Sterile Filtration

PDA EU00192
Manage Your Aseptic Filling Line
4/5 September 2024

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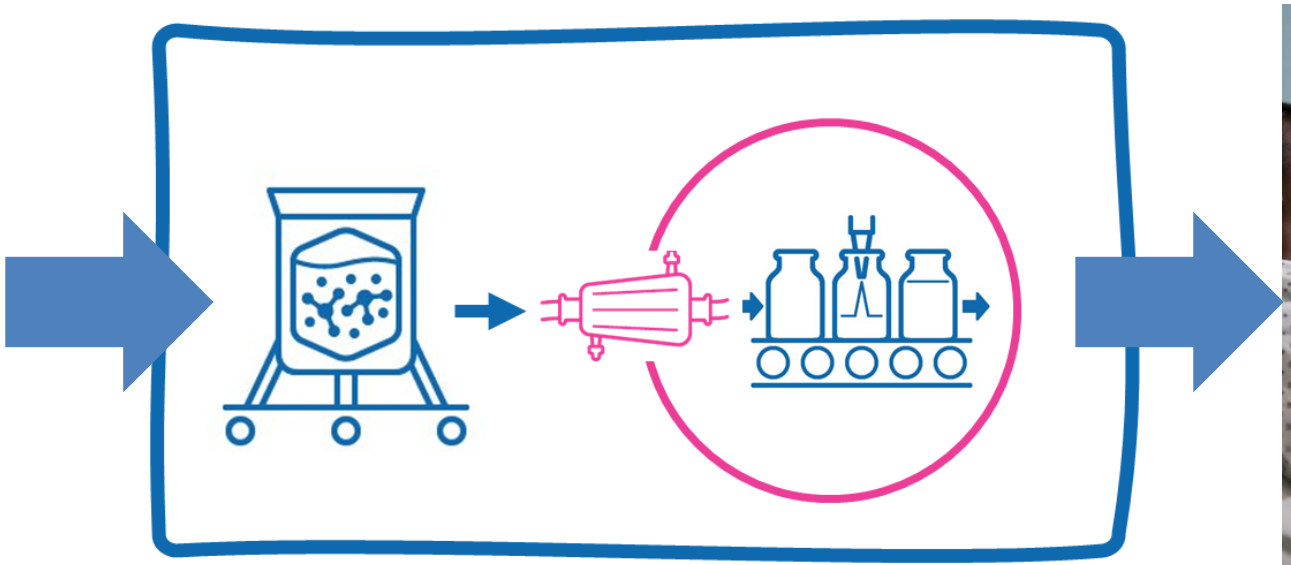
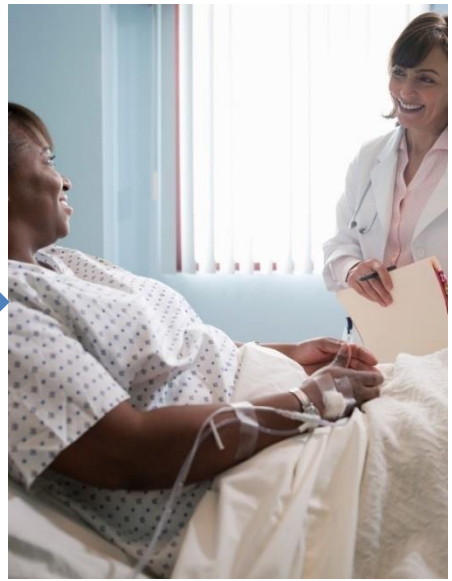
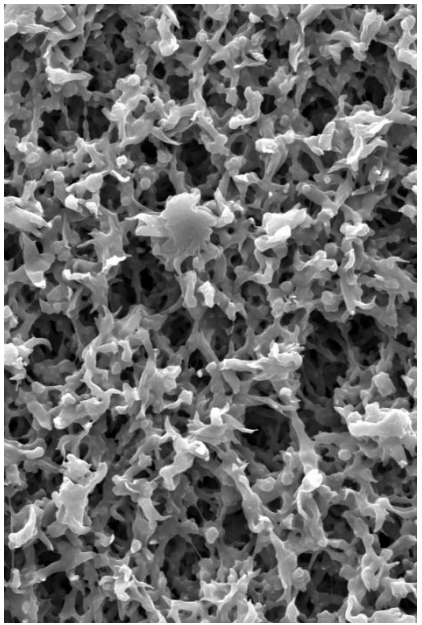
PDA Parenteral Drug Association
PDA TRAINING

The Filter Makes the Drug Sterile





Sterile Filter Definition - more than just “0.22 µm”



EU GMP, Annex 1, 2022
“Sterilizing grade filter – A filter that, when **appropriately validated, will remove a defined microbial challenge** from a fluid or gas producing a sterile effluent. Usually, such filters have a pore size equal or less than 0.22 µm.”

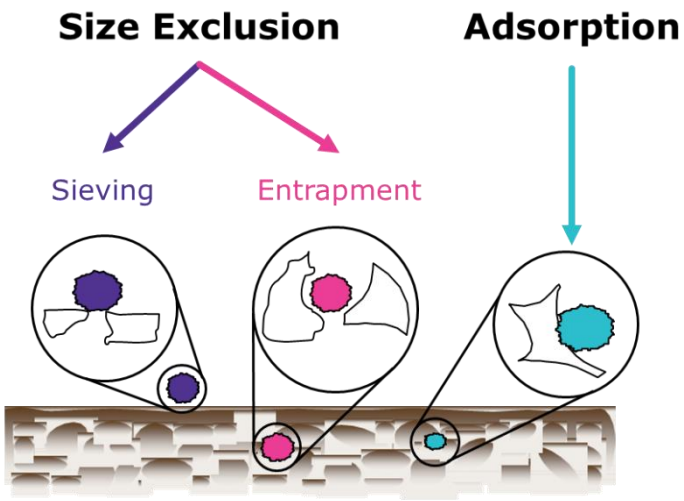
FDA cGMP, Guidance for Industry, 2004
“A sterilizing grade filter should be **validated to reproducibly remove viable microorganisms** from the process stream, producing a sterile effluent. Currently, such filters usually have a rated pore size of 0.2 µm or smaller.”

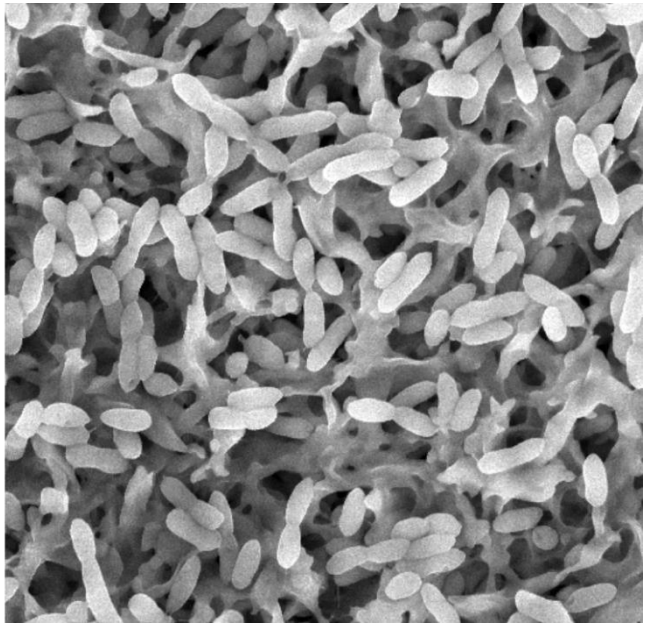
EMA, Guideline on sterilisation of the medicinal product, 2015
Filter retention capacity to be validated by challenging the filter membrane with justified indicator organism (*Brevundimonas diminuta*) at a minimum concentration of **10^7 CFU per cm^2** of filter surface area.

Filter Membrane

The Key Component !

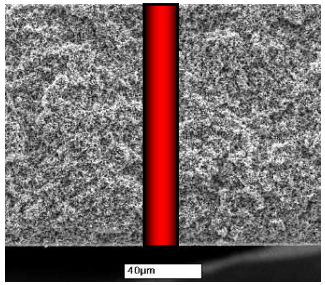
Retention Mechanismus





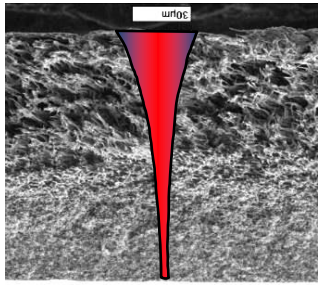
Membrane Characteristics

- **Material**
  - PES (Polyether sulfone)
    - high flux and capacity
  - PVDF (Polyvinylidene fluoride)
    - Low protein binding (adsorption)
- **Pore size**
  - 0.2/0.22 µm
  - Other sizes: 0.45 µm, 0.1 µm
- **Pore structure**
  - Symmetric
  - Asymmetric
  - Composite



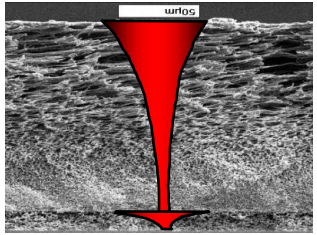
Symmetric

Mean pore size constant through entire thickness



Asymmetric

Mean pore size changes through entire thickness



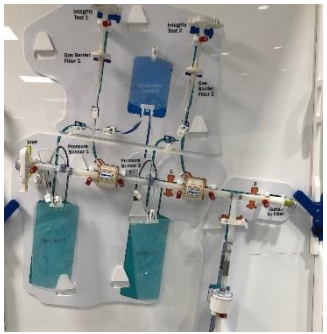
Composite

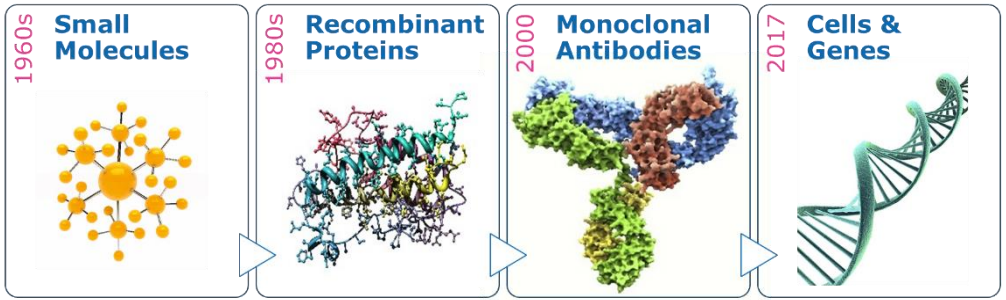
Two distinct layers with different mean pore sizes in a single membrane layer

Filtration and EU GMP Annex 1

Regulatory Background

No one filtration set-up fits all





- Process fluid
- Membrane type and pore size
- How many filters
- Interactions (adsorption, leachables)
- Validation
- Process parameter
- Filter integrity testing (FIT)
- Environment
- …

Sterile Filtration: Annex 1 Must Haves

Sterility Assurance

- Sterile filter
- Filter compatibility
- Bacterial retention
- Integrity

Process Control

- Allow operation within validated process parameters
- pressure, wetting, flushing, hold-time, flow rate, maximum volume

Quality and Efficacy

- No adsorption (API, excipients)
- No leachables
- No particles

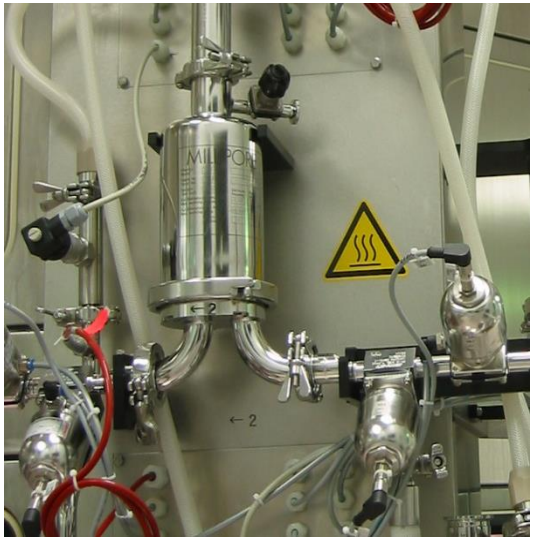
Data to be provided for market authorization

Parameter	Filter	
	Non-sterilising	Sterilising
General information on filter		
Type of material, nominal pore size	X	X
Number of filters	X	X
Filter area	-	X
Filter integrity test	-	X
Filter validation		
Potential sorption of solution components to filter	X	X
Solution Compatibility	X	X
Filter retention capacity	-	X
Filter integrity test limits	-	X
Extractable and leachable substances from the filter	X	X

EMA/CHMP/CVMP/QWP/850374/2015 (2019), Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

Bacterial Retention Test Strategy

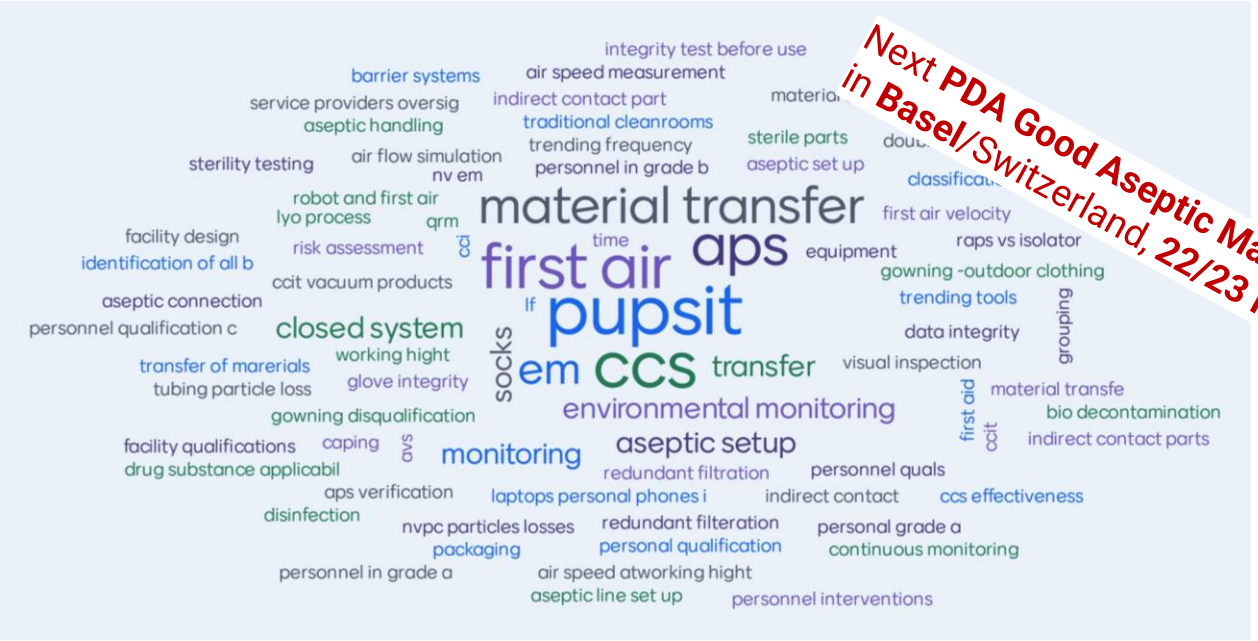
Simulate the actual process on a laboratory scale while **maintaining** / keeping constant parameters:



- Product-filter-bacteria contact time
- Differential pressure and/or flow-rate
- Filtered volume/cm^2
- Temperature
- Active filtration time for pump driven processes

What are the top 3 EU GMP Annex 1 topics still subject to interpretation and where further clarification with authority would be helpful?

PDA Good Aseptic Manufacturing conference in Stuttgart/Germany, 15/16 May 2024. Interactive questionnaire session day 1.



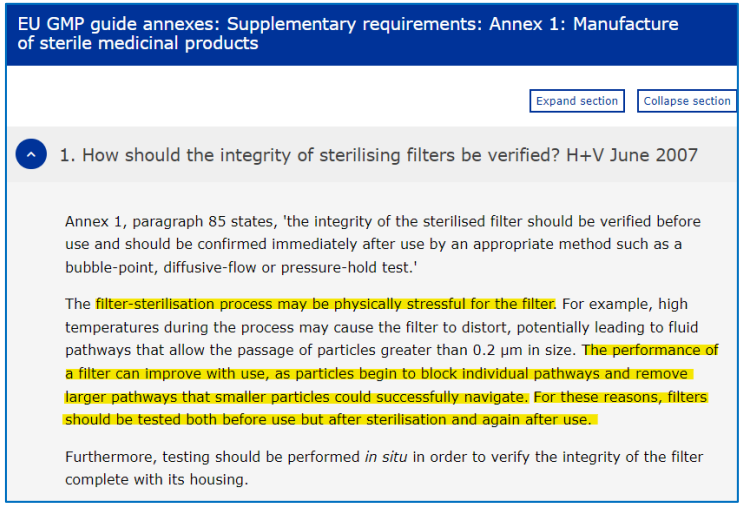
Next **PDA Good Aseptic Manufacturing conference** in **Basel**/Switzerland, **22/23 May 2025**.

PUPSIT – not a new requirement

Annex 1 (previous), *The **integrity of the sterilised filter should be verified before use** and should be confirmed immediately after use by an appropriate method ...*

Annex 1 (2022), *The **integrity of the sterilised filter assembly should be verified by integrity testing before use** (**pre-use post sterilisation integrity test or PUPSIT**), to check for damage and loss of integrity caused by the filter preparation prior to use.*

FDA cGMP, *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.*



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

Expand section | Collapse section

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 0.2 µm 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.

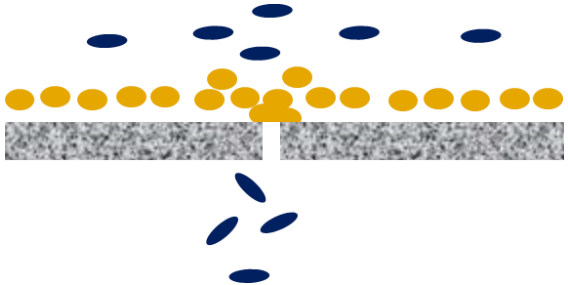
Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

This Q&A was deleted from the EMA Q&A webpage: Guidance on good manufacturing practice and good distribution practice: Questions and answers

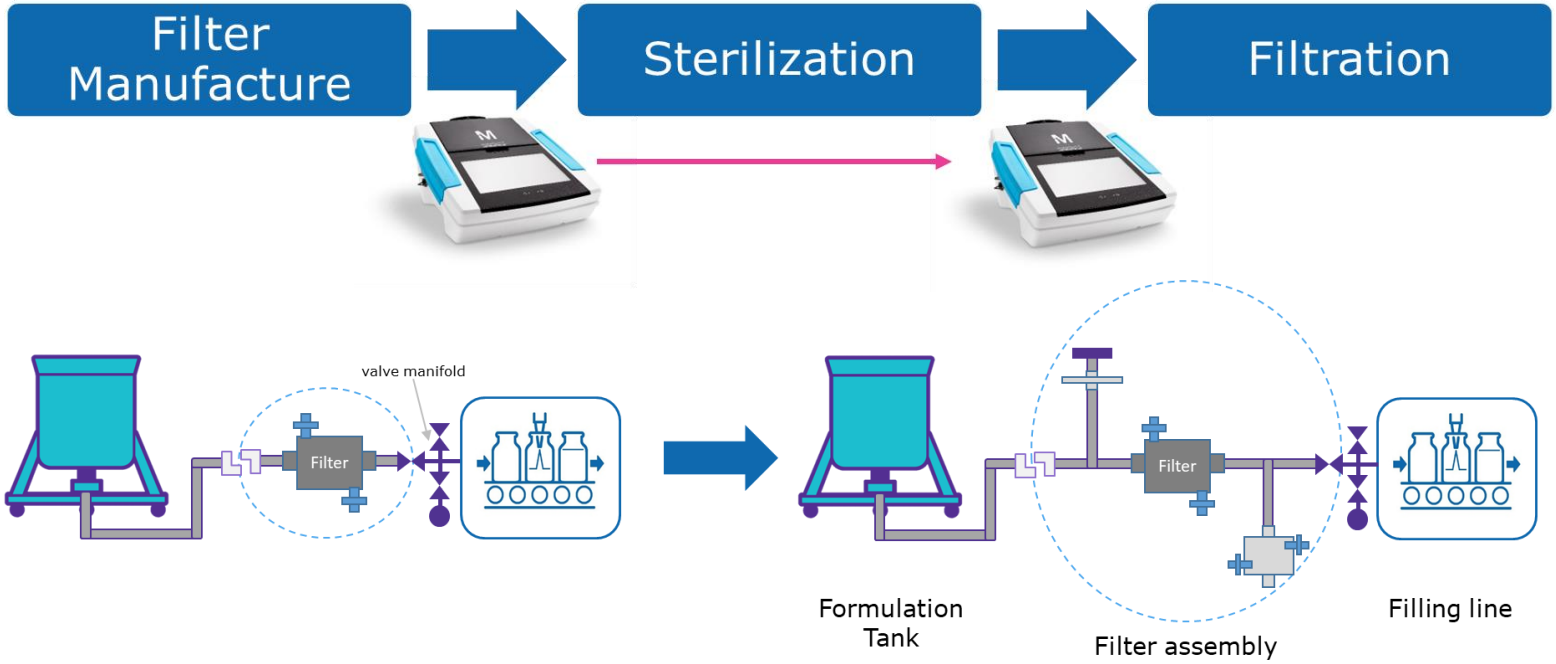
Filter Flaw Masking

Performance of a filter can "improve" with use

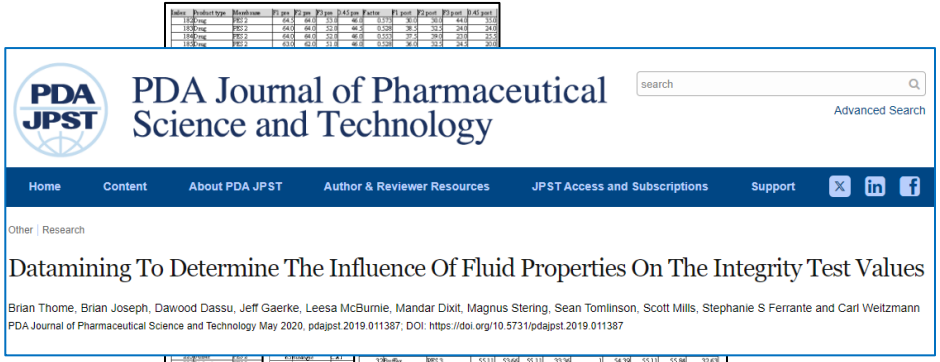
- Flaw **large** enough to **pass microbiological contamination**
- Flaw **small** enough to **be masked by clogging**
- Material/particle burden must be present that can plug the defect to such an extent that it is **not detectable by post-use integrity test**



PUPSIT Implementation



Filter Flaw Masking Test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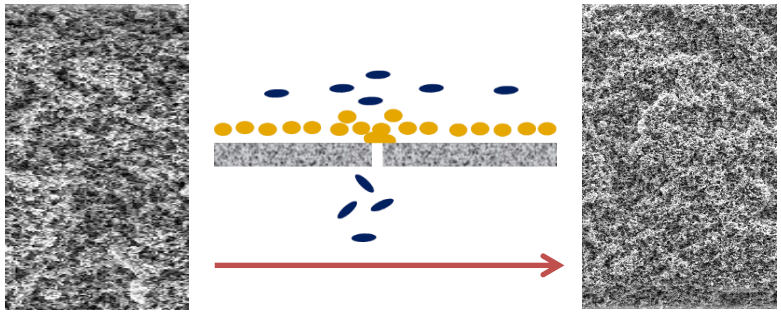
Datamining To Determine The Influence Of Fluid Properties On The Integrity Test Values

Brian Thome, Brian Joseph, Dawood Dassu, Jeff Gaerke, Leesa McBurnie, Mandar Dixit, Magnus Stering, Sean Tomlinson, Scott Mills, Stephanie S Ferrante and Carl Weitzmann

PDA Journal of Pharmaceutical Science and Technology May 2020, pdajpst.2019.011387; DOI: https://doi.org/10.5731/pdajpst.2019.011387

Identify if a 0.45 µm filter appears to meet the specification of a 0.2 µm filter

- **518 process fluid/filter combination**
- **5 combinations where the bubble point shifted**



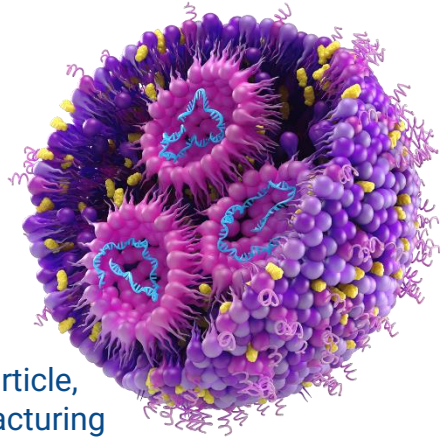
0.45 µm filter appears as a 0.2 µm filter

Exception Process Constraints - “e.g., Small Volumes”

In depth knowledge and control:

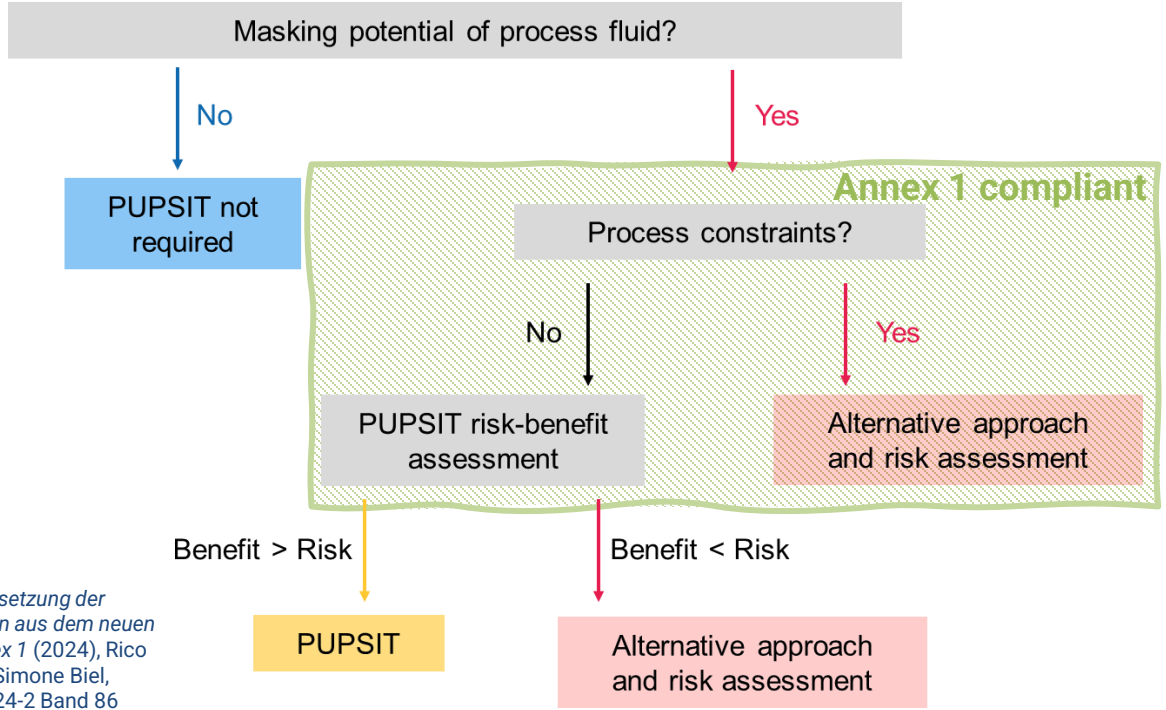
- **filter sterilisation process**
  - **Minimize the potential for damage** to the filter.
- **supply chain**
  - Contract **sterilisation** facilities.
  - **Packaging** and **transport** of the sterilised filter.
- **process knowledge**:
  - Any risk of impact on filter integrity values?
  - **Potential masking effects**?
  - Pre-filtration to clarify the product prior to sterile filtration.

Recombinant protein, large scale manufacturing



mRNA lipid nanoparticle, small scale manufacturing

PUPSIT Exception only in Case of Process Constraints



- Beside “small volumes” no further examples of process constraints
- Regulators emphasize to “ensure drug availability”
- Alternative approach is not to overcome the challenge of PUPSIT implementation

PUPSIT – Umsetzung der Anforderungen aus dem neuen EU-GMP-Annex 1 (2024), Rico Schulze und Simone Biel, Pharmind 2024-2 Band 86

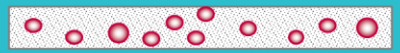
Filter Integrity Test

Test Methods

Filter Test Methods

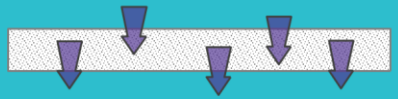
DESTRUCTIVE TEST
–
BACTERIAL CHALLENGE

- Principle : Real filtration test with micro-organism.

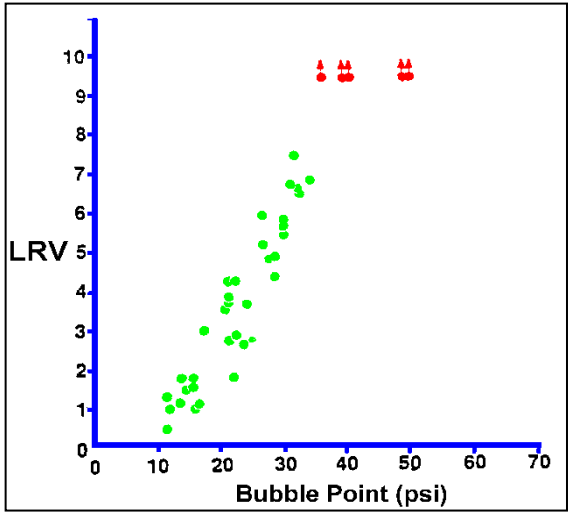


NON-DESTRUCTIVE TEST
–
PHYSICAL TEST

- Principle : indirect test based on pressure hold / gas diffusion correlated to microbial retention



Correlation of physical test methods to bacterial challenge test

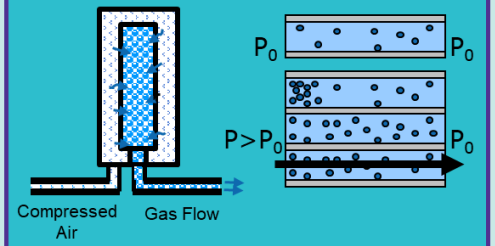


Different Types of Filter Integrity Tests

liquid (=product) filters

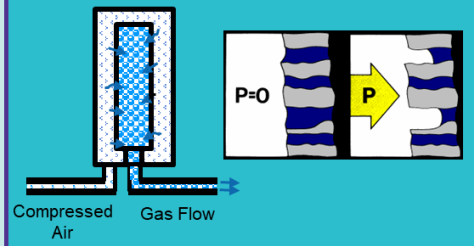
DIFFUSION (forward flow)

- Principle: Diffusion of gas molecules through the wetted membrane at a fixed pressure. The quantity of gas passing the membrane is measured.



BUBBLE POINT

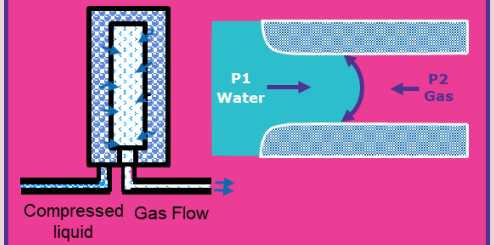
- Principle: Minimum pressure to obtain a continuous flow of gas through the wetted membrane (= when the liquid got pushed through the largest pore)



Vent (=gas) filters

HYDROCORR (water intrusion)

- Principle: Water Intrusion Pressure is the minimum pressure necessary to force water into the largest pores of a hydrophobic membrane



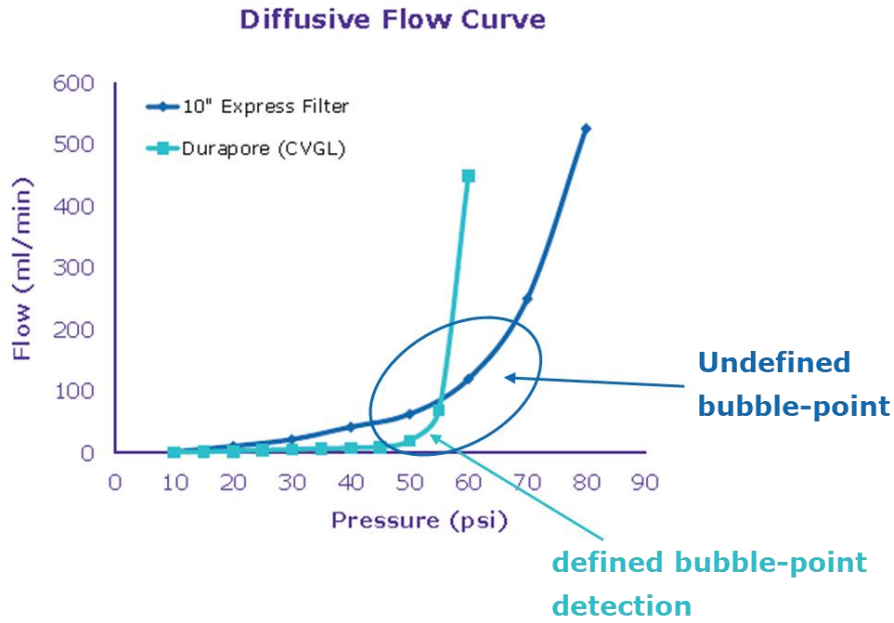
Test depends on the membrane type

Symmetric membranes, e.g. Durapore

- Pores like “cylinders”
- Wetted thickness is uniform until applied gas pressure clos to bubble point

Asymmetric membranes, e.g. Express

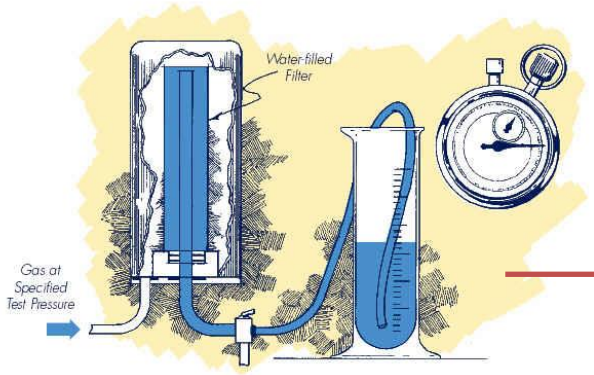
- Pores like “funnels”
- Wetted thickness varies non-uniformly at pressures above diffusion test pressure



FIT Methods Consideration for Single-Use Assemblies

	Diffusion	Bubble Point
PRO	• **Lower test pressure** → reduced stress on SUS • **Less gas volume** generated downstream → minimized flush bag size • **Minimized risk of back pressure** • **Faster** • **Resilient to product excipient adsorption** • **Softer wetting conditions** required	• **Resilient to temperature variation** • **Invariant for one membrane/fluid combination** • **Independent from filter surface area**
CON	• Silicone tubing permeability to gas ~1 ml/min·m	• Higher pressure level → large gas volume → requires large flush bag • Risk for back pressure • Slower • Impacted by polysorbate/tween adsorption • Strong wetting conditions required

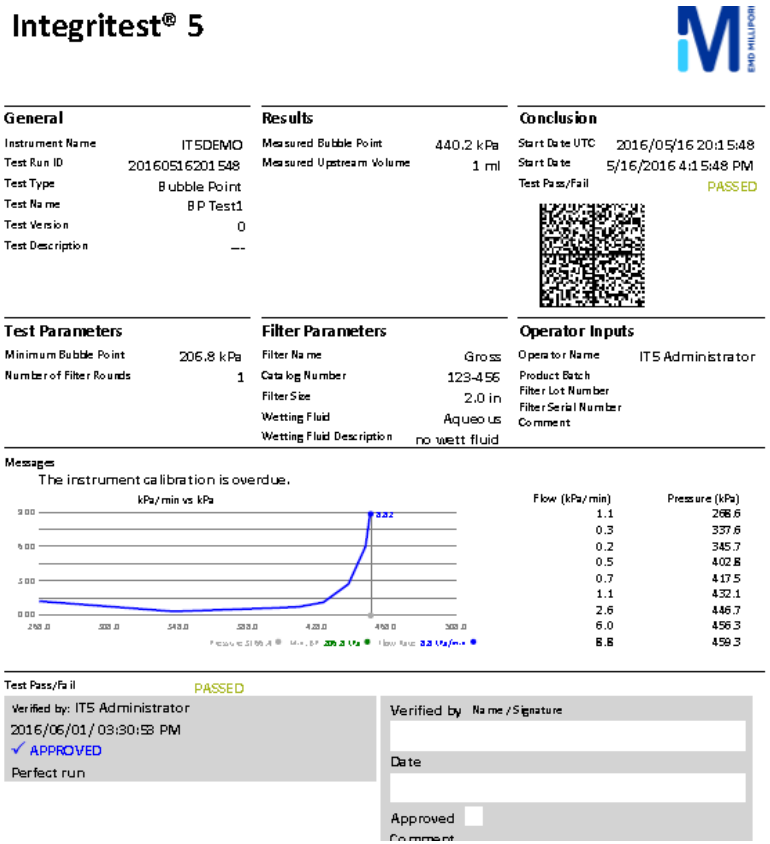
Automated Integrity Tester



- No downstream intervention
- Easy to validate
- Eliminates operator subjectivity
- Record keeping
- Bubble point and diffusion test
- Receipe management

Example of Test Report

- Provides **graph, table, and results** for accurate determination of value when the instrument is stable
- ISO **certified operator training** for customers
- Training enables **correct interpretation of test results**



Integritest® 5

General

Instrument Name	IT5DEMO
Test Run ID	20160516201548
Test Type	Bubble Point
Test Name	BP Test1
Test Version	0
Test Description	---

Results

Measured Bubble Point	440.2 kPa
Measured Upstream Volume	1 ml

Conclusion

Start Date UTC	2016/05/16 20:15:48
Start Date	5/16/2016 4:15:48 PM
Test Pass/Fail	PASSED

Test Parameters

Minimum Bubble Point	206.8 kPa
Number of Filter Rounds	1

Filter Parameters

Filter Name	Gross
Catalog Number	123-456
Filter Size	2.0 in
Wetting Fluid	Aqueous
Wetting Fluid Description	no wett fluid

Operator Inputs

Operator Name	IT5 Administrator
Product Batch	
Filter Lot Number	
Filter Serial Number	
Comment	

Messages

The instrument calibration is overdue.

kPa/min vs kPa

Flow (kPa/min)	Pressure (kPa)
1.1	268.6
0.3	337.6
0.2	345.7
0.5	402.8
0.7	417.5
1.1	432.1
2.6	446.7
6.0	456.3
8.8	459.3

Test Pass/Fail PASSED

Verified by: IT5 Administrator
2016/06/01/03:30:58 PM
✓ APPROVED
Perfect run

Verified by Name/Signature

Date

Approved

Comment

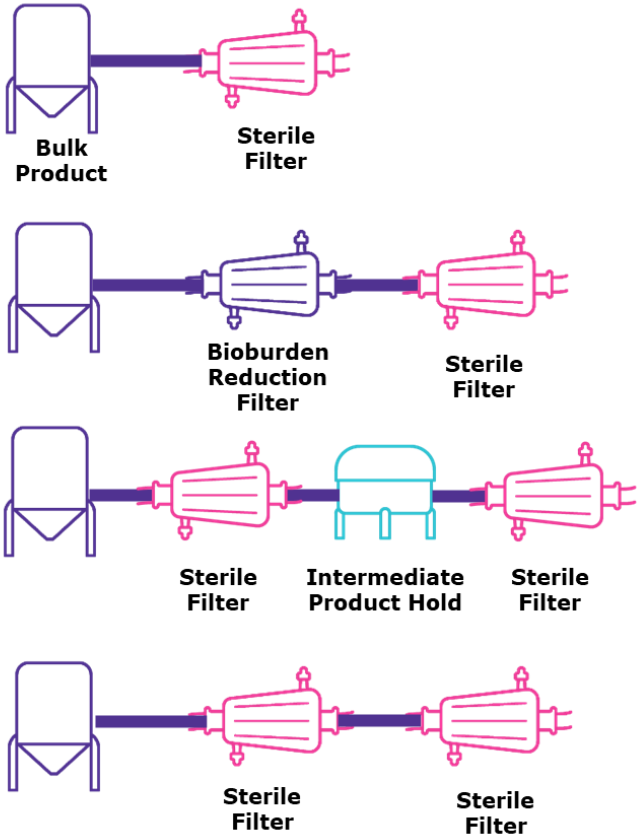
How Many Filters?

Is redundant filtration a must?

Filtration Process Design

Annex 1, 8.80

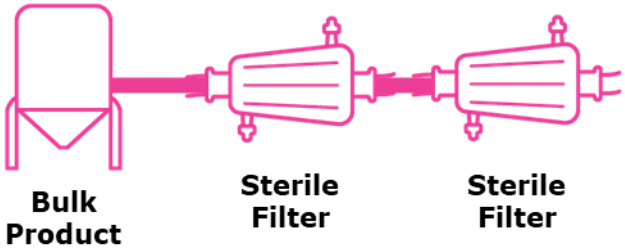
- Suitable **bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points** during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter.
- Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, **an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered** as part of an overall CCS.



Redundant Filtration

Annex 1, 8.92

- a second redundant sterilising grade filter as a **backup**
- sterilising process is **validated as only requiring one filter**
- **in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter** should be performed



Benefits

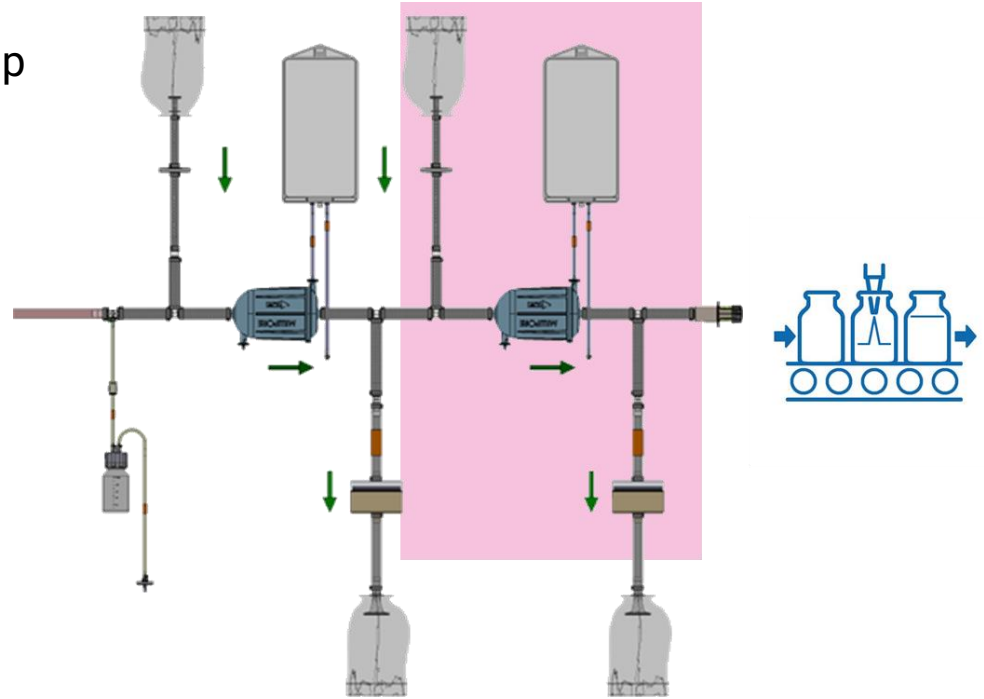
- Potential batch release if primary filter fails integrity test

Considerations

- Higher hold-up volume
- Higher system complexity
- Leachables, Adsorption

Redundant Filtration - Challenges

- Increased complexity of the filtration set-up
- Filter inside/outside isolator?
- As close as possible to the point of fill?
- Manipulation of the sterilized filtrate side
- Closed system on the filtrate side
- Additional vent filters to be tested
- Product dilution with wetting fluid
- Protein adsorption
- Leachables
- …



Filtration Process

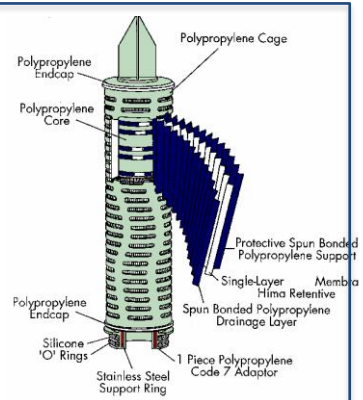
Process Design Considerations

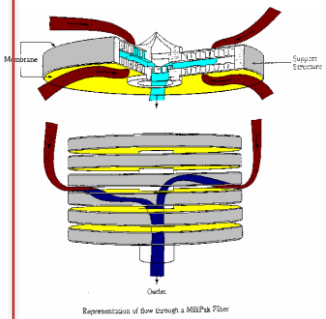
Filter Device Design

Pleated Membrane

- Available in PES of PVDF
- Pleated membrane enable higher filtration flow rate
- Available from XL150 to XLT 30”
- Good forward and reverse pressure resistance

Preferred for **high flow**





Stacked Disk

- Available in PVDF
- Stacked disk enable low hold up volume & increased product recovery
- Available from 100cm² to 1000cm²
- Low resistance to back pressure

Preferred for **low hold-up volume**

Filter wetting with product is the best option

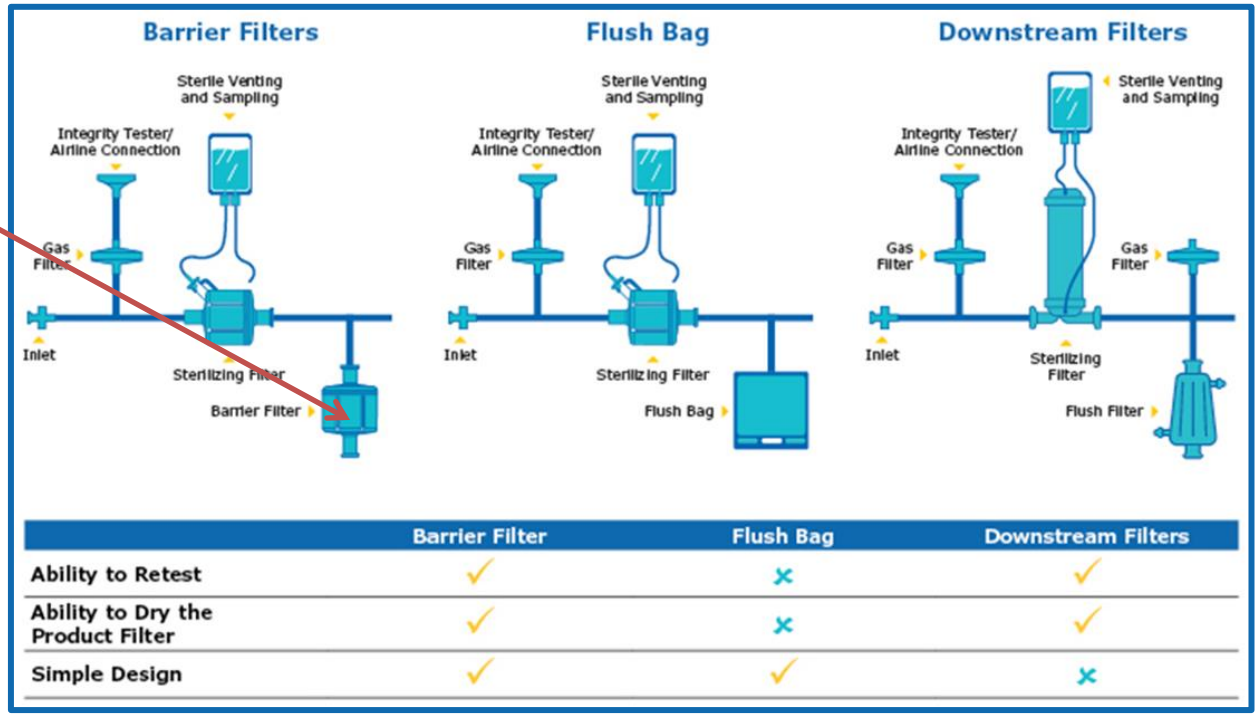
	Water	Product
PRO	• Inexpensive fluid → **COST EFFECTIVE** • Unlimited amount for flushing • e.g., large filtration system, leachables removal, repeated wetting • Test specification published • No risk for flaw masking	• Leaner design → **EASE OF USE** • No dilution • No drying • Negligible risk of flaw masking

CON	• More sophisticated design
	  • water/air inlet and outlet
	• Product discard for diluted product removal
	• Filter blow down
	  • Duration 15' to 3h
	  • Mechanical stress 4 bar
		• Product specific FIT limit
		• Product discard for leachables removal
		• Product filtration "at risk" until PUPSIT result
		• PUPSIT to be included as process condition in filter validation – revalidation might be needed.

Single-Use Assembly Supporting PUPSIT

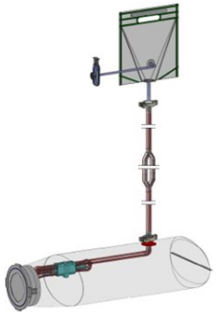
Millipak Barrier Application

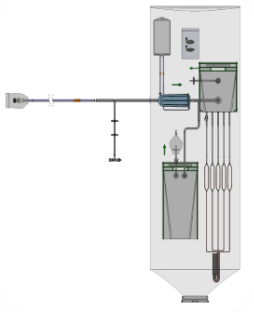
- PUPSIT
- Flushing of leachables
- Venting a sterile system during filter drying post-flushing

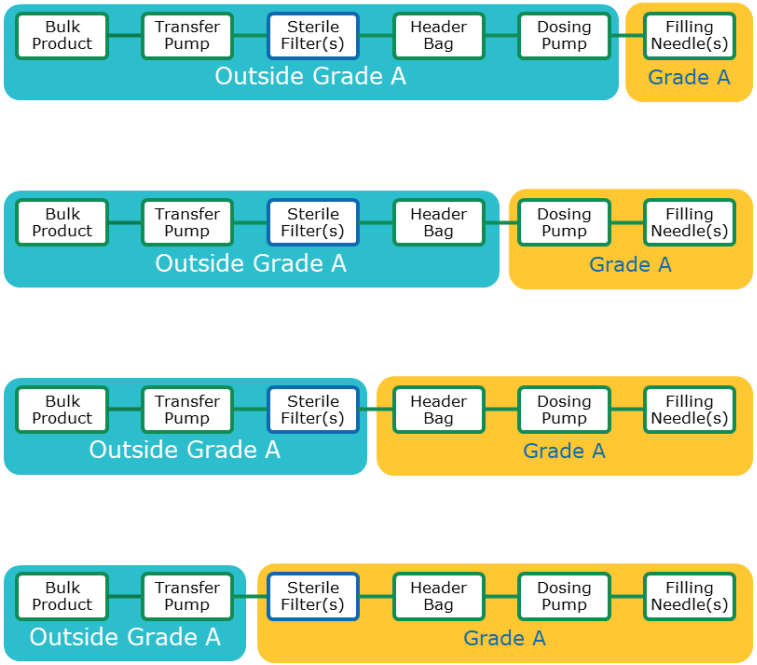


	Barrier Filter	Flush Bag	Downstream Filters
Ability to Retest	✓	✗	✓
Ability to Dry the Product Filter	✓	✗	✓
Simple Design	✓	✓	✗

Filter Inside or Outside of the Isolator?







No “one solution fits all” - decision embedded in overall Contamination Control Strategy

Points to consider:

- Handling inside the isolator
- Filter integrity test in line
- Point-of-use integrity test of SUS
- Sufficient isolator space
- Environment
- …

Closed System

Single-Use Filtration Assembly

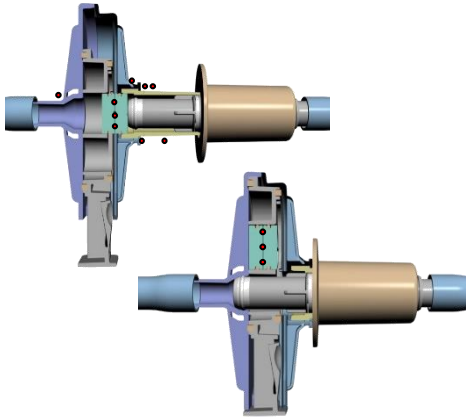
Sterile Connection Device – Reduce Complexity

Courtesy of PSM GmbH

Complex assembly (PUPSIT ready and redundant filtration)

- Limitations in packaging
- Risk to lose integrity (handling!)

(“Intrinsic”) Sterile Connection Device



Brevundimonas diminuta aerosol

Design

- Robust and consistent performance
- 100% air-integrity tested in manufacturing

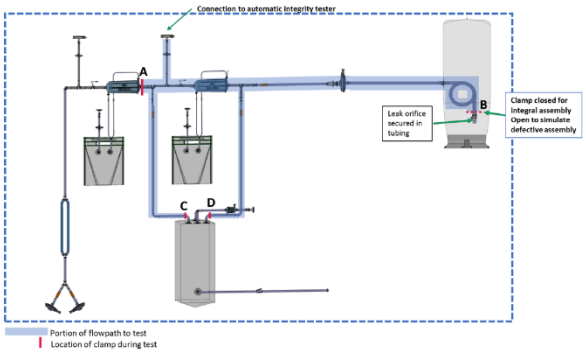
Validation

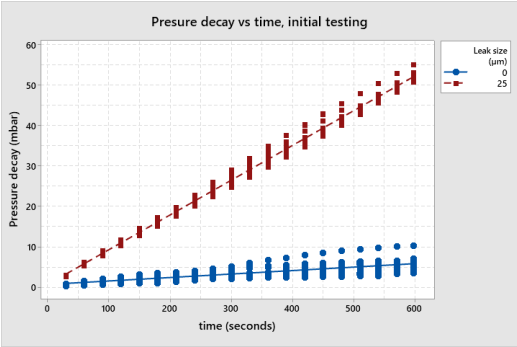
- Aerosolized microbial challenge test
- Aseptic Process Simulation

Handling

- Quick and easy
- Avoid operator mistakes

Onsite Single-Use System Integrity Test



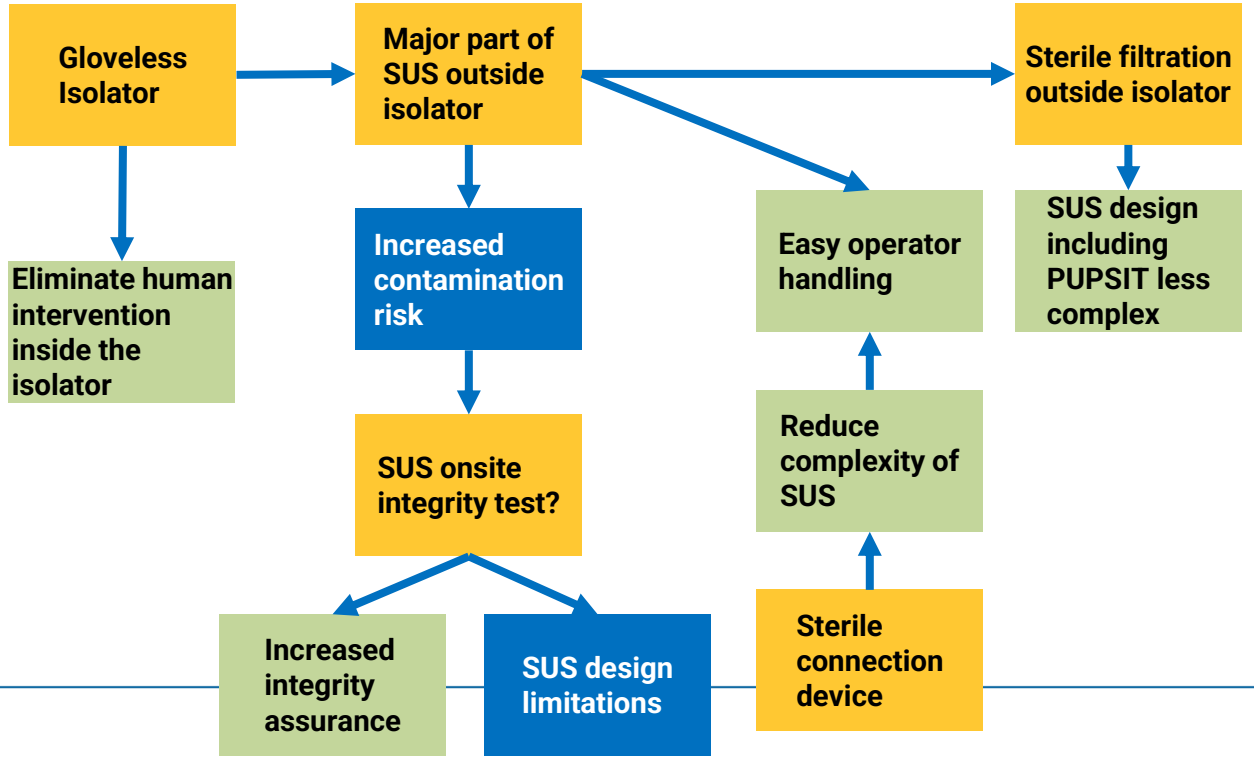


Nicholas Batt et al., Chem. Ing. Tech. 2022, 94, No. 12, 1985–1994

SUS Integrity Assurance - More than a Test

Contamination Control Strategy (CCS)

Brainstorming Example: if the isolator doesn't have gloves



Key Component Filter Membrane…

…select the right membrane – material, filter area, pore size

…the more filter the better? – to be assessed during filter validation

…sterility assurance – is more than PUPSIT

CONNECTING PEOPLE SCIENCE AND REGULATION®

Let‘s practice PUPSIT – after lunch !

PUPSIT Animation