FILTER INTEGRITY TESTING

PUPSIT CURRENT PRACTICE

Good Filtration Practices on Aseptic Processing

Roberto Uchimura

MERCK

Overview

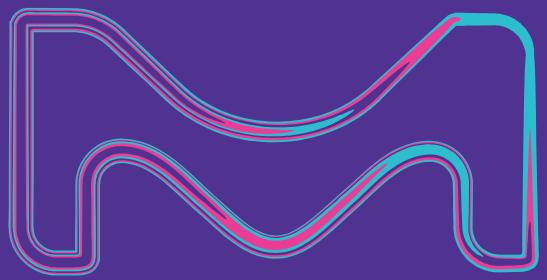
Filter integrity test

Filtration line design for pre-use integrity test

- Regulatory overview
- Current practices
- Qualification

Filter at POF perspectives

FILTER INTEGRITY TEST



MERCK

Why perform Integrity Testing?

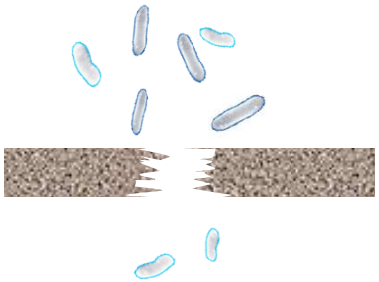
Check correct installation
- Detects system leaks due to o-rings, gaskets, faulty seals

Confirms manufacturers specifications
- Assures the correct pore size filter

Check for damages
- Assures integrity before/after sterilization

Sterility assurance
- Sterile filter is at the core of the aseptic process

Regulatory requirements
- Link between validation and current processing conditions
- GMP Requirement



Integrity
Test sensitivity

Sensitivity

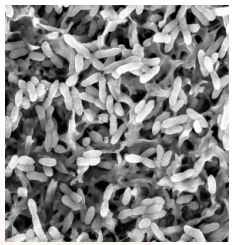
- Virus retention
- Bacteria retention
- Aerosol
- Air binary gas
- Freon Diffusion
- Current flow test for PTFE
- Air Diffusion
- Bubble point, WIT
  - Water
  - Low surface tension fluid

Gold standards

In development

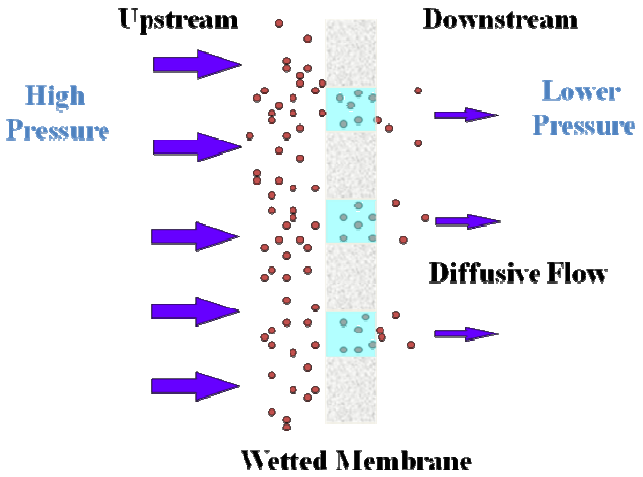
Proprietary
High sensitivity

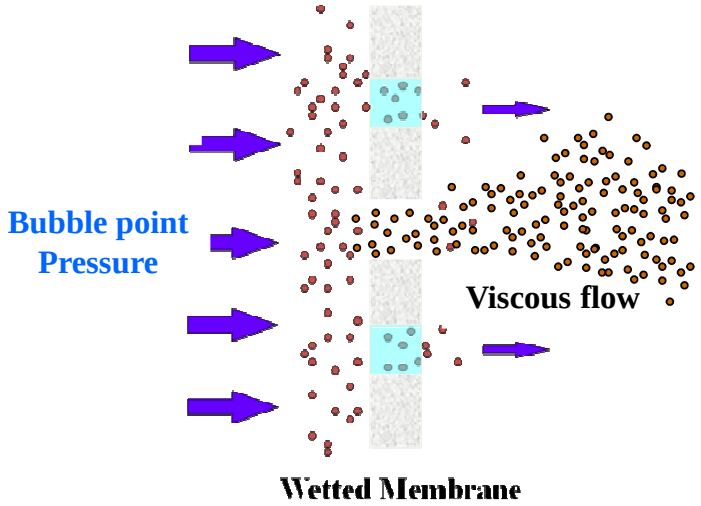
Industry
Standards

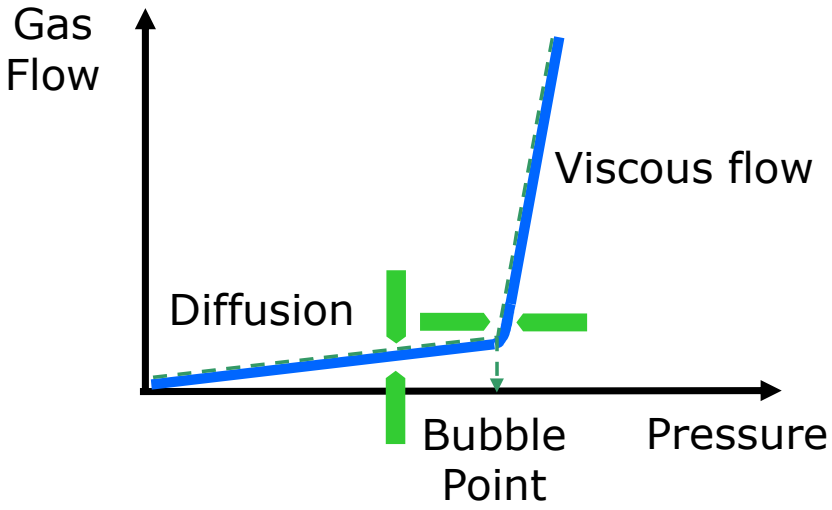


Defect
made visible
by smoke

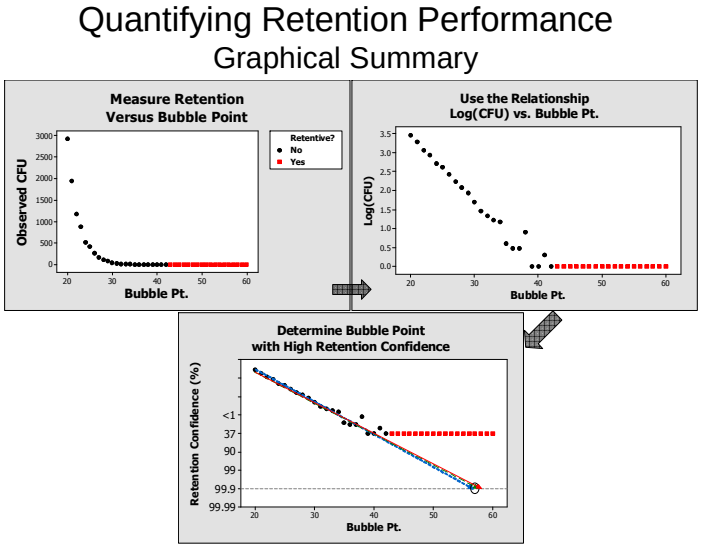
Physical integrity test
Diffusion + Bubble point



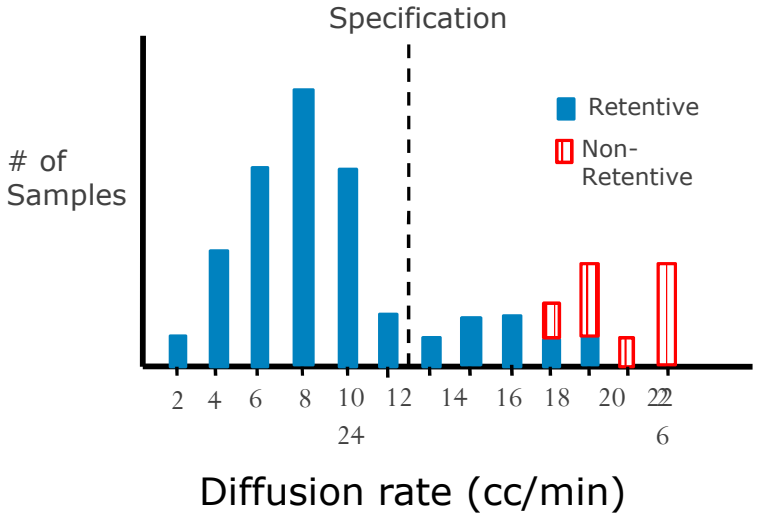




Correlation to bacteria retention



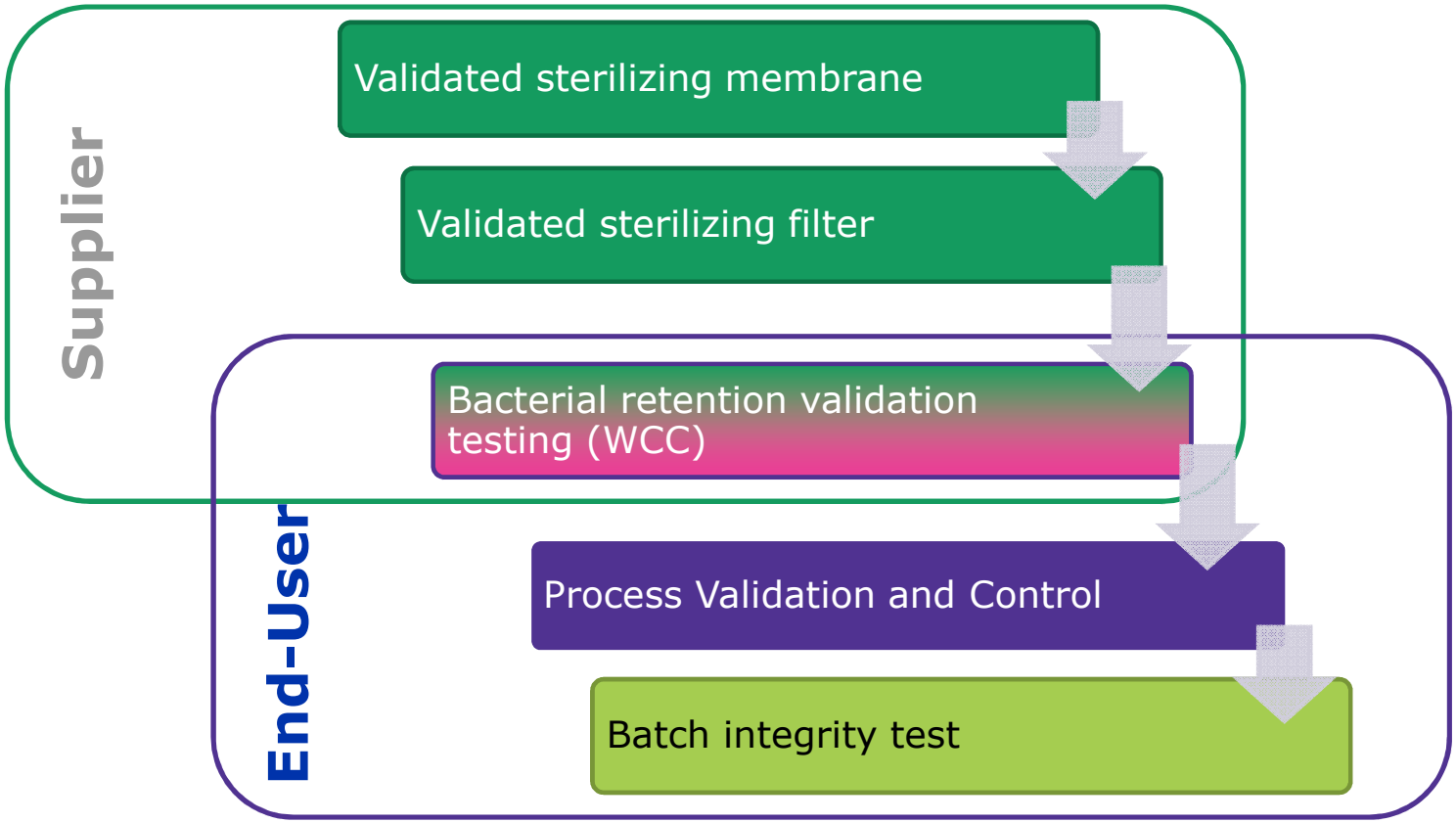
Bubble point can have a direct correlation



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

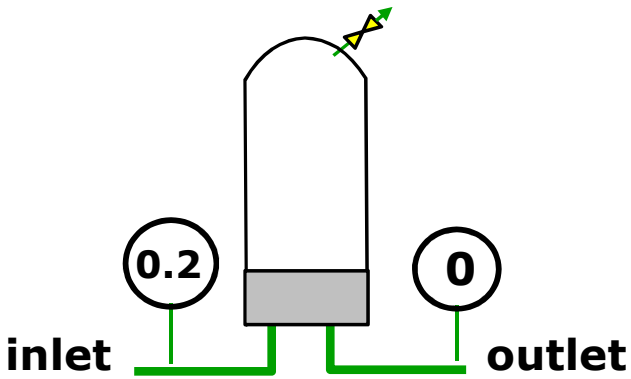
Integrity Testing

A critical element of overall sterility assurance strategy



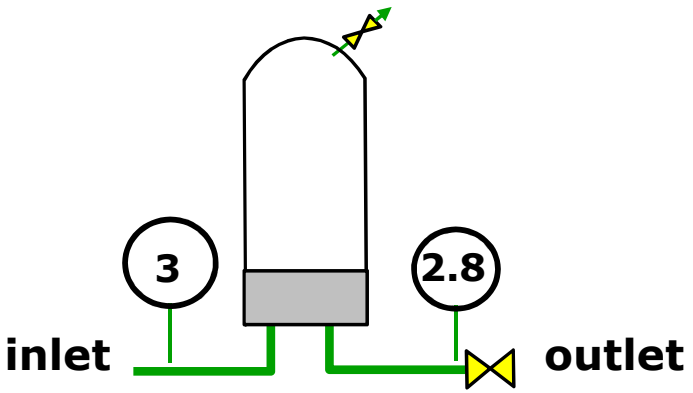
Wetting procedure

Low Pressure

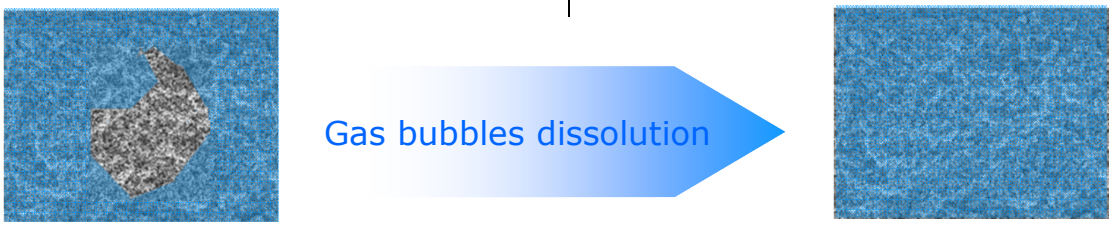


1 lpm/0.1 m² - 5 min
Differential pressure = 0.2 bar

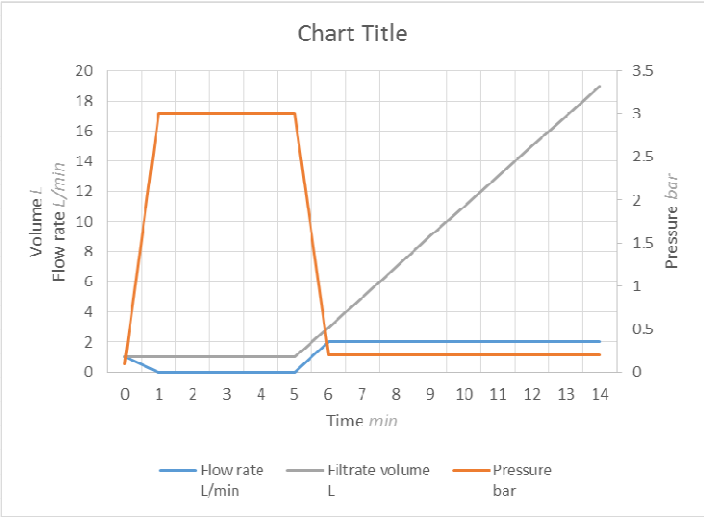
High Pressure



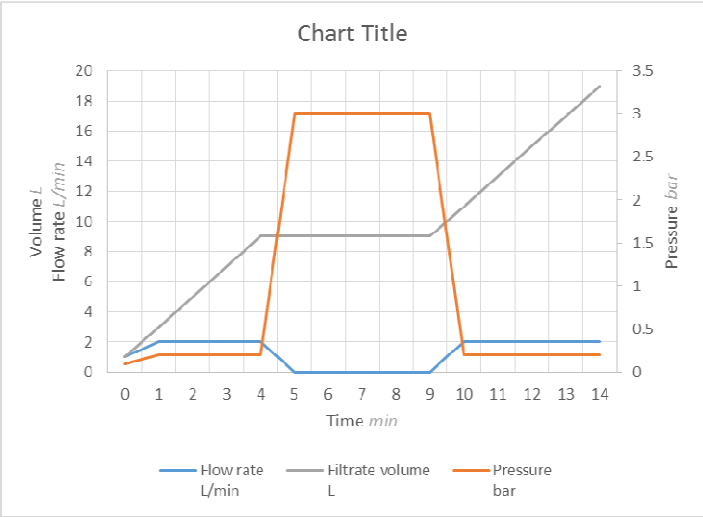
1 lpm/0.1 m² - 5 min
Differential pressure = 0.2 bar



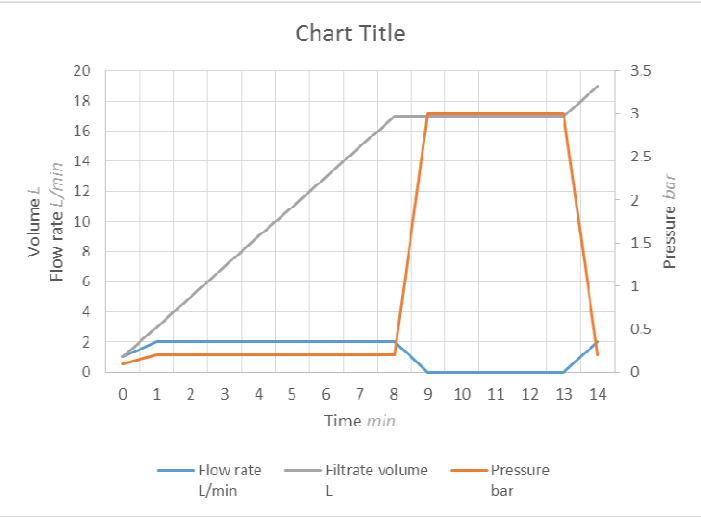
Static pressure phase during filter wetting



Start



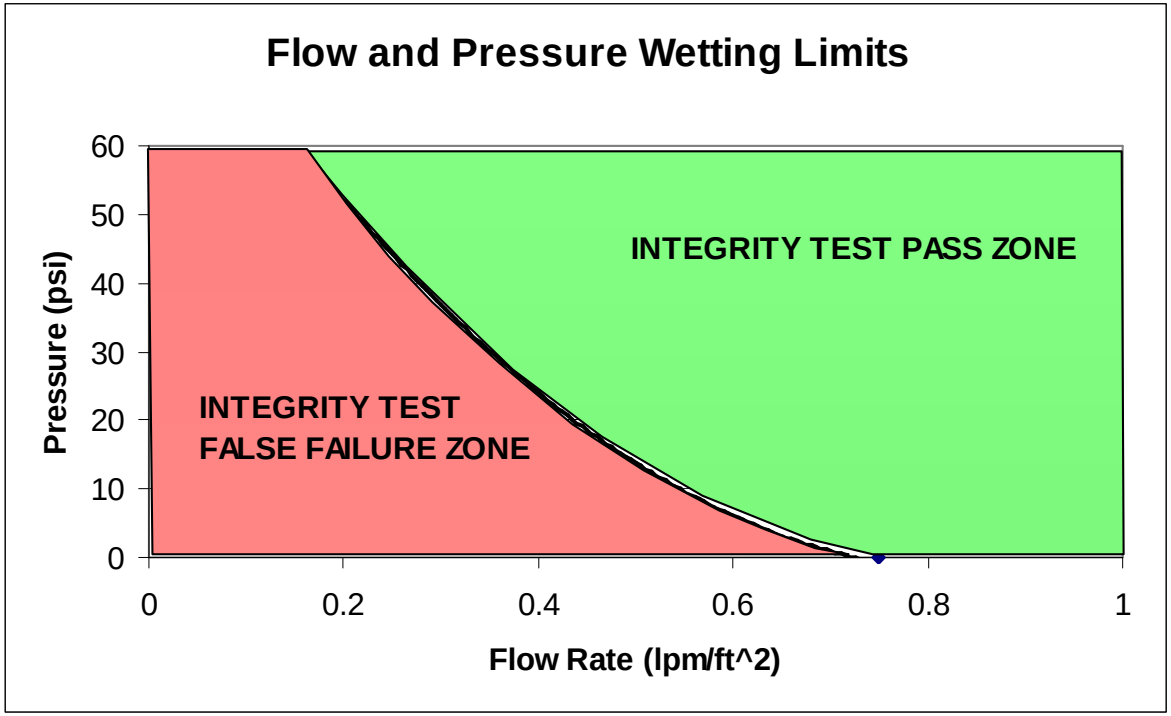
Middle



End

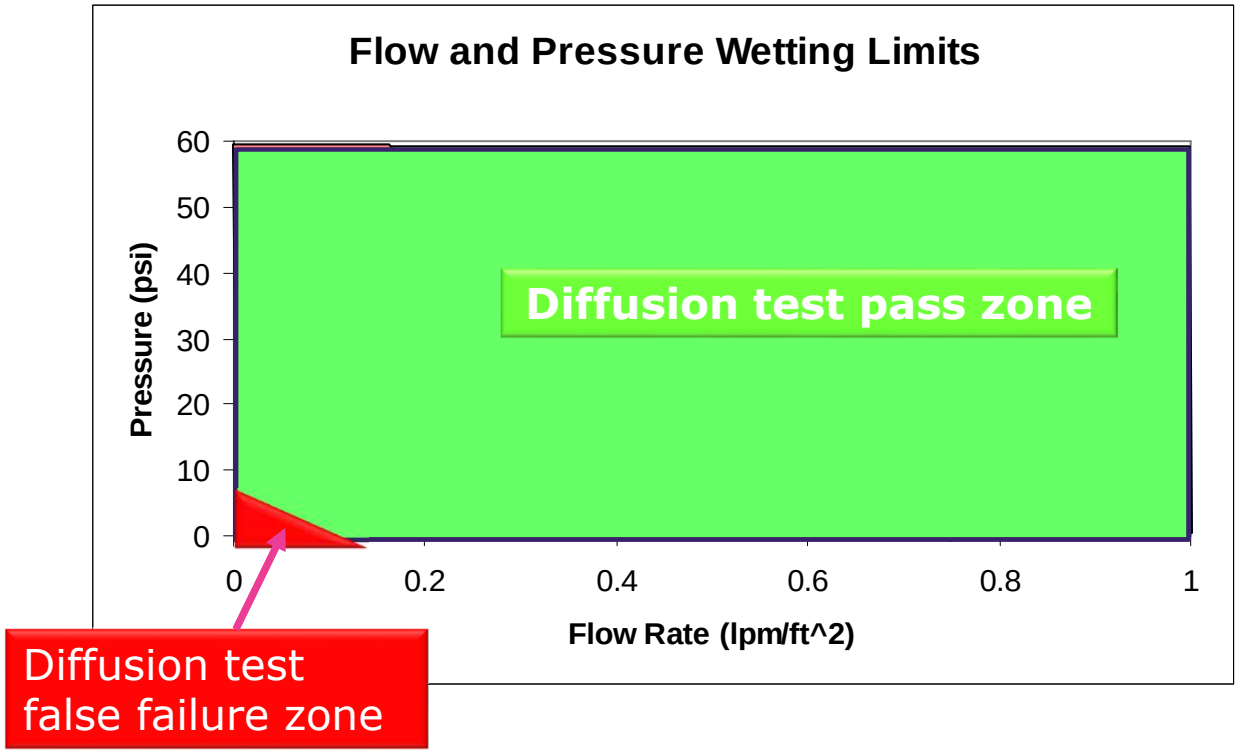
Design space for robust wetting – Bubble Point

Critical parameters : Time, pressure, volume/unit area



Design space for robust wetting – Diffusion

Critical parameters : Time, pressure, volume/unit area



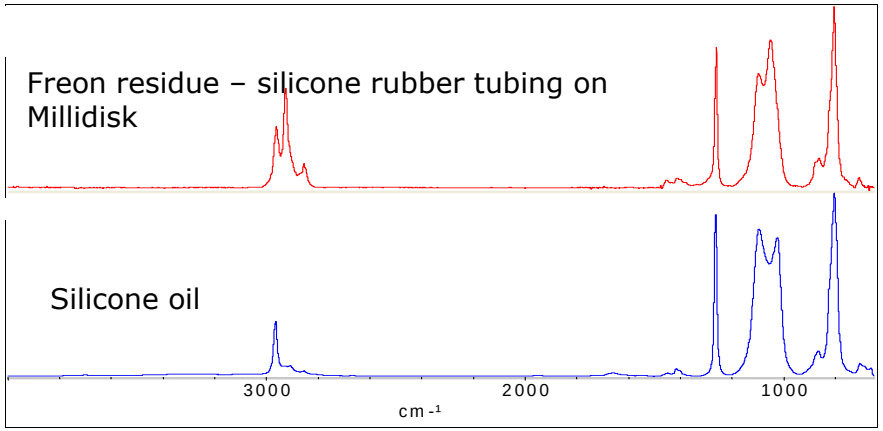
Silicon oil interference

Tubing Material	Water Bubble Point (psig)	Pre-use Product Bubble Point (psig)	Post-use Product Bubble Point (psig)	Difference Pre-use BP minus Post-use (Δ, psig)
Pt-cured silicone	55.14	52.88	39.02	13.86
Peroxide-cured silicone	53.69	51.95	41.49	10.46
C-Flex®	56.59	54.85	51.06	3.79
PharMed®	55.90	53.40	53.26	0.14
BioPharm	55.85	54.10	54.12	−0.02

Impact of tubing material on the failure of product-specific bubble points of sterilizing grade-filters Meyer Vargas Merck & Co
PDA Journal of parenteral science Vol 60 n° 4 2006

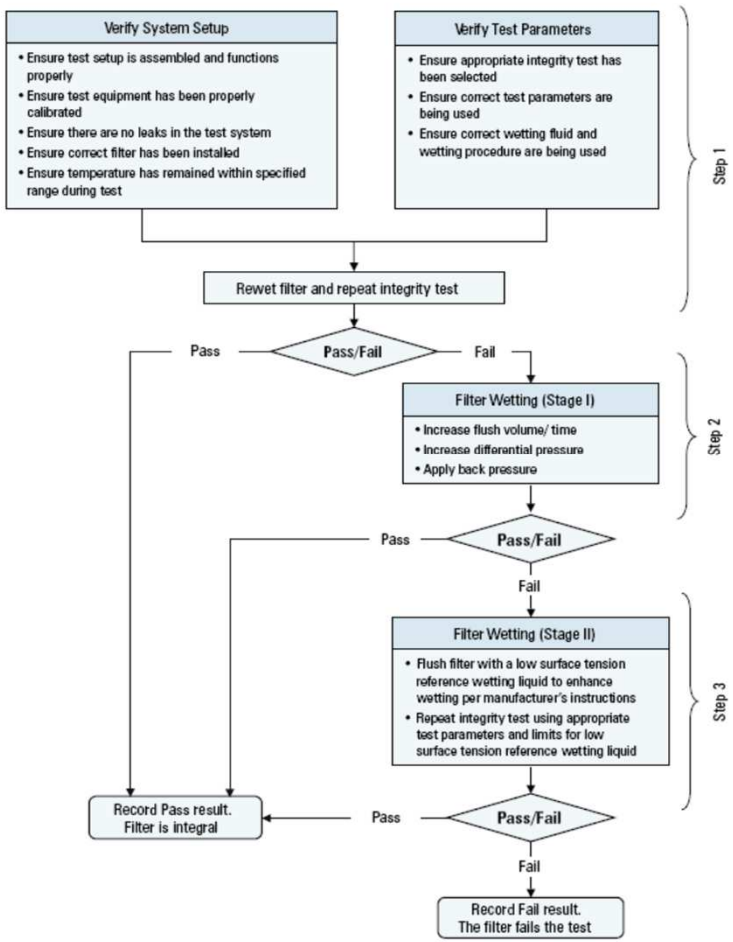
Membrane extracted with Tetrahydrofuran

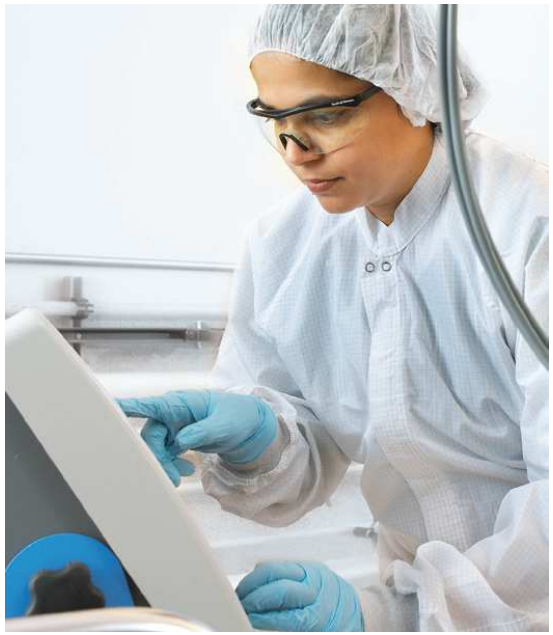
Aliquots on diamond ATR crystal



Decision tree PDA TR26

Figure 7.7-1 Integrity Test Failure Analysis Decision Tree





FILTRATION LINE DESIGN FOR PRE-USE INTEGRITY TEST

How to implement pre-use integrity testing?

Remove

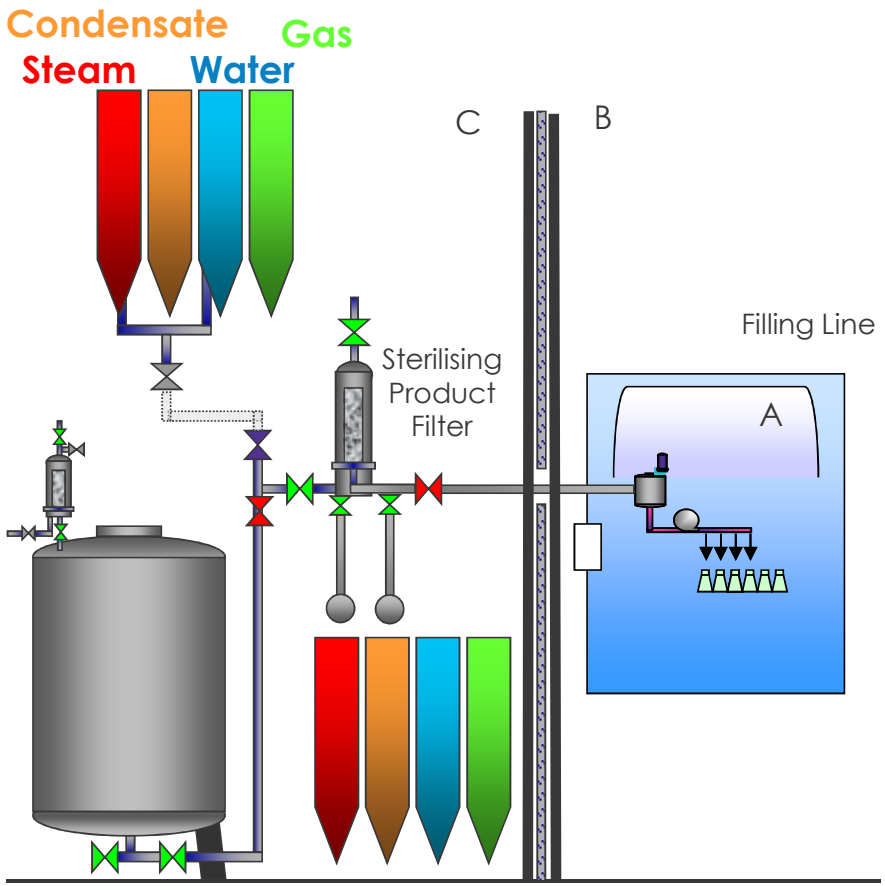
- Wetting Liquid
- Test Gas

Maintain downstream

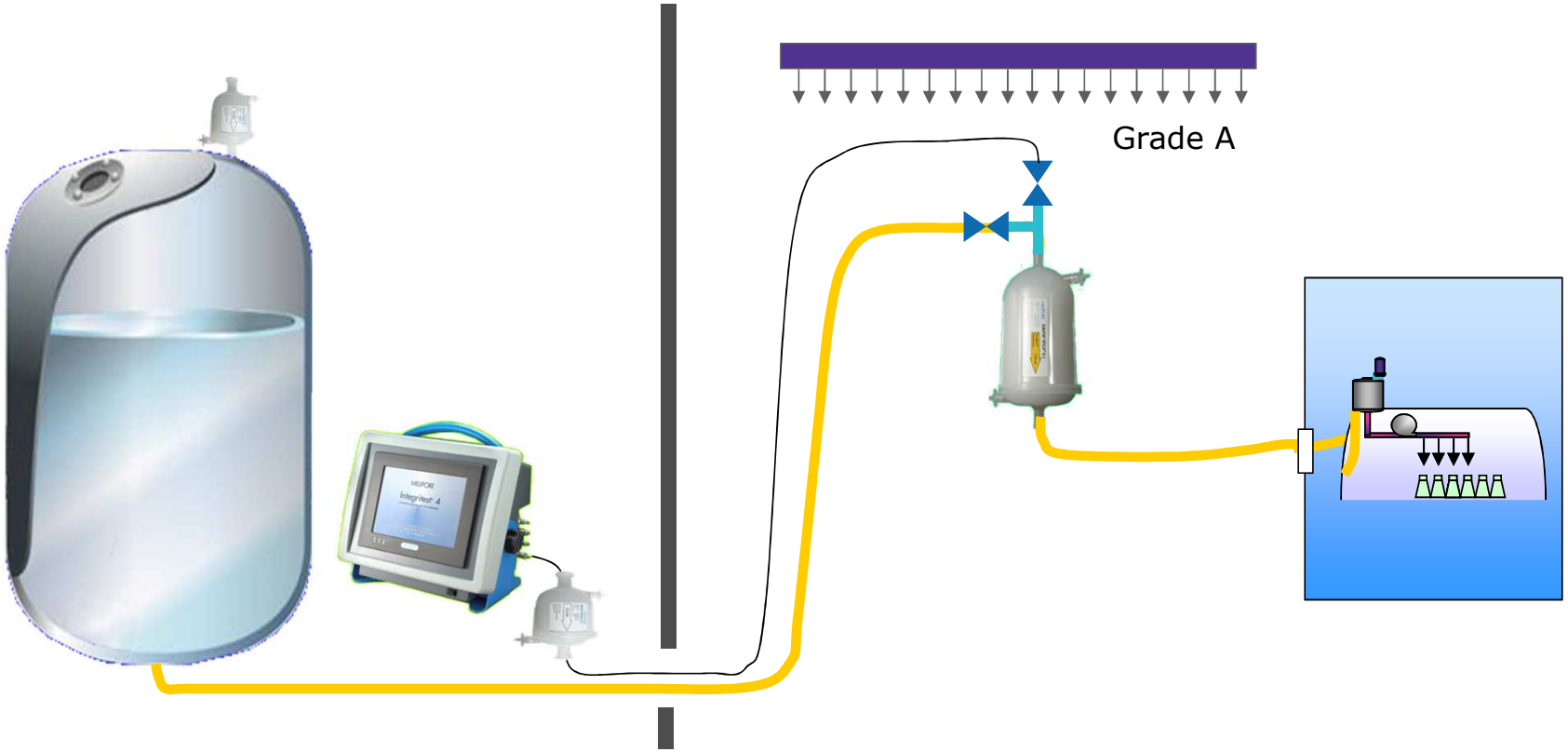
- Sterility
- Atmospheric pressure (test)

Avoid product dilution

Maintain upstream sterility
(biological product)



How to implement pre-use integrity testing?



Overview

Regulatory overview

Current practices

MilliBarrier Technology

Qualification

Regulatory Requirements

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

EU GMP Annex 1 for the manufacture of sterile medicinal products, February 2008

US FDA: Integrity testing of the filter can be performed prior to process and **should be routinely performed post-use**.

US FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, 2004

SFDA
国家食品药品监督管理局

SFDA: **After sterilizing filter is used, the integrity of the filter should be tested and the results recorded.** The test methods could be bubble point, diffusion or pressure hold.

SFDA Guidelines, 2010

Where sterility is claimed: IT before use is recommended, after use is required

Industry Guidance

PDA® TR26 – 2008 Sterilizing filtration of liquids

- Where the claimed purpose of the filter is to sterilize, **pre and post filtration** integrity tests **should be performed**.
- Prefiltration integrity test may be performed prior to sterilization of the filter and, preferably, after sterilization.
- Steps should be taken to ensure that the **downstream side of the system remains sterile** when performing a post sterilization, pre-use integrity test.

p 34

PUPSIT mandatory regardless of method of sterilization

- ***PDA® TR 66 - 2014 Single-Use systems***

- It is **less important** to conduct a **pre-use integrity test** of a sterilizing filter that has been **sterilized with gamma radiation.**
- The pre-use test has a primary purpose of detecting a damaged filter, a purpose that has roots in steam sterilization, which has known mechanisms by which filters can be damaged. These **mechanisms do not exist with gamma radiation sterilization**.

p 33

PUPSIT less important for gamma sterilized filters

Industry Guidance

ISO® 13408: The filtration system should be designed to permit in-place integrity testing as a closed system prior to filtration.

ISO® 13408, 2003

PDA® recommends IT pre-use and post-use. Industry guidance emphasizes that maintaining process sterility is of critical concern

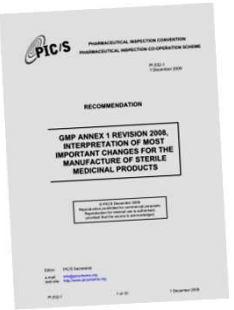
Inspectors guidelines

PIC/S : … the integrity of each individual product filter used for routine production should be tested before and after use.

Recommendation on the validation of aseptic processes July 2009

PIC/S : However, if a system of two filters with redundancy is used (the second filter is used for security, if one fails the required SAL is still achieved), sampling should be performed upstream of these filters in order not to compromise the filtration step.

GMP annex 1 rev 2008, Interpretation guide (PI-032A 1) Dec 2009



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Human medicines

Home ▸ Regulatory ▸ Human medicines ▸ Inspections ▸ GMP/GDP compliance ▸ Q&A

EU GMP guide annexes - Supplementary requirements: Annex 1 Manufacture of sterile medicinal products

Back to top

Expand all items in this list

1. How should the integrity of sterilising filters be verified? - H+V June 2007

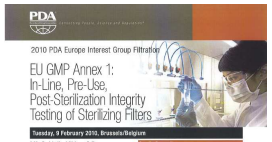
Annex 1, paragraph 85 states "The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test."

The filter sterilisation process, may be physically stressful for the filter. For example high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons filters should be tested both, before use but after sterilisation, and again after use.

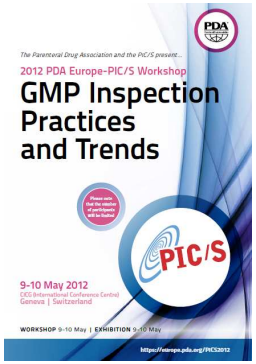
Furthermore, testing should be performed in-situ in order to verify the integrity of the filter complete with its housing.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&jsenabled=true

The debate

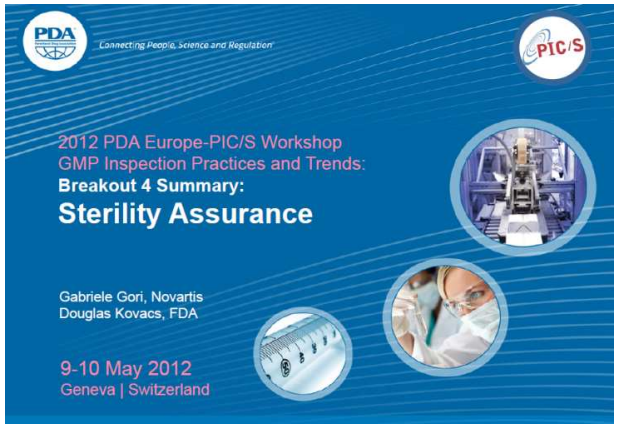

PDA
2010 PDA Europe Interest Group Filtration
EU GMP Annex 1:
In-Line, Pre-Use,
Post-Sterilization Integrity
Testing of Sterilizing Filters


PDA
PDA/EMA 2011
Conference
Regulation, Cooperation, Innovation:
An Effective Partnership among Authorities
and Industry in Europe
3-6 May 2011
Hotel Sofitel
London Heathrow, UK


PDA
2012 PDA Europe-PIC/S Workshop
GMP Inspection
Practices
and Trends
PIC/S
9-10 May 2012
Geneva | Switzerland


PDA
2013 PDA Europe
Current and Emerging
EU Regulations and
Inspection Trends
In Cooperation with The Irish Medicines Board
9-10 July 2013
The Gresham Dublin Hotel
Dublin | Ireland


Review
BioPharm
Pre-use Filter Integrity Testing:
To Test or not to Test?
2012 PDA
INTEREST GROUP


PDA
Connecting People, Science and Regulation
PIC/S
2012 PDA Europe-PIC/S Workshop
GMP Inspection Practices and Trends:
Breakout 4 Summary:
Sterility Assurance
Gabriele Gori, Novartis
Douglas Kovacs, FDA
9-10 May 2012
Geneva | Switzerland

PDA commentary

Association Commentary

Pre-use/Post-sterilization Integrity Testing of Sterilizing Grade Filters

PDA Pre Use/Post-Sterilization Integrity Test Task Force: KAREN BARTEL[1], HAL BASEMAN[2], GABRIELE GORI[3], RICHARD LEVY[4], HEMISHA LY[5,*], MAIK JORNITZ[6], RUSSELL MADSEN[7], MICHIEL ROOK[8], and SUE SCHNIEPP[9]

[1]Roche-Genentech; [2]ValSource; [3]Novartis; [4]PDA; [5]Merck, Task Force Chair; [6]Sartorius-Stedim Biotech; [7]The Williamsburg Group, LLC; [8]Global-Consepts; and [9]OsoBio

Issue

EU Annex I, paragraph 113 states: "The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as bubble point, diffusive flow or pressure hold." The paragraph wording, stating a recommendation for an activity, does not allow for applicability of the pre-use/post-sterilization integrity test based on risk evaluation.

PDA's Position

Damage to an integral filter during moist heat sterilization is most commonly caused by exceeding manufacturer's recommended pressure differential and temperature parameters. This damage, if it occurs, is prominent enough that it would assuredly be detected during the post-use integrity test. Sterilizing-grade filter validation data demonstrates that pore enlargement after moist heat exposure does not occur. For sterilization via gamma radiation, the filter is not exposed to pressure differential or high temperature and filter validation data again demonstrates that pore enlargement after radiation also does not occur. In these instances, the risk of not performing a pre-use/post-sterilization integrity test is a business or loss-of-product risk and not a product quality risk. A failed post-use integrity test indicates the product should

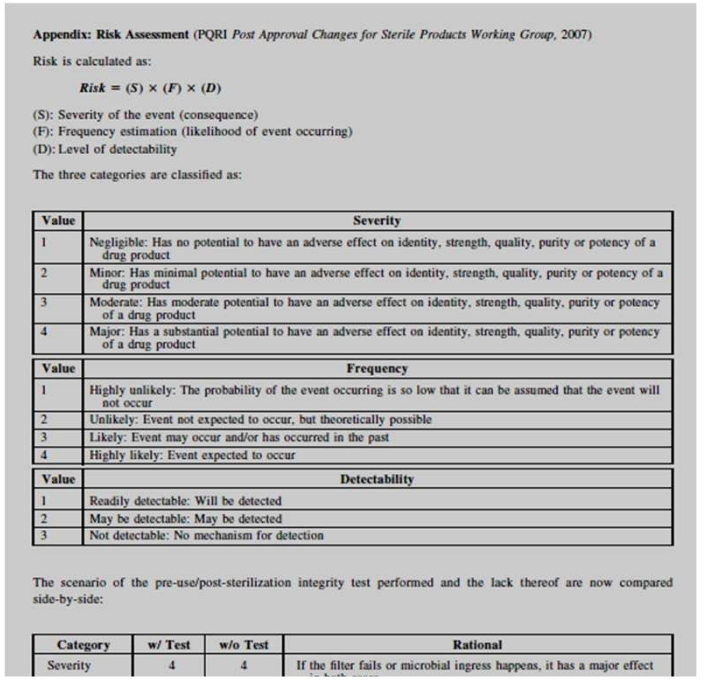
pressure and room temperature, creating the potential for microbial ingress. The impact of a sterile filtrate side manipulation may lead to a breach in sterility of the system, thus adding an unnecessary residual risk to product quality and patient safety.

PDA's Recommendation

The need of a pre-use integrity test of a sterilized filter should be left to the discretion of the filter user and should not be mandatory.

The decision to perform or not perform a pre-use/post-sterilization integrity test should be made by the filter user upon thorough, documented risk-based analysis in accordance with ICH guidelines. Based on the risk analysis, a control strategy should be implemented that includes validation, in-process monitoring and control of temperatures and pressures during sterilization to ensure that the vendor recommended parameters have not been exceeded. Careful consideration and precautions must be taken to avoid the potential for microbial ingress should the user perform a pre-use integrity test of the sterilized filter.

Additional Reading



Appendix: Risk Assessment (PQRI *Post Approval Changes for Sterile Products Working Group*, 2007)

Risk is calculated as:

$$Risk = (S) \times (F) \times (D)$$

(S): Severity of the event (consequence)
(F): Frequency estimation (likelihood of event occurring)
(D): Level of detectability

The three categories are classified as:

Value	Severity
1	Negligible: Has no potential to have an adverse effect on identity, strength, quality, purity or potency of a drug product
2	Minor: Has minimal potential to have an adverse effect on identity, strength, quality, purity or potency of a drug product
3	Moderate: Has moderate potential to have an adverse effect on identity, strength, quality, purity or potency of a drug product
4	Major: Has a substantial potential to have an adverse effect on identity, strength, quality, purity or potency of a drug product

Value	Frequency
1	Highly unlikely: The probability of the event occurring is so low that it can be assumed that the event will not occur
2	Unlikely: Event not expected to occur, but theoretically possible
3	Likely: Event may occur and/or has occurred in the past
4	Highly likely: Event expected to occur

Value	Detectability
1	Readily detectable: Will be detected
2	May be detectable: May be detected
3	Not detectable: No mechanism for detection

The scenario of the pre-use/post-sterilization integrity test performed and the lack thereof are now compared side-by-side:

Category	w/ Test	w/o Test	Rational
Severity	4	4	If the filter fails or microbial ingress happens, it has a major effect

PUPSIT decision should follow a risk based analysis for microbial ingress linked to:

- filter failure
- absence of over pressure.

PDA conference June 2013

Science

snapshot

PDA Talks PUPSIT in Dublin at EU Regulations Meeting

In June, PDA's PUPSIT (pre-use/post-sterilization integrity testing) task force, represented by task force leader **Hemisha Ly,** Merck, presented at the PDA conference, *Emerging EU Regulations and Inspection Trends,* in Dublin, Ireland. The presentation represented another step toward aligning PDA's position with that of the Irish Medicines Board (IMB) and eventually EMA Annex 1. Not only was the presentation well received but there was considerable feedback from the audience, summarized below:

- IMB is in agreement that this requirement needs to be revisited. They have already submitted a "problem statement" to EMA to remove this requirement from Annex 1. They have mentioned that they have put together a position paper internally. IMB took this step due to the issue being brought to their attention from industry as well as through PDA.
- They are willing to accept a well-documented risk assessment that includes control strategies and scientific data for this requirement—but again—it is in Annex 1, so they cannot guarantee the acceptance of the risk assessment.
- IMB (via the Inspectors Working Group) will also work to modify the current Q&A to allow for a risk-based approach. IMB agreed that this might be faster than getting the Annex 1 changed. The Q&A, from an inspector's standpoint, is treated equally to Annex 1 paragraphs as it goes through a formal approval process before being posted. So, if the Q&A suggests a risk assessment, even if Annex 1 is not changed, the inspector will accept it.
- PDA will also recommend (as it has previously already committed) for the current Q&A to be modified, allowing for a risk-based approach.

The idea of risk based approach is progressing…

PDA Letter • October 2013

PDA Points to consider for Aseptic Processing
Part 1 January 2015

Topic J: Pre-Use, Post Sterilization Integrity Test of Sterilizing Filters (PUPSIT)

Problem Statement

Should a PUPSIT of sterilizing filters be performed?

Recommendation

The PUPSIT of sterilizing-grade filters as a means to ensure a filter's integrity throughout its use and product sterility should be evaluated on a case-by-case basis by a comprehensive risk assessment.

NOTE: The current requirement in the EU is to perform a pre-use, post-sterilization integrity test.

The risk assessment should be executed by line and by product to include a side-by-side comparison of conducting versus not conducting the PUPSIT.

The risk assessment should include risk-related elements, such as the following:

- Effect of a filter failure, should one occur including the potential introduction of nonsterile product into an aseptic area
- Risk of contamination due to additional manipulations on pre-sterilized filters (e.g., ready-to-use filters)
- Ability to detect a potential breach
- Likelihood of microbial ingress to the downstream side of the filter (when a PUPSIT is performed)
- Potential for blocking the sterilizing filters due to the processing stream (particulate or bioburden)
- Whether the existing production lines can be modified to add the ability to perform a PUPSIT and assess the potential risk to the product or sterile boundary by implementing such modifications
- Whether there is a control strategy in place for the steam sterilization process (SIP) to prevent filter damage during SIP
- Impact of wetting fluid on product dilution and product attributes
- Impact of the additional time required on time-sensitive processes

If the outcome of the risk assessment indicates that the PUPSIT procedure reduces product quality (or business) risk and that the PUPSIT procedure does not increase the overall product quality risk, then the PUPSIT procedure may be implemented. However, if the risk assessment indicates that the PUPSIT procedure results in additional risk to product quality, then the PUPSIT procedure should be avoided.

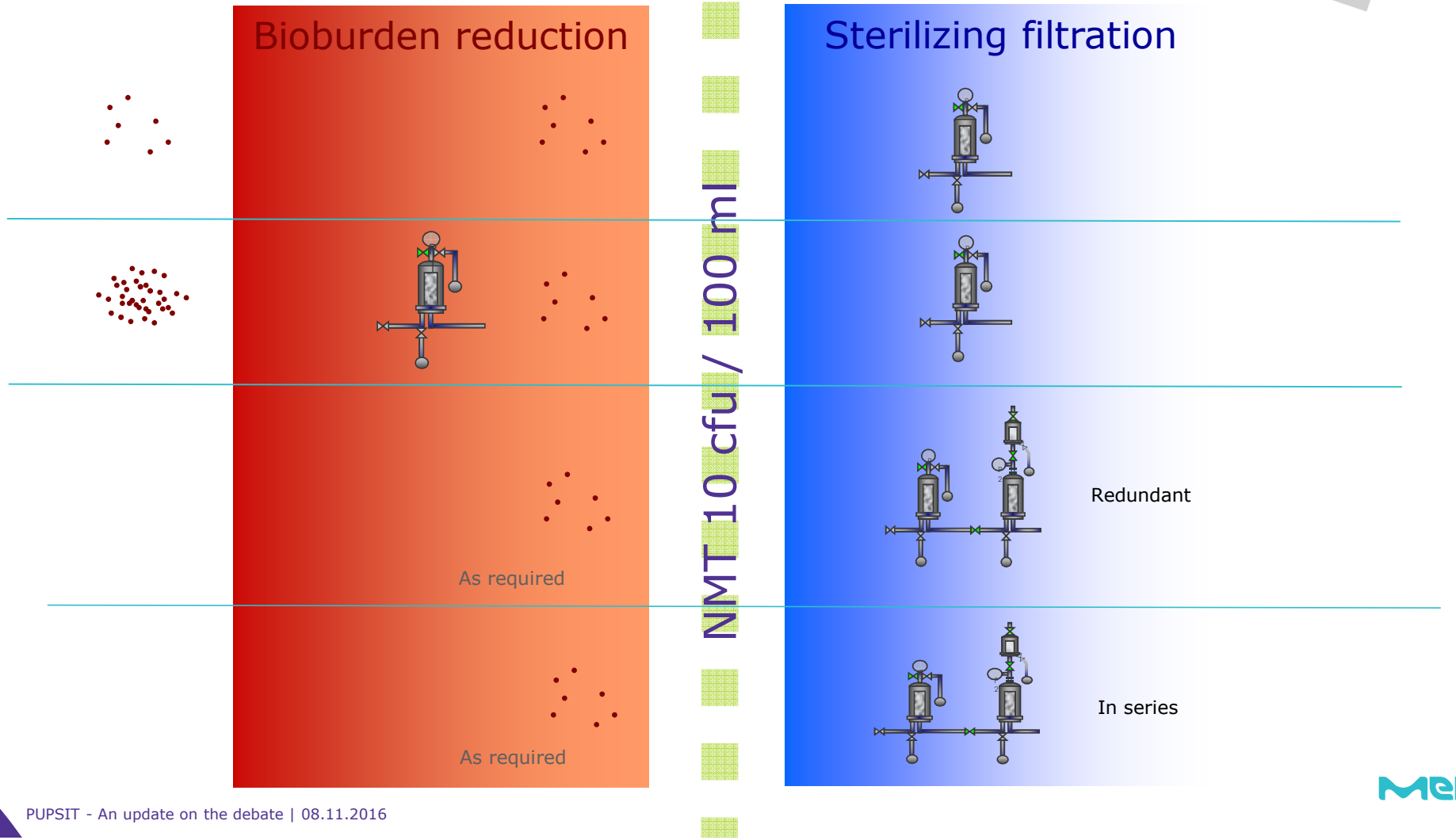
Rationale for Recommendation

Whereas a PUPSIT could provide added assurance of a filter's integrity throughout processing and reduce the risk of product loss, the risk of implementation of such a test must be assessed for each process and manufacturing site. A PUPSIT procedure may result in a higher risk to product quality. Integrity

PUPSIT decision should follow a risk based analysis
Elements for justification are getting more precise.

Sterilizing grade filter Identification

…Manufacture of finished dosage form guideline 3AQ2a



PDA TR26 pp 35-36
7.6.1. Pre-Use Integrity Test Considerations

7.6.1 Pre-Use Integrity Test Considerations

In addition to performing integrity tests post use, a pre-use integrity test may be performed, either pre- or post-sterilization, as depicted in **Figure 7.6-1**. Testing the filter as installed (online) in its process housing is preferred; however, there may be instances in which offline testing is necessary because of process considerations. Presterilization integrity tests may be performed to demonstrate that the filter has been properly installed and is integral prior to use. A risk assessment may be performed to determine its utility.

When performing an integrity test after sterilization, care should be taken not to compromise sterility. Prior to testing, the filter should be flushed with fluid to wet the membrane. The wetting fluid passing the filter should be collected under sterile conditions. Pressurization and measurement are performed on the upstream side of the filter with the filter under test as a sterile barrier.

For serial filter installations, the first filter should be wetted (wetting fluid should be collected after the first filter) and tested in a first approach. If this filter fails, the second filter has to be tested. This is more complex, as the space between the two filters may need to be maintained as sterile (the test gas has to be sterile). If a second filter is to be tested through the first filter, the first filter should allow free gas flow (the bubble point exceeded to expel liquid from largest pores) to avoid influencing the test.

Integrity tests are based on a differential pressure across the filter membrane; therefore, the downstream side should be open to the atmosphere. If this cannot be achieved, the downstream side should be large enough to avoid a pressure increase, or the pressure on the downstream side should be controlled, and the test aborted if there is a significant increase in pressure.

Test online
Pre–sterilization?

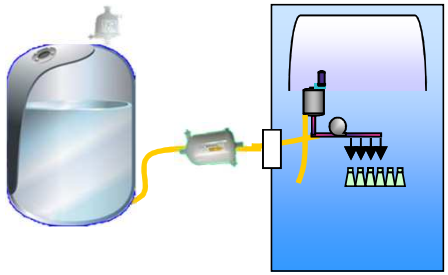
Sterile system for
wetting and
testing

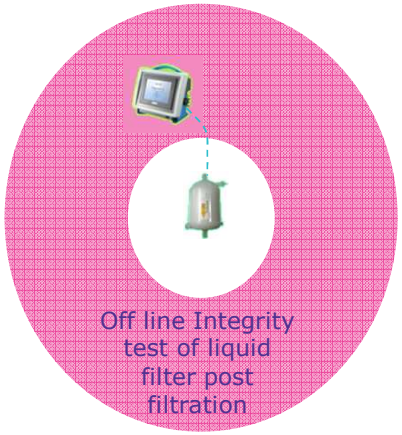
Serial filtration:
Test F1 first
Sterility between F1&F2

Sterile side opened to
atmosphere or large volume
or equipped with P sensor

Current Practice 1 - No pre-use test

In certain filling operation where test is not yet implemented or impossible to implement due to process limitation (product (e.g. foam)/low volume/water presence/ line design & Isolator)



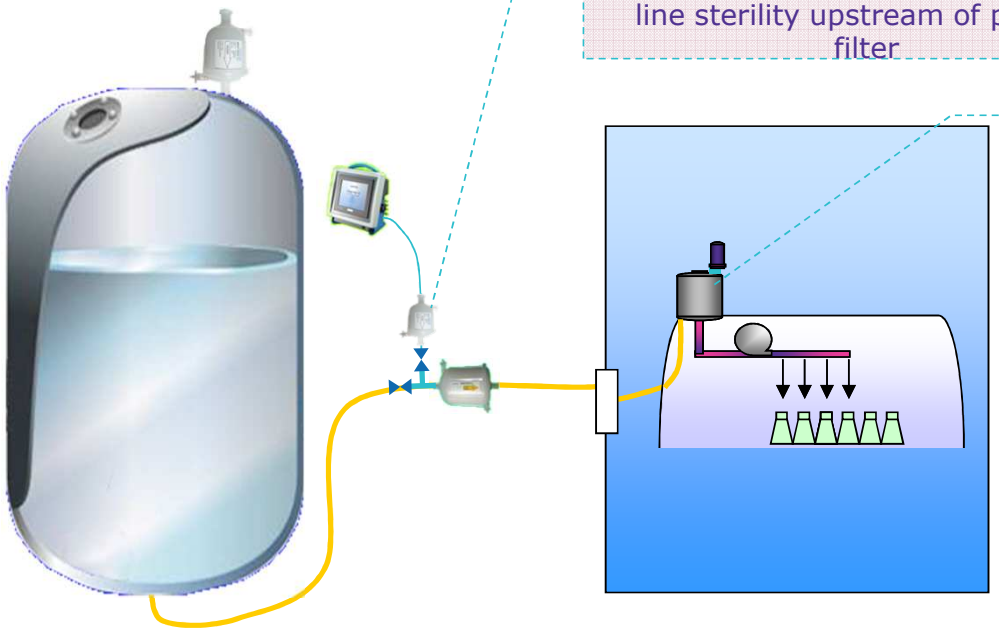


Sterilization → Formulation → Filtration & Filling → Integrity test

Justification for such SOP is required!

Including e.g. non plugging fluid assurance (pre-filtered), Tank to tank transfer, possibility for rework , Identification of responsibilities, detailed SOPs for failure mode, risk evaluation and acceptance for filtration failure

Current Practice 2 - Pre-use test: to downstream equipment



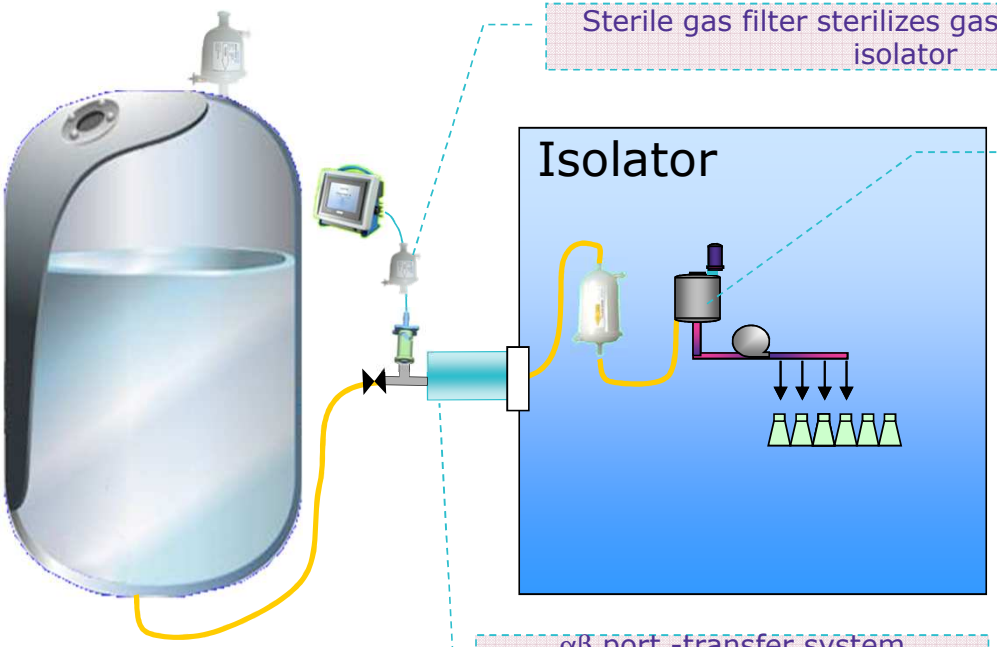
Optional: sterile gas filter maintains line sterility upstream of product filter

buffer tank
is used to collect wetting liquid and test gas

Points to consider

- Limited buffer tank volume
- Limitations to re-wetting and re-test
- Failed integrity test triggers complete new line preparation

Current Practice 3 - Pre-use test: Isolator case



Sterile gas filter sterilizes gas flowing into the isolator

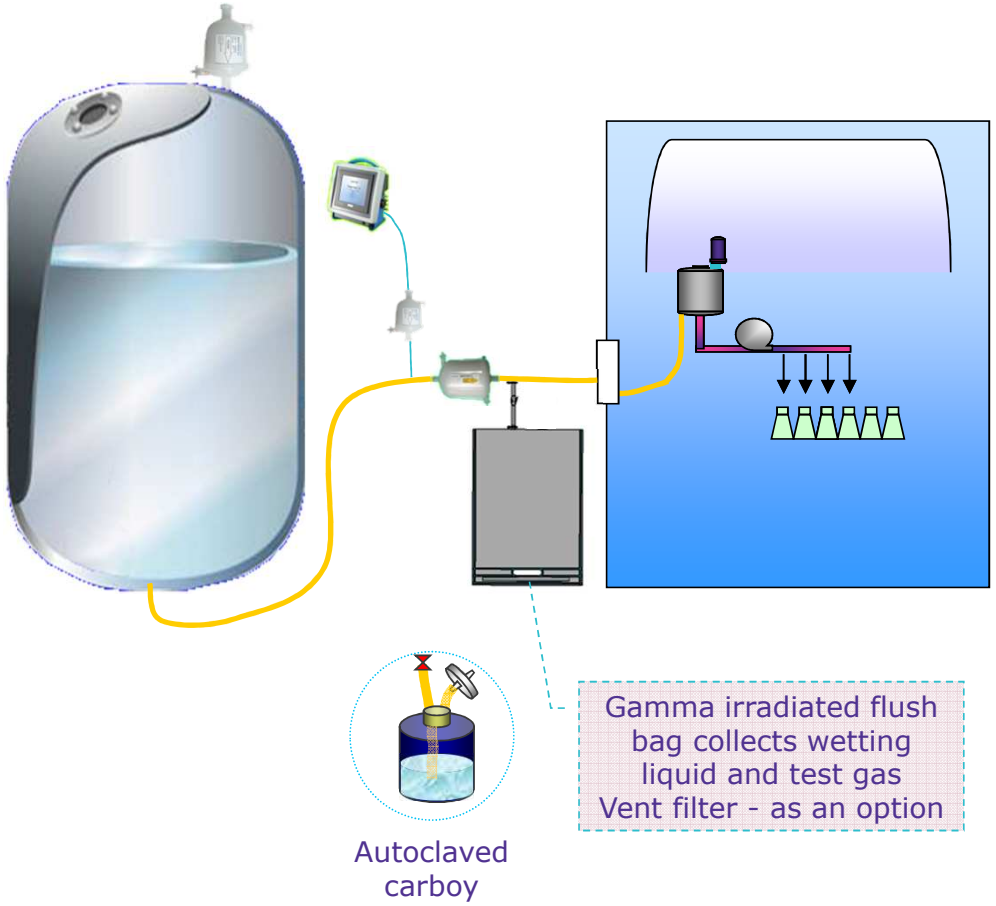
buffer tank
is used to collect wetting liquid and test gas

αβ port -transfer system
La Calhène canister / single use β bag

Points to consider

- Limited buffer tank volume
- Limitations to re-wetting and re-test
- Failed integrity test triggers complete new line preparation
- Millibarrier or flush bag implementation

Current Practice 4 - Pre-use test: to flush bag/derivation tank

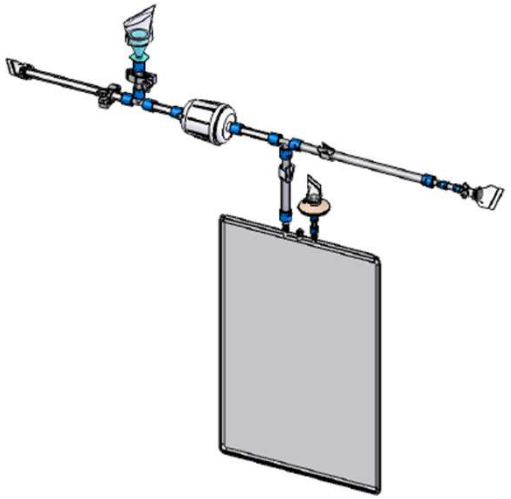


Points to consider

- Limitations to re-wetting and re-test
- Failed integrity test triggers complete new line preparation
- Carboy handling and preparation is cumbersome
- Drying is impossible
- Risk of over pressure is mitigated with diffusion test

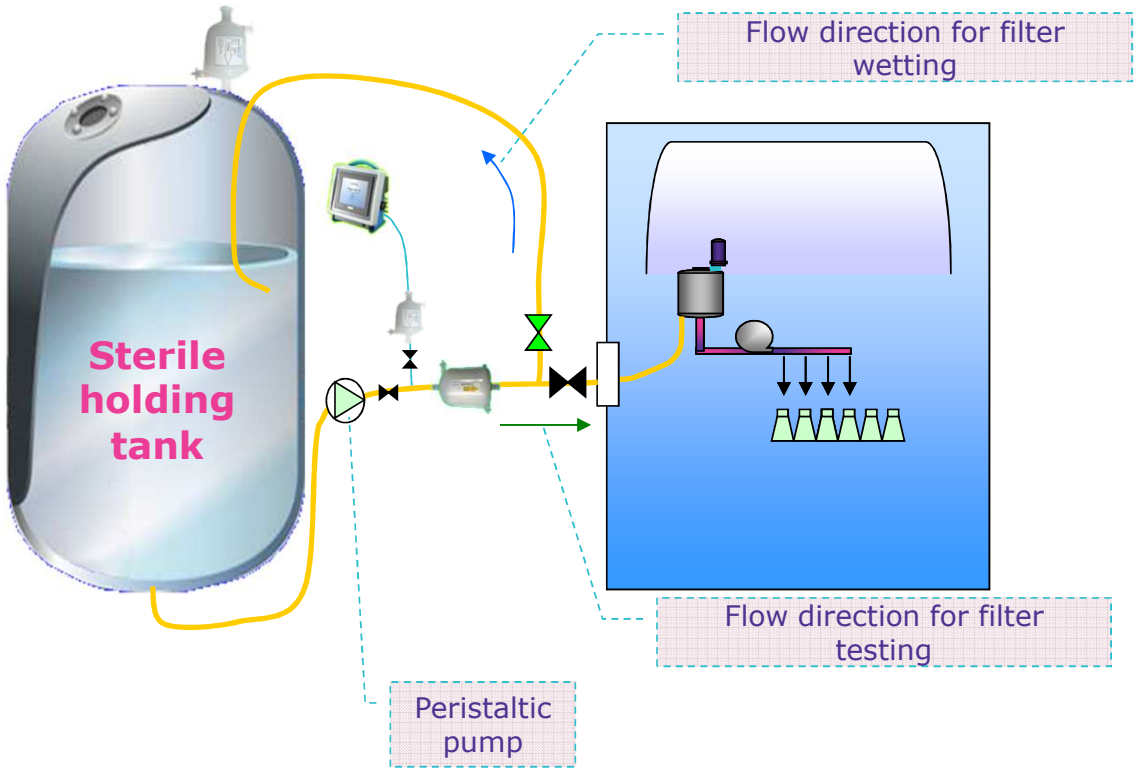
Current Practice 4 - Pre-use test: to flush bag

γ Sterile flush bag and connector



γ Sterile filtration set with flush bag and test port

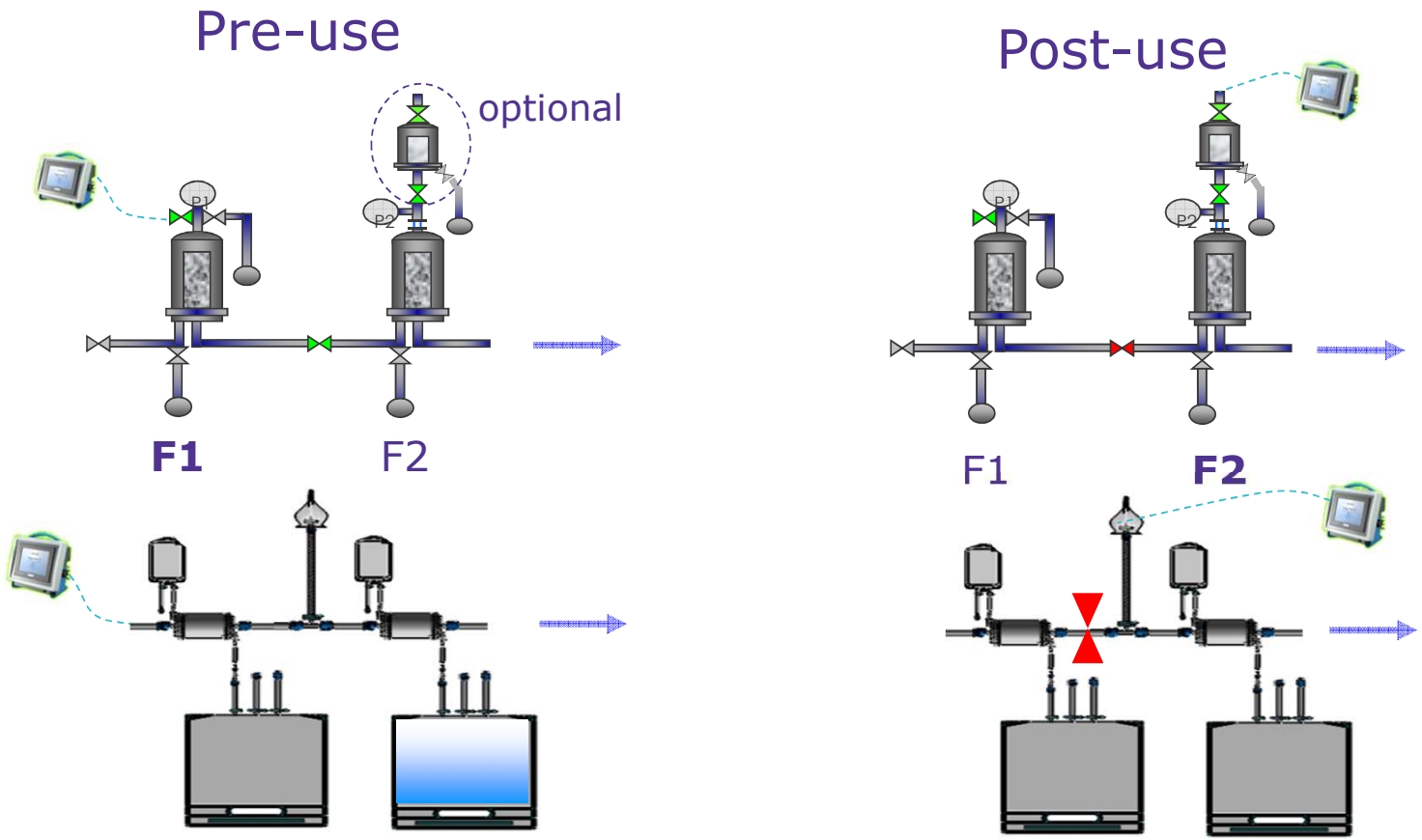
Current Practice 5 - Pre-use test: recirculation to feed tank



Points to consider

- Unlimited volume
- Excellent preconditioning
- Extractables diluted into the whole batch volume
- Return loop could be seen as a bypass….
- Valve sequencing & liquid flow direction must be **unambiguous**
- Filtered product is “recycled”
- Feed tank is a sterile holding tank

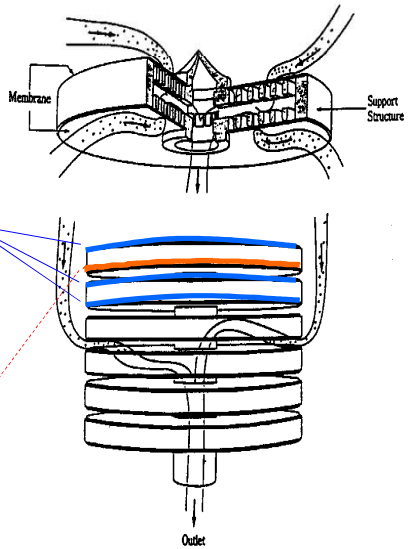
Current Practice 6 - Redundant filtration – Enable a valid test



How to precondition your filter?
Millibarrier technology

What is MilliBarrier?

One disk pair



Liquid

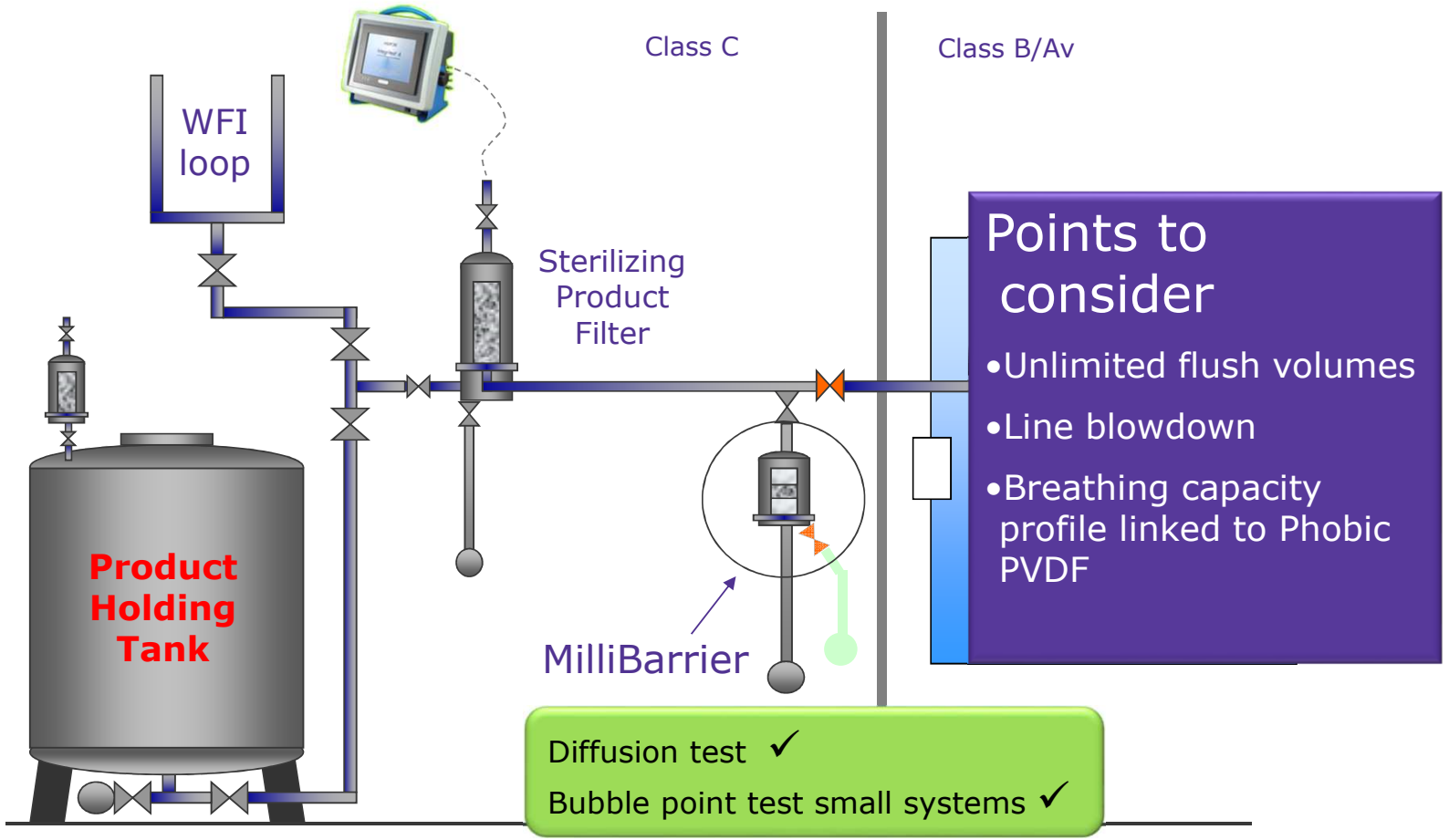
Condensate

3 x Hydrophilic membranes

Gas

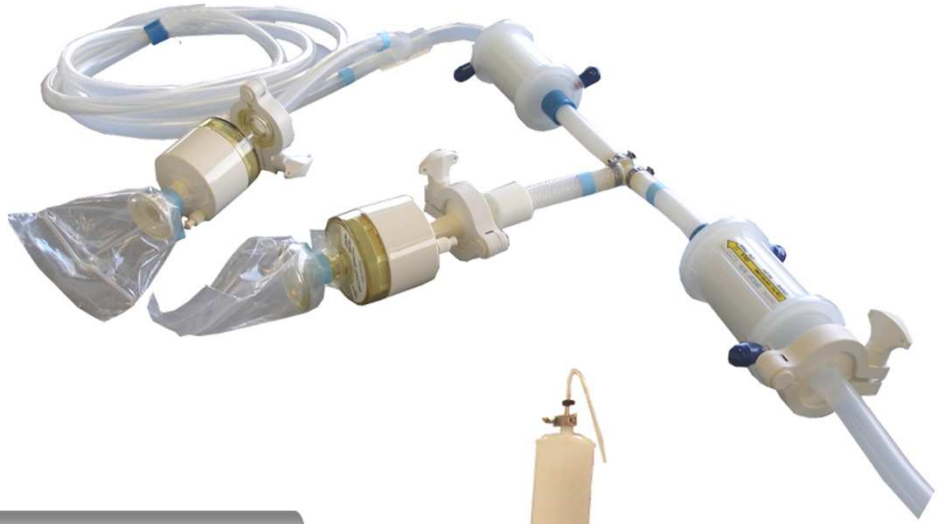
1 x Hydrophobic membrane

Current Practice 7 – Pre-use test : to drain through MilliBarrier

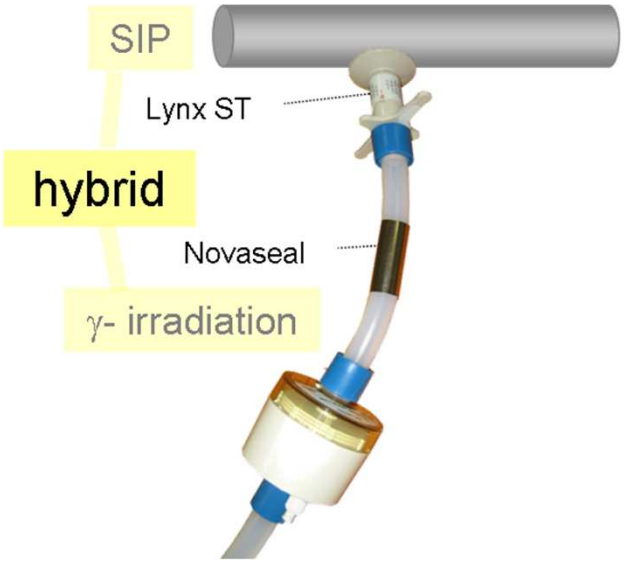


Examples

γ- Irradiation

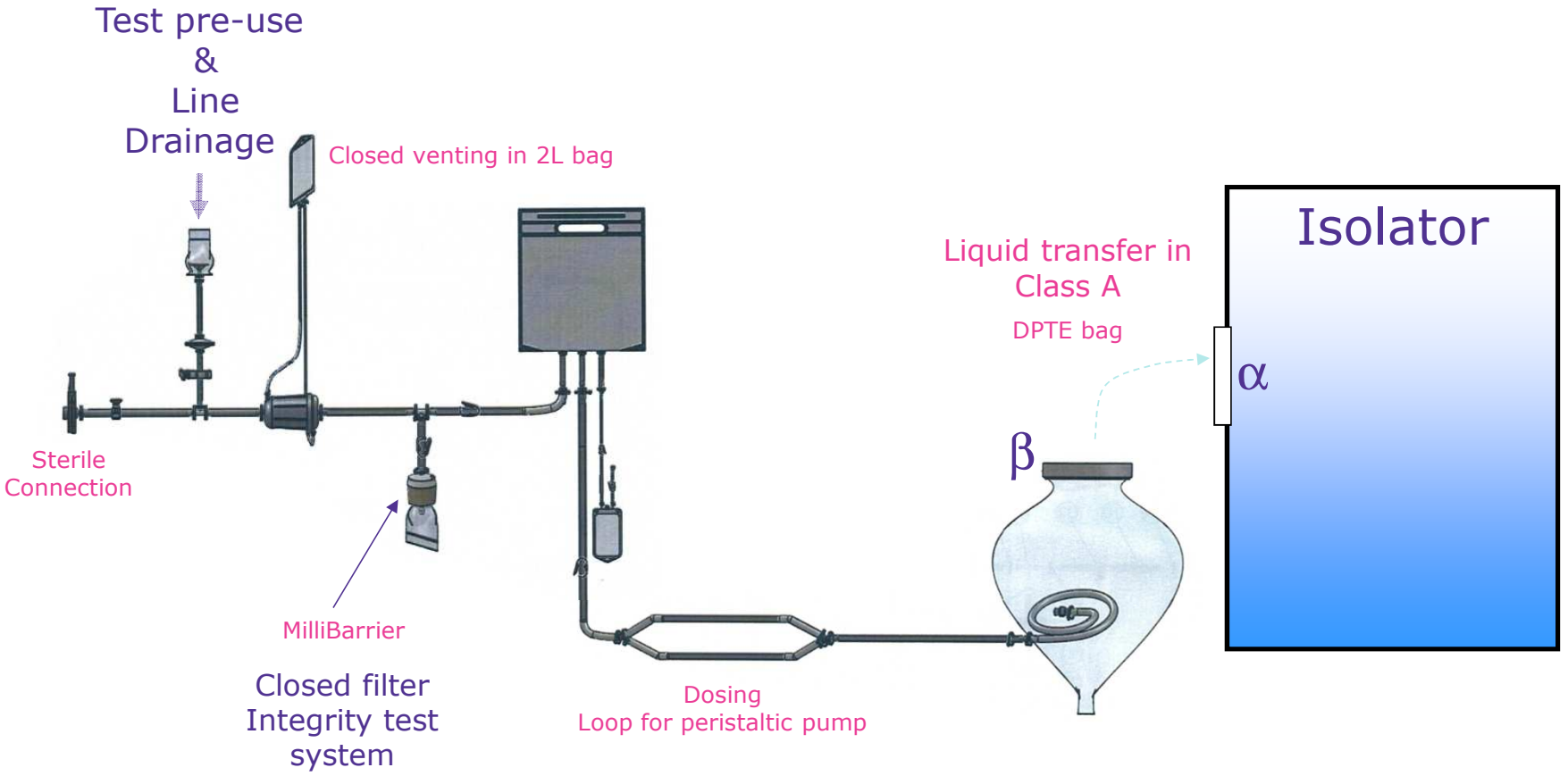


SIP

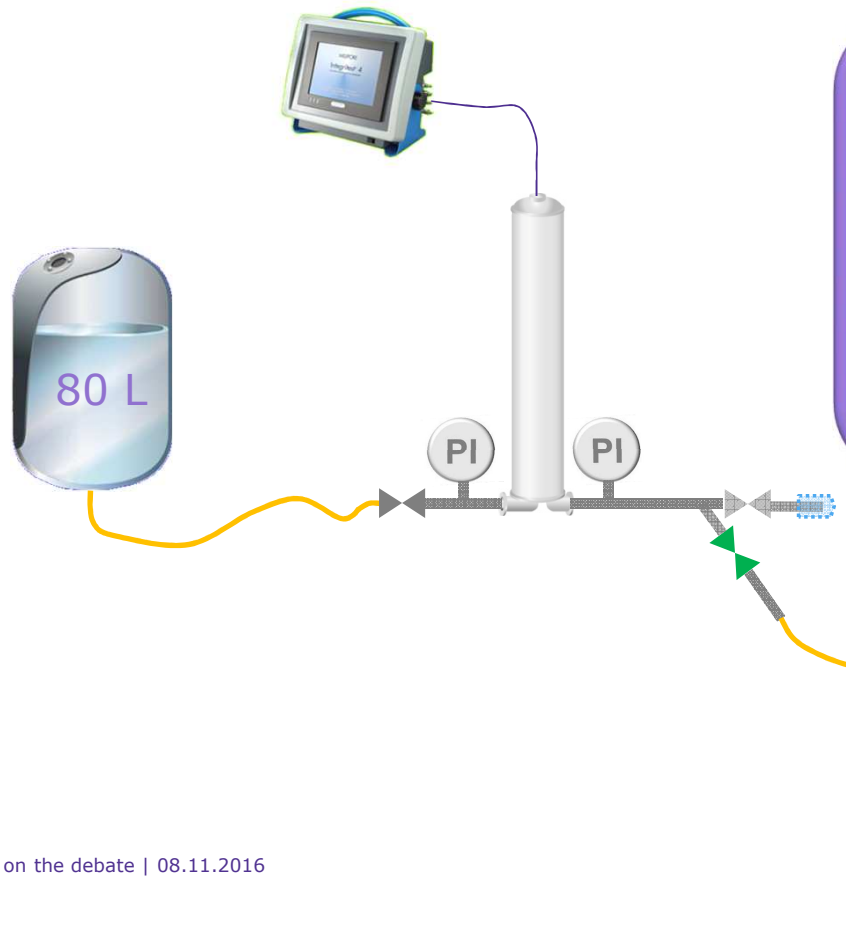


Autoclaved

Single use assemblies in final filling



Current Practice 8 – Pre-use test : to drain through Philic - Phobic filtration system



- Unlimited flush volumes
- Line blowdown

- Diffusion test ✓
- Bubble point test - Large systems ✓
- Passive draining ✓
- Two ancillary filters to test

Hydrophobic

Hydrophilic

FILTER AT POINT OF FILL PERSPECTIVES

MERCK

Drug manufacturer perspectives with implementation of filter at Point Of Fill

Line flush

Filter preconditioning

Pre-use integrity test?

Line stoppage concerns

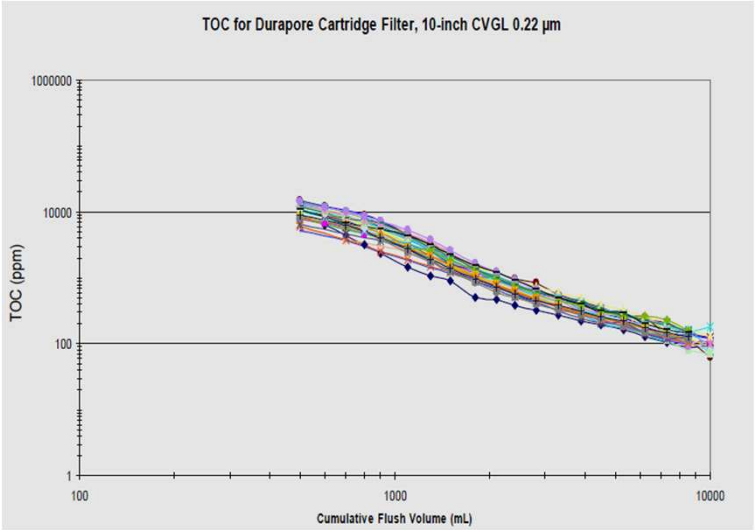
- Impact on adsorption
- Impact on filter capacity

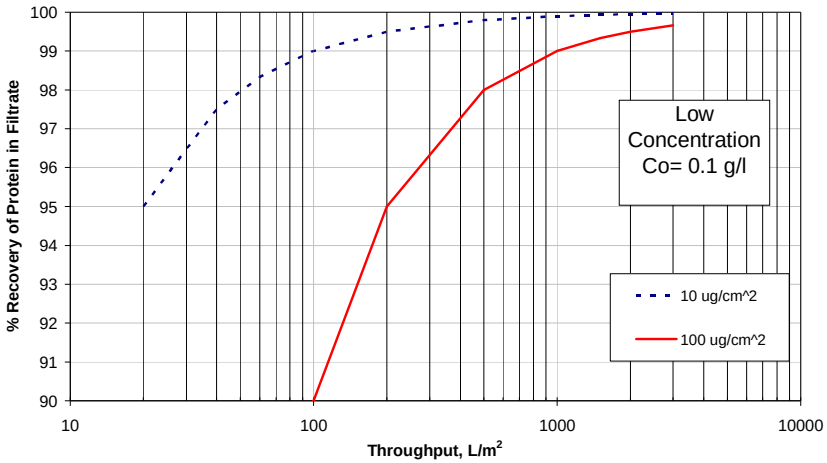
Filling Machine 5 µm filter

Flushing volume

Flushing volume established during qualification for:

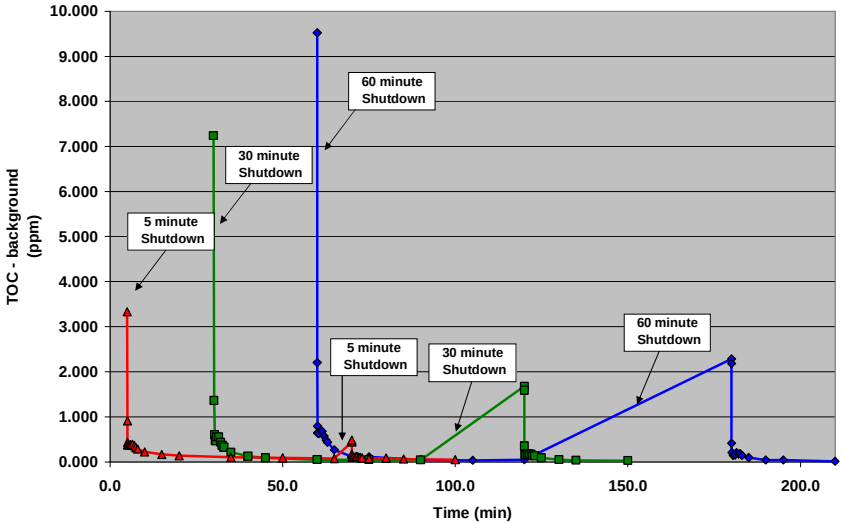
- Particles flushing
- TOC / Conductivity / Oxidizable subtances
  - Extractables flushing
- pH stabilization
- Pharmacopeia strains viability
- Air removal
- Membrane preconditioning to minimize aggregation
- Flush volume to recover 99 % [excipients]
- Robust integrity test



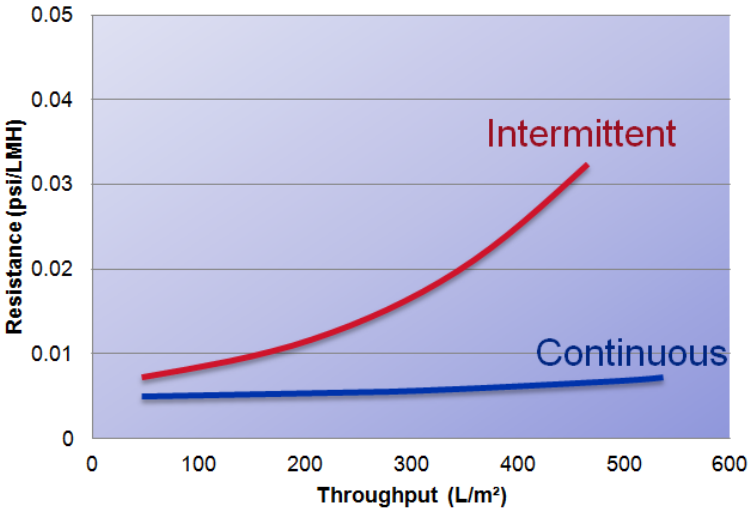


Line stoppage concerns

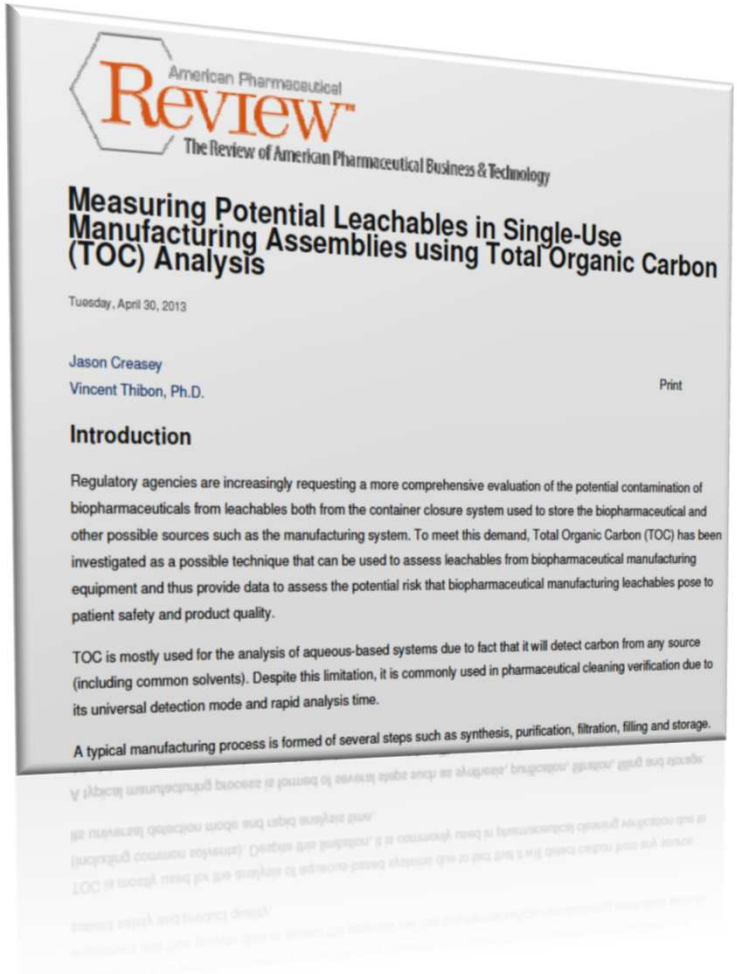
Impact on adsorption/extractables?



Impact on filter capacity?



Example



American Pharmaceutical Review
The Review of American Pharmaceutical Business & Technology

Measuring Potential Leachables in Single-Use Manufacturing Assemblies using Total Organic Carbon (TOC) Analysis

Tuesday, April 30, 2013

Jason Creasey
Vincent Thibon, Ph.D.

Print

Introduction

Regulatory agencies are increasingly requesting a more comprehensive evaluation of the potential contamination of biopharmaceuticals from leachables both from the container closure system used to store the biopharmaceutical and other possible sources such as the manufacturing system. To meet this demand, Total Organic Carbon (TOC) has been investigated as a possible technique that can be used to assess leachables from biopharmaceutical manufacturing equipment and thus provide data to assess the potential risk that biopharmaceutical manufacturing leachables pose to patient safety and product quality.

TOC is mostly used for the analysis of aqueous-based systems due to fact that it will detect carbon from any source (including common solvents). Despite this limitation, it is commonly used in pharmaceutical cleaning verification due to its universal detection mode and rapid analysis time.

A typical manufacturing process is formed of several steps such as synthesis, purification, filtration, filling and storage.

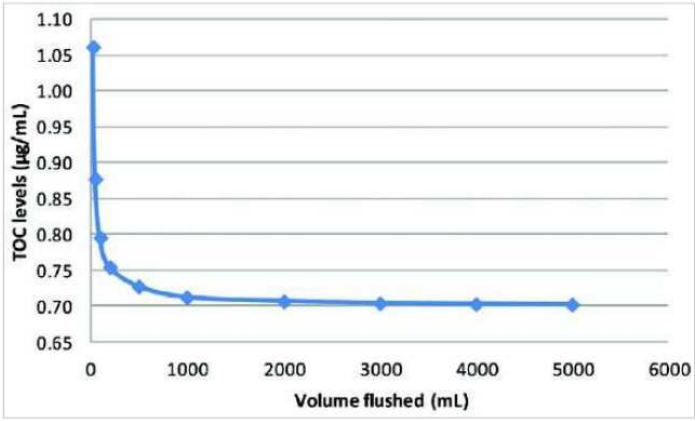
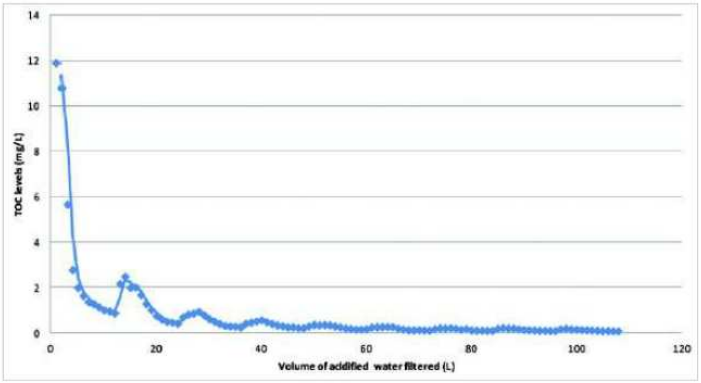


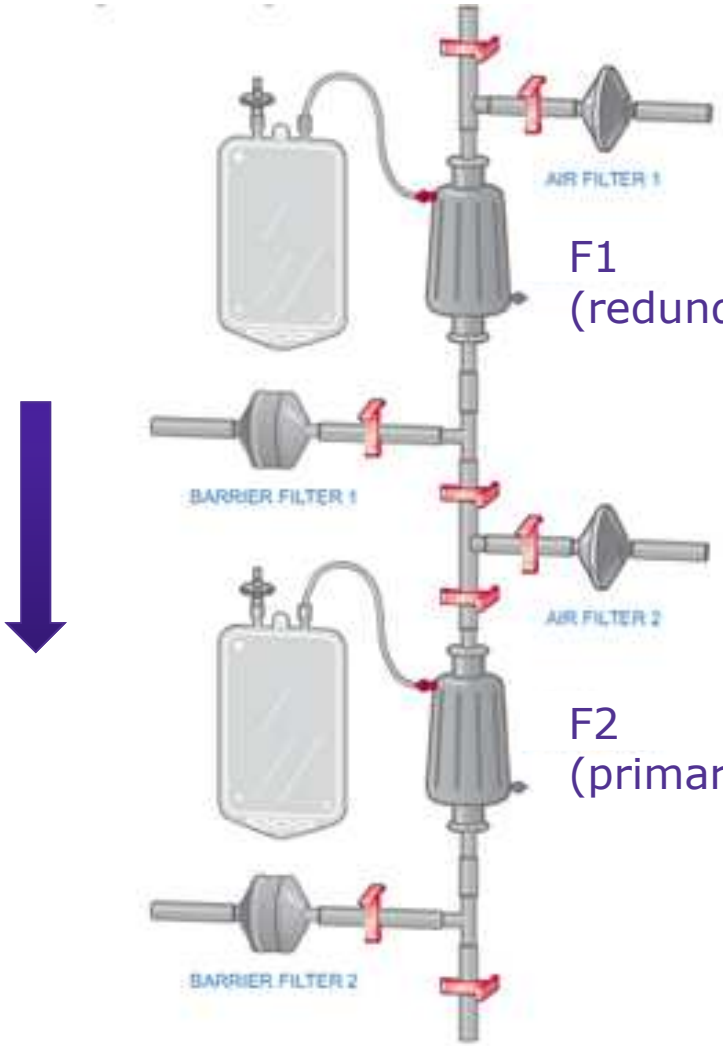
Figure 6. Simulated leaching profi le for the custom-made single-use assembly



Particulate risk mitigation at POF

Particle removal (5.0 µm units)

Final sterilization (0.22 µm units)



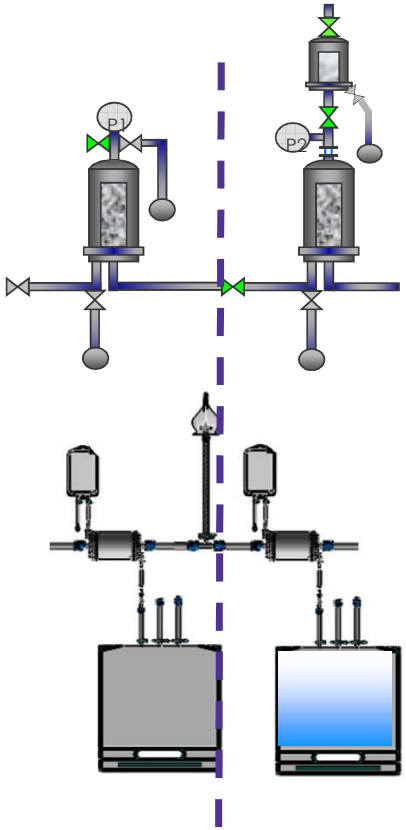
F1
(redundant filter)

F2
(primary filter)

Qualification

Risk Assessment

- Filter Identification
- Filter mix-up
- Wetting volume
- Bioburden
- Product dilution
- Closed valve
- Filter resistance
- Tubing resistance
- Impact on bacteria retention
- Diffusion / bubble point
- Gas volume generated
- Foam & API degradation
- Filter drying



Bioburden reduction - Sterilizing filter?

Redundant filtration?

FMEA

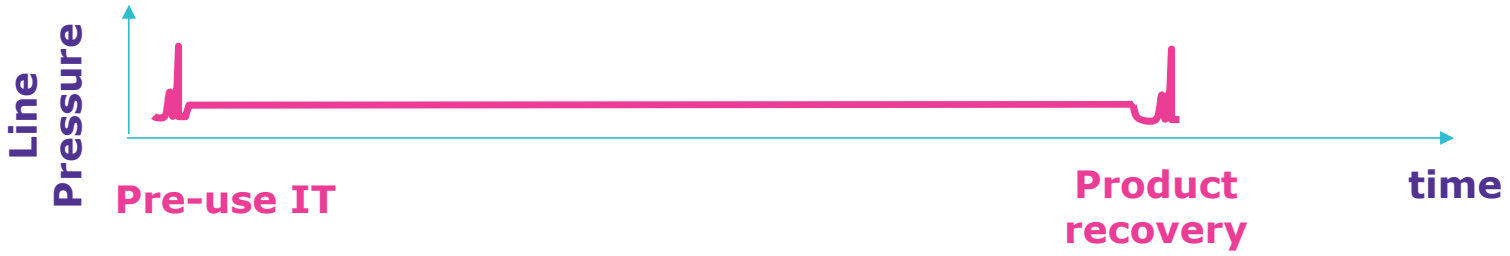
- Filter failure /absence of F1, F2, Vent
- Filter blockage
- Filter Identification and tester printout
- Improper wetting
- Pressure build-up
- Diffusion vs. bubble point
- Closed valve
- Failure detection with additional pressure sensors

Test

- Accuracy
- Sensitivity
- Product specific diffusion / bubble point
- Failure mode

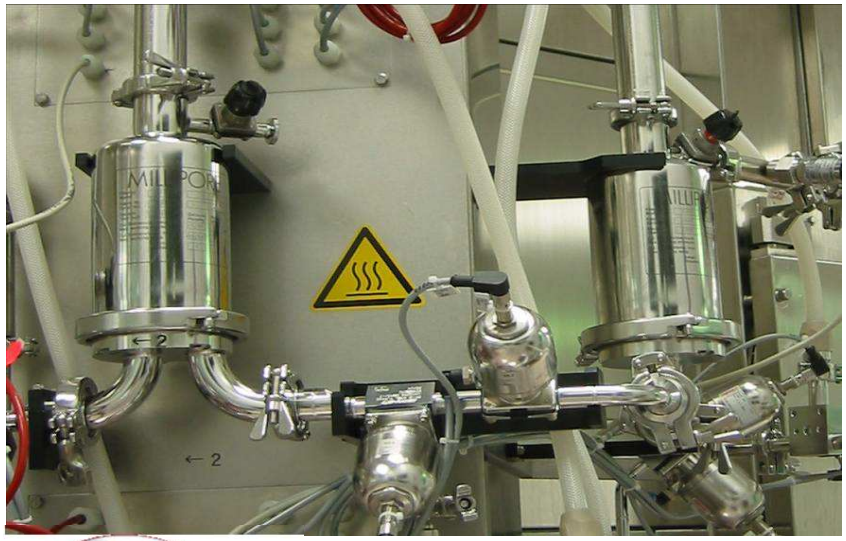
Qualification

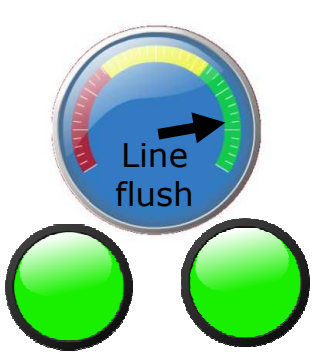
- Does my bacteria retention test includes integrity test?



- Pre-use test included in media fill
- as applicable

Sterile filtration dashboard





Sterilization

Filter Integrity

Pre-use

Filter Integrity

Post-use

Conclusion

Integrity test fundamentals and practical aspects - PDA TR26

Pre-use integrity test was recently under inspector scrutiny.

Implementation is easy

Qualification is critical with complex system

Thank you. Any questions?