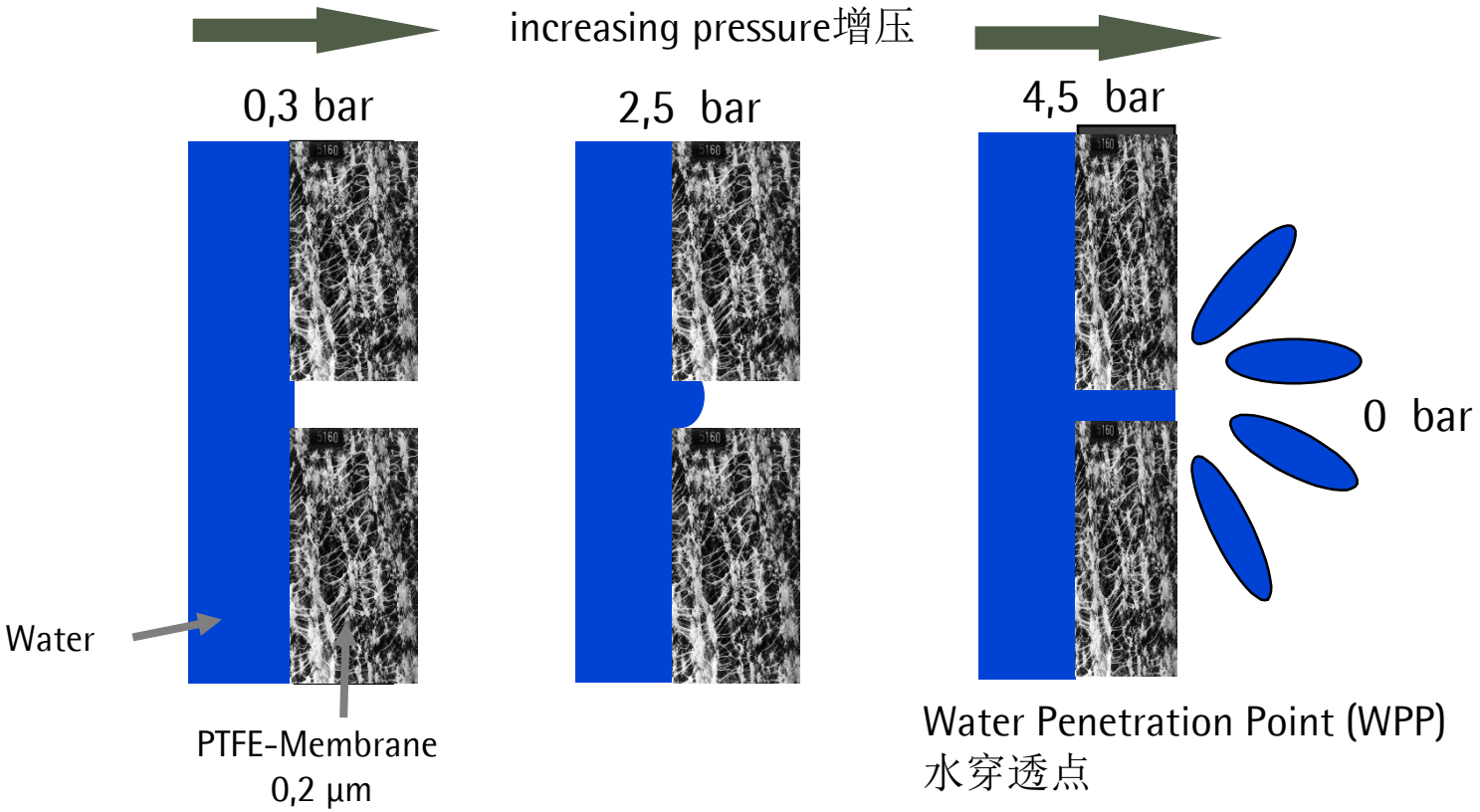
Different physical principles are used 不同的测试原理

Testing hydrophobic membranes | "IPA" test 疏水滤器测试的 IPA法

Wetting with 60% IPA/water mixture then do the integrity test (BPT, Diffusion Test)

- ✓ Test can only be performed before sterilization 只能灭菌前测试
- ✓ IPA have to be reliably removed 去除IPA
- ✓ Degree of hydrophobicity is not tested 无法检测滤器疏水性
- ✓ Correct installation of cartridge in the housing is not tested 离线测试，无法测试滤器安装
- ✓ Safety problem (explosion)安全问题
- ✓ Test criterion: max. pressure decay 测试标准：最大压力降

Testing hydrophobic membranes | WIT 疏水滤器测试WIT法

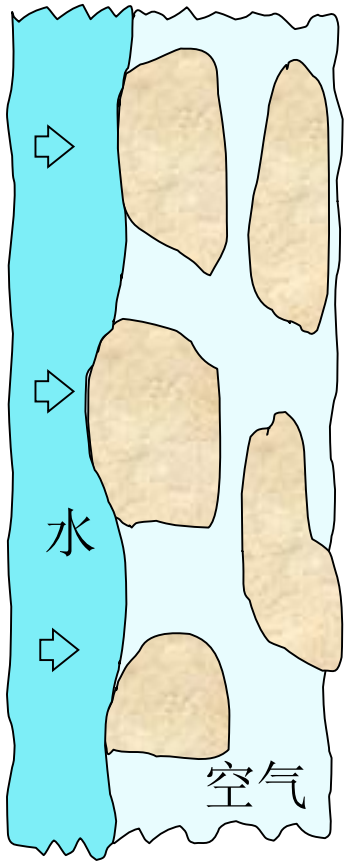


Testing hydrophobic membranes | Principle 疏水滤器测试原理

- Small pore size, less intrusion孔越小，侵入就越少
- The biggest pore size has the most intrusion最大的侵入发生在最大的孔
- Water will penetrate when pressure is too high 孔太大，水会穿透

$$WIT(ml/10min) = \frac{\triangle\ p\ (mbar) \bullet V_{ups}\ (ml)}{t\ (10min) \bullet 大气压\ (mbar)}$$

$\triangle$ p	: differential pressure压差(mbar)
t	: test time 测试时间(min)
p_{atm}	: atmosph. pressure 大气压(mbar)
V_{ups}	: upstream net volume 静体积



WIT should be correlate directly to the bacterial challenge test
水侵入的极限值与微生物挑战测试的结果直接相关

Water Intrusion (WIT) | Water Flow (WFT)

$$Intrusion = \frac{\Delta p \cdot V_n}{t \cdot P_0}$$

$$WaterFlow = \frac{\Delta p \cdot V_n}{t \cdot P_{abs}}$$

$$\frac{WIT}{WFT} = \frac{\Delta P \cdot V_n}{t \cdot P_0} \cdot \frac{t \cdot P_{abs}}{\Delta p \cdot V_n}$$

$$WIT = 3.5 \cdot WFT$$

ΔP： Pressure drop压降

P_{abs}： Absolute test pressure绝对压力(P_0 + test pressure)

$Vn_:$ Net gas volume 静体积

P_o ： Standard atmospheric pressure (1000 mbar)标准大气压

t： Test time测试时间

Selection Guide for Filter Integrity Test Method 完整性测试方法选择

Membrane /system膜/系统	Type of test 测试方法			
hydrophilic filter 亲水性膜	Diffusion	Bubble point	Multipoint diffusion	WIT / WFT
Single layer	+++	+++	See syst. config.	N/A
Heterogeneous double layer	+++	+++	See syst. config.	N/A
Homogeneous double layer	+++	+	N/A	N/A
Type of hydrophobic filter 疏水性膜				
Single layer *	++	++	See syst. config	+++
Homogeneous double layer *	++	+	See syst. config	++
System configuration 系统结构				
Small surface (e.g. < 150 cm²)	N/A	+++	N/A	N/A
Single round （单芯系统）	+++	+++	!	+++
Multiround （多芯系统）	+	++	+++	++

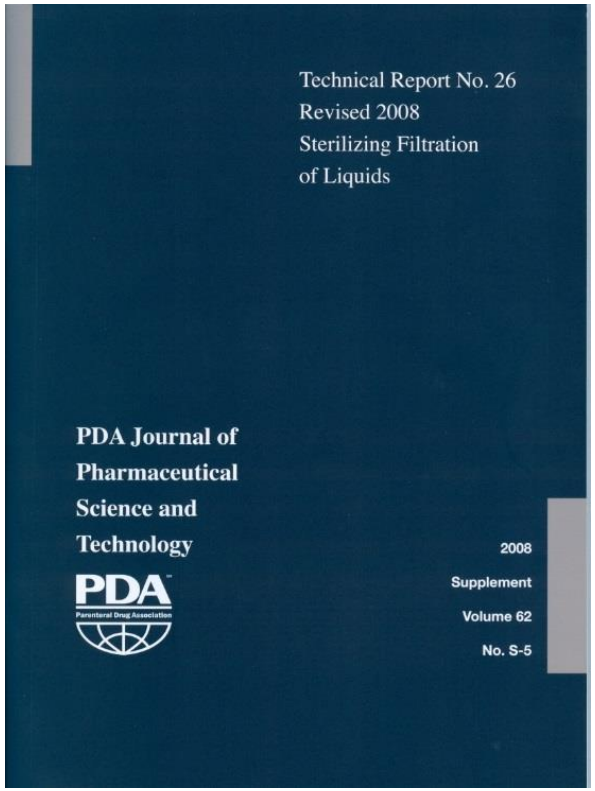
How to Deal with Failure Integrity Test? 如何处理完整性测试失败问题？

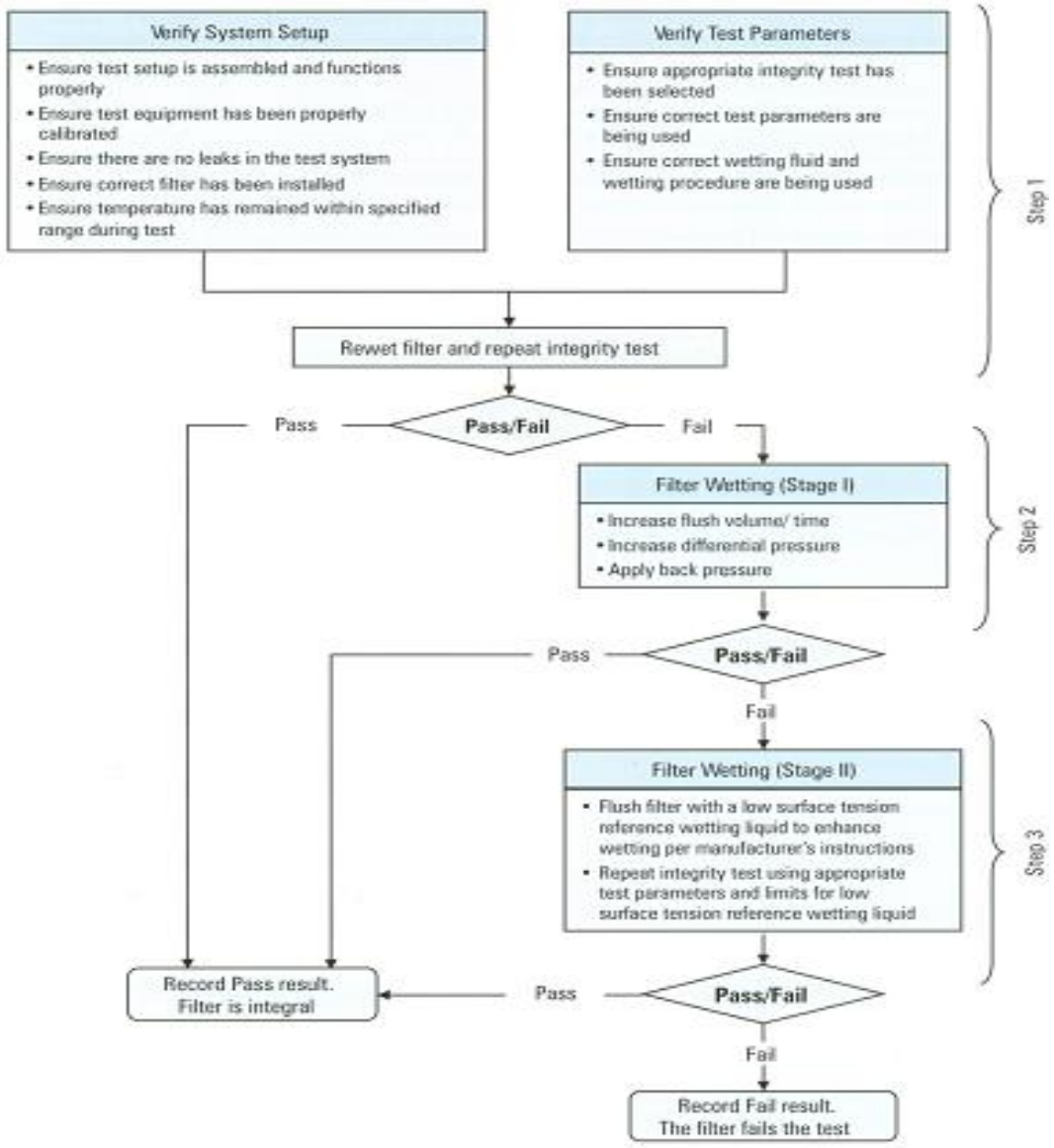
Important Note:

- A failed integrity test does not automatically mean that the cartridge is defect. 完整性测试失败并非意味着滤器有缺陷/破损 ！

- Therefore, detailed investigations are needed to find the underlying reason. 需要进行进一步分析判断以便找到根本原因。

How to Deal with Failure Integrity Test? 如何处理完整性测试失败问题？

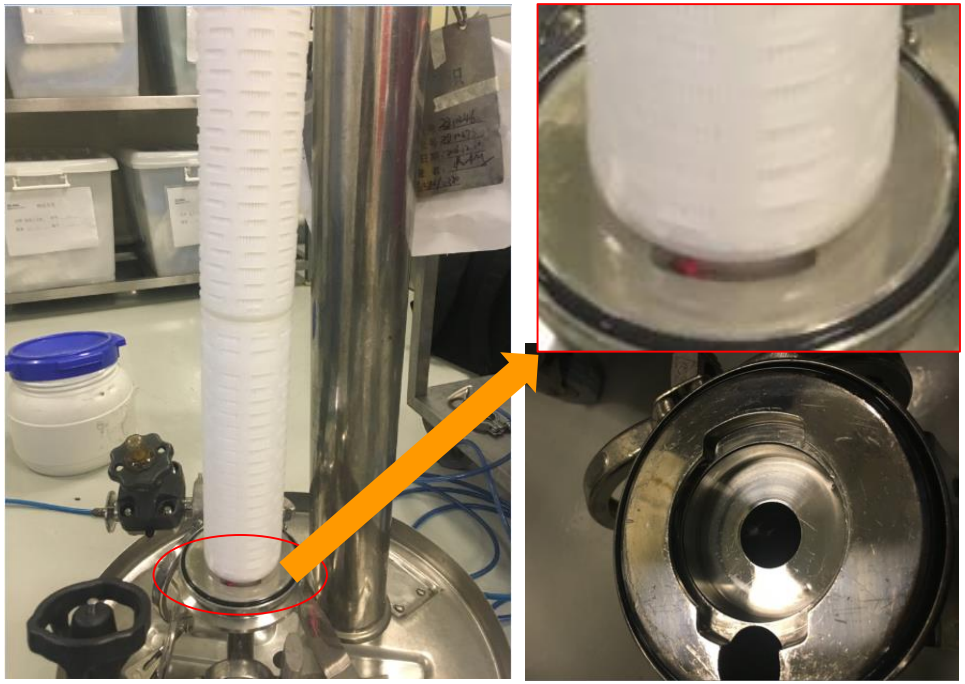


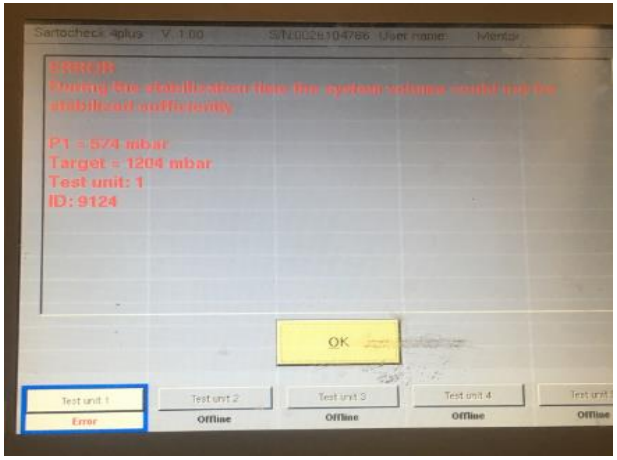


Integrity Test Case 1

A China local pharmaceutical company didn't pass the Integrity test after filtration 过滤后未通过完整性测试

Reason: Incorrect filter installation/ housing design 不正确的安装/钢壳设计

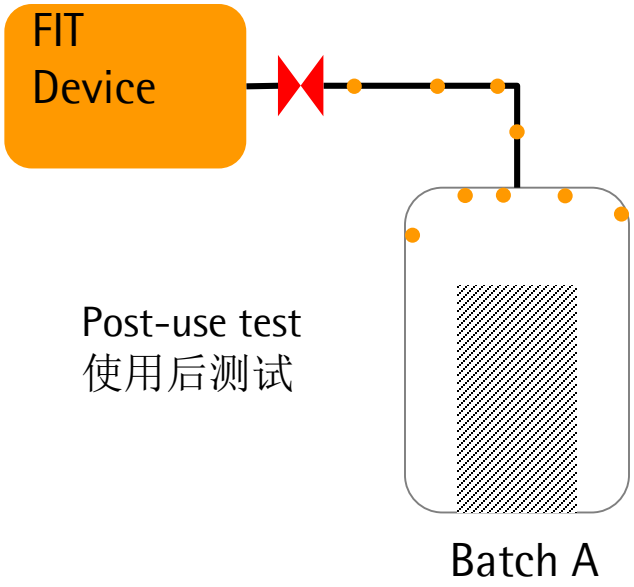


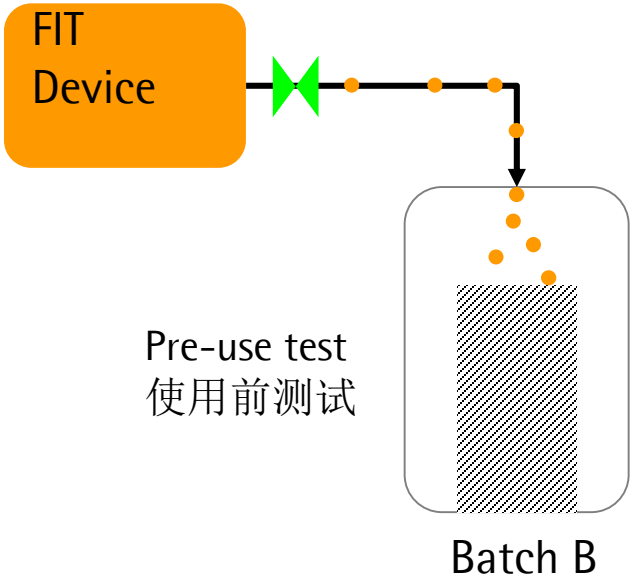


500,000 RMB
Economic loss !

Integrity Test Case 2

An European pharmaceutical company received FDA 483 Warning letter Because of the cross contamination during Integrity test
因为在完整性测试过程中存在交叉污染收到FDA警告信





Integrity Test Case 3

2.9.2 T-Style MaxiCaps®, MaxiCaps®|Gamma MaxiCaps® & MidiCaps®|Gamma MidiCaps®

Temperature [°C]	20	50
Pressure [bar]	5	3
Pressure [psi]	72.5	43.5

2.9.3 Capsules|Gamma Capsules Size 4|Size 5

Temperature [°C]	20	50
Pressure [bar]	4	2
Pressure [psi]	58	29

MidiCaps®|Gamma MidiCaps®

Temperature [°C]	20	50
Pressure [bar]	2	1.5
Pressure [psi]	29	21.8

2.11 Wetting the Filters for Integrity Testing

For each filter element, rinse the filters in the direction of flow for 5 minutes with a differential pressure of 0.3 bar|4 psi backpressure 0.5 bar|7 psi in order to assure that the filters have been wetted completely. Generally, filters are wetted with water. In cases where a different wetting medium is used, if the surface tension of the fluid is different from water (> 70 dynes/cm), different integrity test values than indicated on the next page may be required.

In-line steam sterilization of wetted cartridges with a maximum of 2.3 bar|34 psi inlet pressure and 2 bar|29 psi outlet pressure (max. Δp= 0.3 bar|5 psi)

or

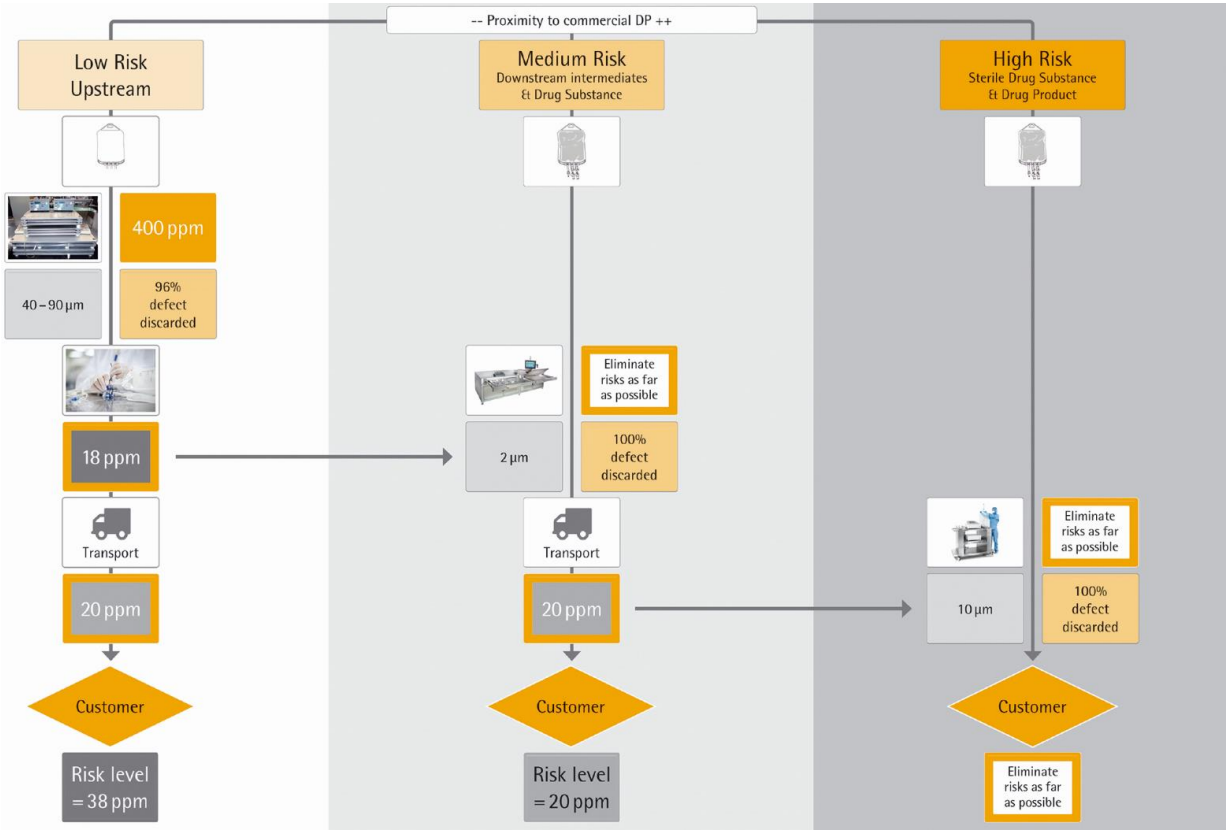
Gamma irradiation of T-Style MaxiCaps®, Gamma MaxiCaps®, Gamma MidiCaps® and Gamma Capsules with ≤ 50 kGy.

Note

Only Cartridges can be in-line steam sterilized.

Integrity Test Case 4 – Bag Integrity test

Quality Risk Management Plan (Example: 2D Bag Storage and Shipping)
质量风险管理计划 (以2D袋子为例)



Integrity Test Case 4 – Bag Integrity test

附表 1 ： Flexsafe STR 袋子完整性测试相关参数及标准

	50L	200L	500L	1000L	2000L
Test pressure 测试压力(mbar)	50				
Stabilization Time 稳定时间(min)	20				
Test time 测试时间(min)	20				
Max. Pressure drop 最大压力降(mbar)	3.8	3.0	2.1	3.7	1.9
Filling Time 填充时间(min)	4	20	35	65	120
Min. detectable leak size(µm)	100	200	200	400	600

温度对完整性测试的影响

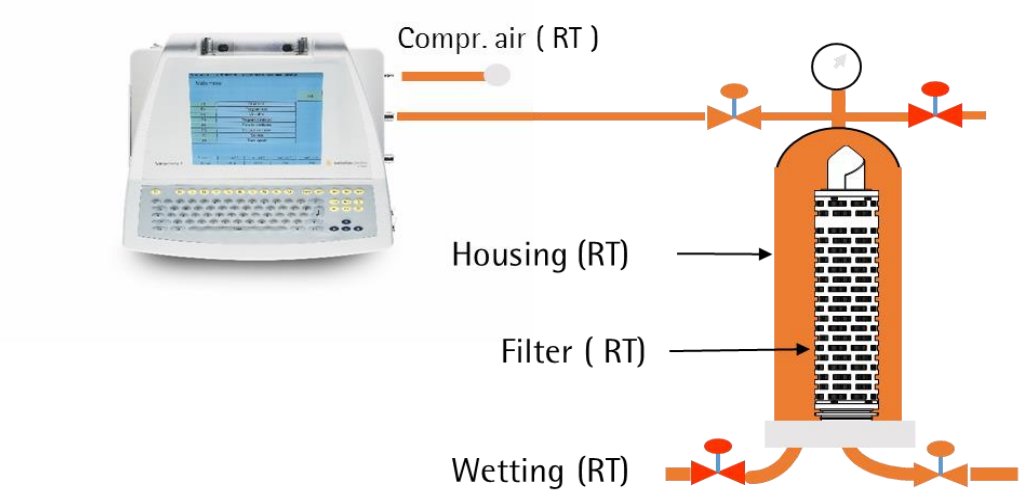
测试温度对测试值的影响　(理论值)

温度 [°C]	泡点值偏差 [%]	扩散流值偏差 [%]
15	+1.0	-3.0
20	±0	±0
25	-1.1	+1.8
30	-2.1	+11.0

只有在室温条件下(20 – 25°C) 测得的完整性测试数据才是有效的！

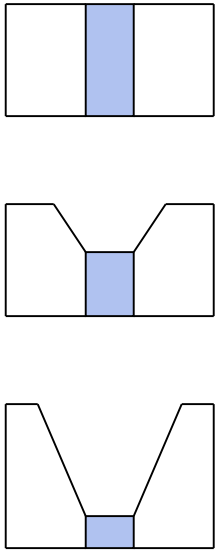
Failure Mode ： Temperature influence
Risk mitigation:环境（温度）对测试的影响（解决方案）

- Make sure testing is at room temperature condition.（室温测试）
- Make sure air、wetting liquid、housing、filter at the same temperature.（确保气源、润湿液体、滤壳、滤芯皆在同样的温度）



Diffusion & Bubble Point 扩散流与泡点

Cross section of a pore
孔的横截面



Diffusion Test	Bubble Point Test	
Thickness, 厚度 Surface area 面积	Pore Radius 半径	
e.g. 4 mL/min	e.g. 3.7 bar	symmetric membrane 对称性膜
e.g. ? mL/min	e.g. ? bar	asymmetric membranes 非对称性膜
e.g. ? mL/min	e.g. ? bar	

Testing hydrophobic membranes | Principle 疏水滤器测试优点？

Intrusion rate is extremely low WIT 值很低，不适用于小膜片.

Advantages of the WIT优点：

- ✓ Water based 以水为介质
- ✓ In-place tests are possible 在线测试
- ✓ Test after steaming is possible可以灭菌后测试
- ✓ Hydrophobicity of the membrane is tested 可以检测膜的疏水性
- ✓ The complete system is tested, not only the cartridge测试整个系统
- ✓ Safety 安全
- ✓ Membrane is not wetted 滤膜没被润湿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Thank You!