sterile filtration

How to Keep Flexibility and Regulatory Compliance

Pharma Congress, June 1, 2022

Dr. Simone Biel, Senior Regulatory Expert

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Frequently Asked Questions

- Filter **inside or outside the isolator**?
- What if the isolator is in **Grade D**?
- A single filter or **redundant filtration**?
- What would be an exception to skip the **PUPSIT** (pre-use post-sterilization integrity test)?
- **Post-approval change** of the sterilizing filter?
- **Multiple use** of a filter?
- **Filter as part of a ready to use single-use system** – how to ensure integrity downstream of the filter?

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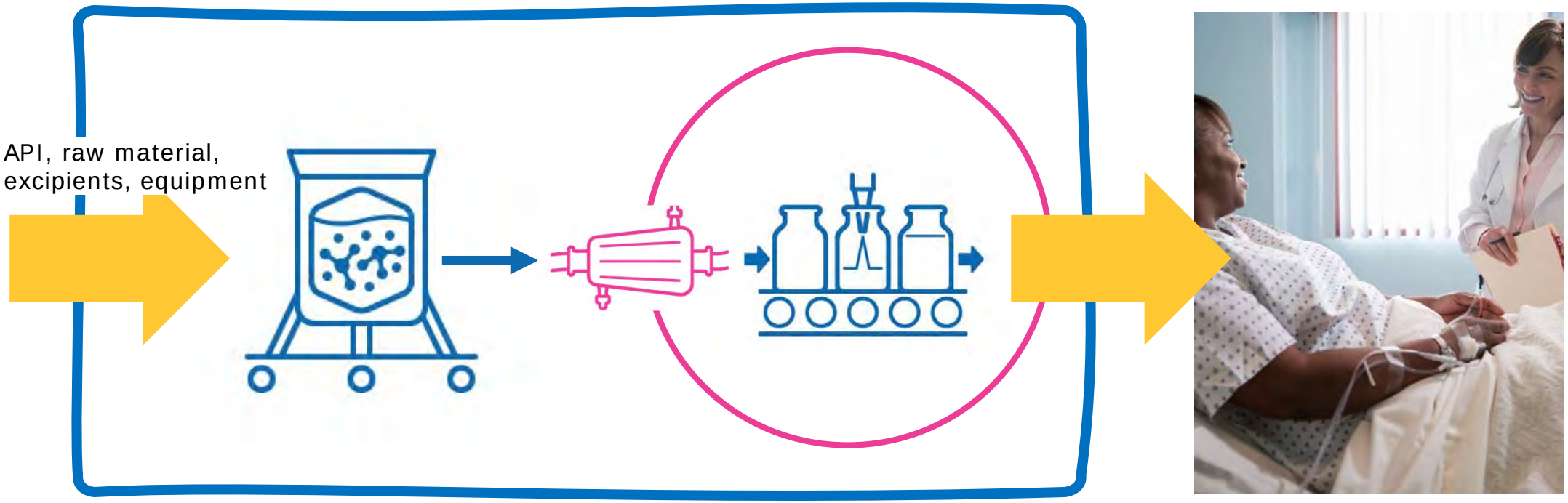
Premises, Equipment, and the Filter

Quality Risk Management (QRM)



Annex 1 draft (2020): "…ensure that microbial, particulate and pyrogen **contamination is prevented in the final product**."

Patient Safety

Filter Sterilization if Autoclaving is Not Possible

Sterility Assurance

- Sterile filter
- Filter compatibility
- Bacterial retention
- Integrity

Quality and Efficacy

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

Industry Needs
Process Flexibility

New formulations (novel excipients) and **new modalities** (Cell and Gene Therapy)

- Filtration characteristics

Speed to market

- Process development in timely manner

Small batch size

- Product loss (filtration, sampling)

Multiproduct facilities

- Product mix-up

Increase capacity

- Quick change over

Process improvements

- Gloveless isolator
- Single-use systems

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Filtration Must-Haves

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Filter Data to Be Provided for Market Authorization

No Compromise if the Claim is “Sterile Filter”

Parameter	Filter		Comment	
	Non-sterilising[1]	Sterilising[1]		
General information on filter				
Type of material, nominal pore size	X	X		
Number of filters	X	X		
Filter area	-	X		
Filter integrity test	-	X	Principle of the test, details on when the tests are performed, solution(s) used in the test and acceptance criteria before and after filtration should be described.	
Filter validation			**Solution used**	**Comment**
Potential sorption of solution components to filter	X	X	Product	
Solution Compatibility	X	X	Product	Worst case conditions with regards to for instance sterilisation process, contact time, filtration time, pressure, filtered volume.
Filter retention capacity	-	X	Product [2]	Minimum 10^7 CFU/cm² using a justified indicator organism and the actual solution.
Filter integrity test limits	-	X	Product [3]	
Extractable and leachable substances from the filter	X	X	Product [4]	Justified surrogate solution may be used.

EMA/CHMP/CVMP/QWP/850374/2015 (6 March 2019), Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

“Filter validation

*Acceptable information has been provided during the procedure for **filter validation on the filters used for sterile filtration**, describing the **material, pore size and surface area**. All study results met the predetermined acceptance criteria and the studies for **microbial retention, membrane compatibility, extractable substances and integrity test determination** have shown that the filters are appropriate for sterile filtration of the finished product.”*

Public Assessment Report, Comirnaty, COVID-19 mRNA vaccine, EMA/707383/2020

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Filter Integrity

More than Just One Test

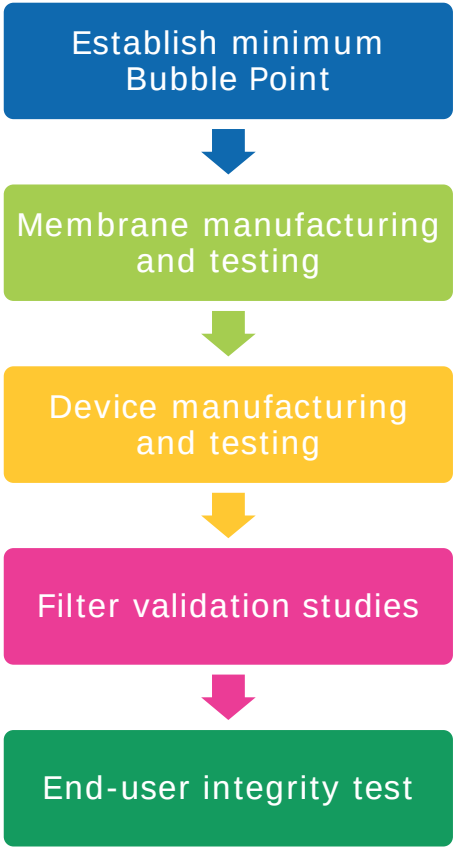
EU GMP Annex 1 draft, 2020:

- Integrity test before use and post-use (main reason: **filter flaw masking effect**)
- **"…(PUPSIT) may not always be possible after sterilization due to process constraints (e.g. the filtration of very small volumes of solution).** In these cases, an alternative approach may be taken…."

PDA Technical Report 26:

"**Integrity testing alone is insufficient** to assure the sterility of the filtrate. At least two other elements must be in place:

- **The production controls and quality assurance systems used by the filter manufacturer …**
- And the **validation studies** used to show that a particular combination of product, processing conditions and sterilizing grade filter will meet the requirements of the bacterial challenge test."



Annex 1 Draft: Specific Expectations for Filter Sterilization

New Draft Guidance Provides More Details

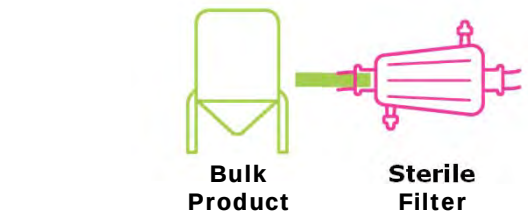
- **Sterile filtration should be validated**
  - validation can be grouped
  - but done under worst case conditions
  - rationale for grouping justified and documented
- Filter validation wherever possible with product
- Justify challenge organism used in bacterial retention test
- Establish appropriate integrity test value specification

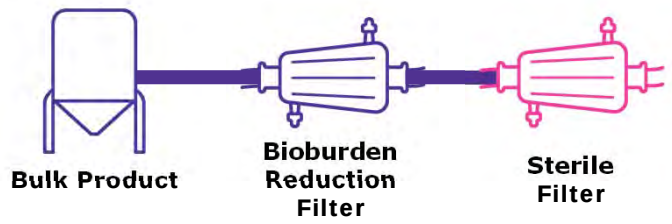
- **Validation of maximum filtration time**/total time filter is in contact with fluid
- Discard filter after processing of a single lot
- Don't use filter for more than one working day (unless validated)
- Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use does not compromise performance of the sterilizing filter or filtrate quality

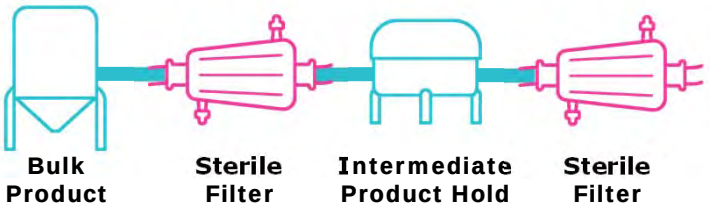
- **Filter selection**
  - minimize generation of fibers and particulates
  - no unacceptable levels of impurities
  - compatible with the fluid
  - evaluate adsorption and extraction/leaching
- **Filtration concept** (serial, redundant, bioburden reduction)
- **Process parameters**
  - pressure, wetting, flushing, hold-time, flow rate, maximum volume
  - Allow operation within validated process parameters
- In-place **integrity testing** pre- and post-use

Final Filtration System Designs

Number of Filters in the System







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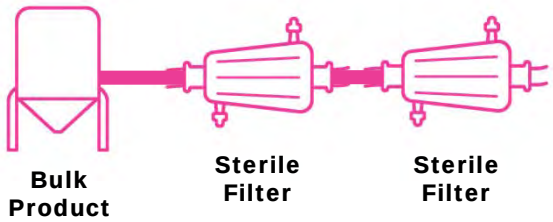
Single-use Redundant Filtration



BENEFITS

- ✓ Potential batch release if primary filter fails the integrity test
- ✓ Meets regulatory expectations

(US FDA cGMP - Sterile Drug Products Produced by Aseptic Processing)

CONSIDERATIONS

- Higher hold-up volume
- Higher cost
- Higher system complexity

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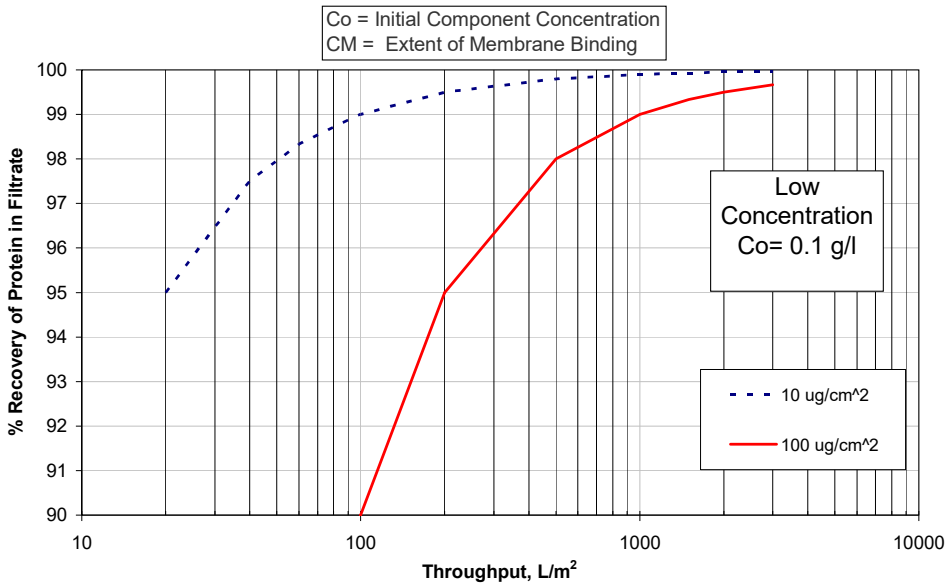
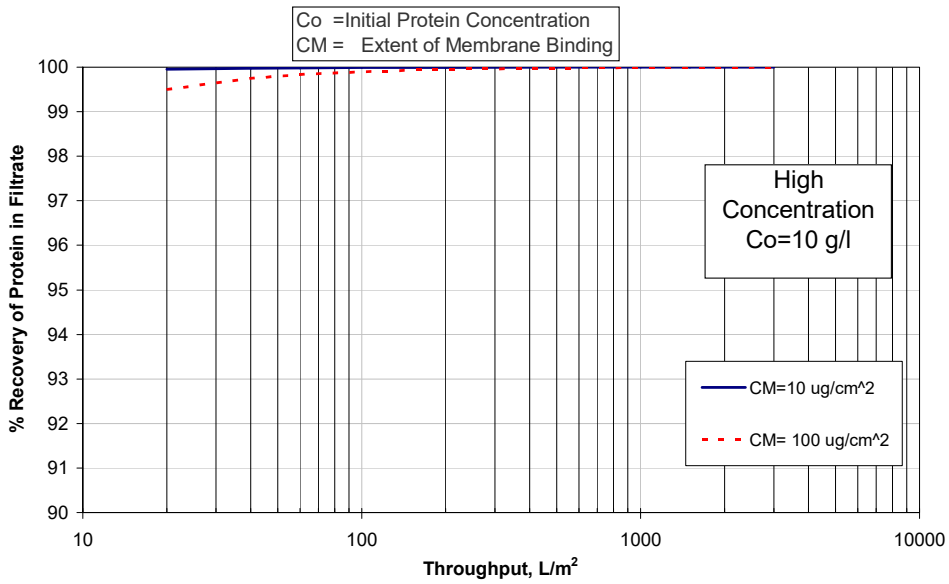
Drawback of Double the Filter Membrane Area

Protein Binding

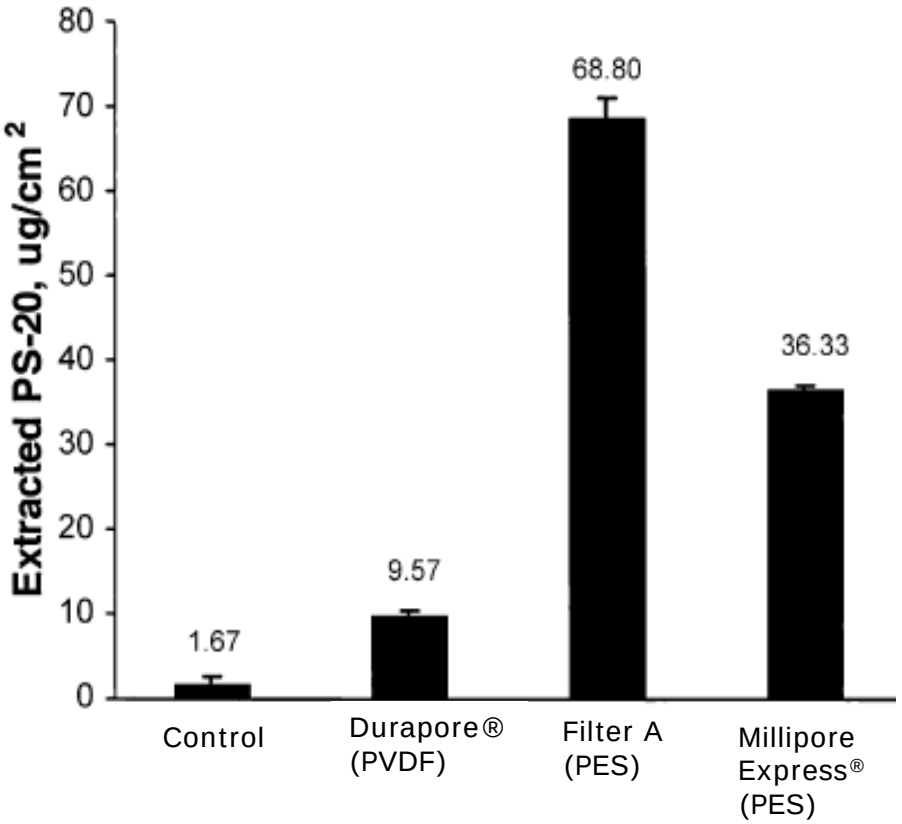




- Not all proteins bind the same (protein A adsorbs 10 µg/m^2, protein B 100 µg/m^2)
- The higher the product concentration the less pre-flush

No One Filter Membrane Fits All

Polysorbate 20 Binding



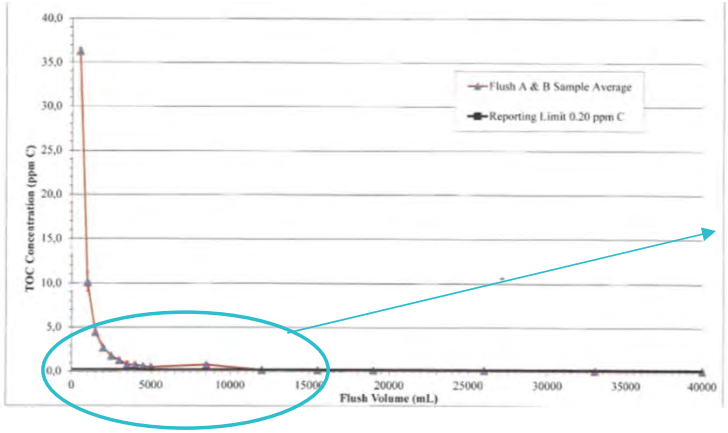
Polysorbates are widely used as stabilizers in protein and mAb formulations

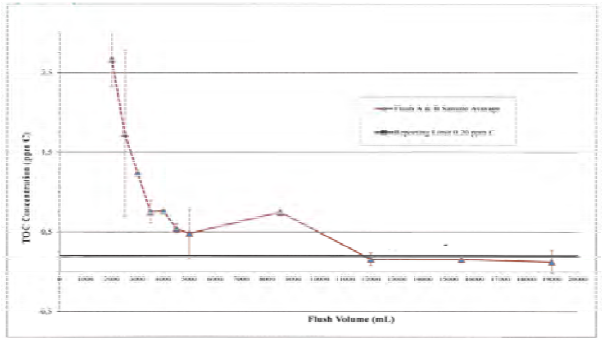
- Precise concentration is critical
- A lower concentration of polysorbate reduces protein stability and increases aggregation
- Not all filters bind the same even if they are out of same material
  - e.g., Filter A vs Millipore Express®
- Membrane material impacts binding,
  - e.g., polyethersulfone (PES) vs polyvinylidene fluoride (PVDF)

Risk Mitigation of High Amount of Extractables

Filter Flush Studies

- Representative conditions applied
- Filter flushing with water under dynamic mode
- Sampling at different timepoints
- TOC to evaluate the level of leachables
- Evaluate the appropriate flush volume





Post Approval Change

Risk Assessment to Evaluate the Impact

		Bacterial Retention	Product Bubble Point	Product Diffusion	Compatibility	E&L Patient Safety
Product	**Change in product formulation** (concentration, pH,…)	X	X	X	X	X
	Change in posology (dosage, frequency)					X Re-evaluate risk assessment
Filter	**Change in filter membrane** (type, materials of construction)	X	X	X	X	X
	Same membrane – Change in device type (e.g., from a capsule to a cartridge)			X May need risk assessment	X	X
	Same membrane – Change in pore size	X	X	X	X May need risk assessment	X May need risk assessment
	Same membrane – Change in filtration surface area	X If filtered volume/surface area is increased		X		X May need risk assessment

closed processing

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Closed System – Some Quotes

Single-Use Systems to Reduce Cross-Contamination

“Closed system. Where a **drug substance or product is not exposed to the immediate room environment during manufacture**.” (1)

“Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and **utilizing single use components and engineering measures such as closed systems**.” (1)

“**Closed or contained equipment should be used whenever appropriate**.” (2)

“Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, **closed and contained systems may be used to separate activities**...” (3)

The use of closed systems [i.e. single use systems] **can reduce the risk of extraneous contamination** such as microbial, particulate and chemical from the adjacent environment (4)

(1) EudraLex Vol 4, Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use

(2) EudraLex Vol 4, Part II: Basic Requirements for Active Substances used as Starting Materials

(3) EudraLex Vol 4, Part IV: GMP Guidelines specific to Advanced Therapy Medicinal Products

(4) EudraLex Vol 4, Annex 1 draft (2020): Manufacture of Sterile Products

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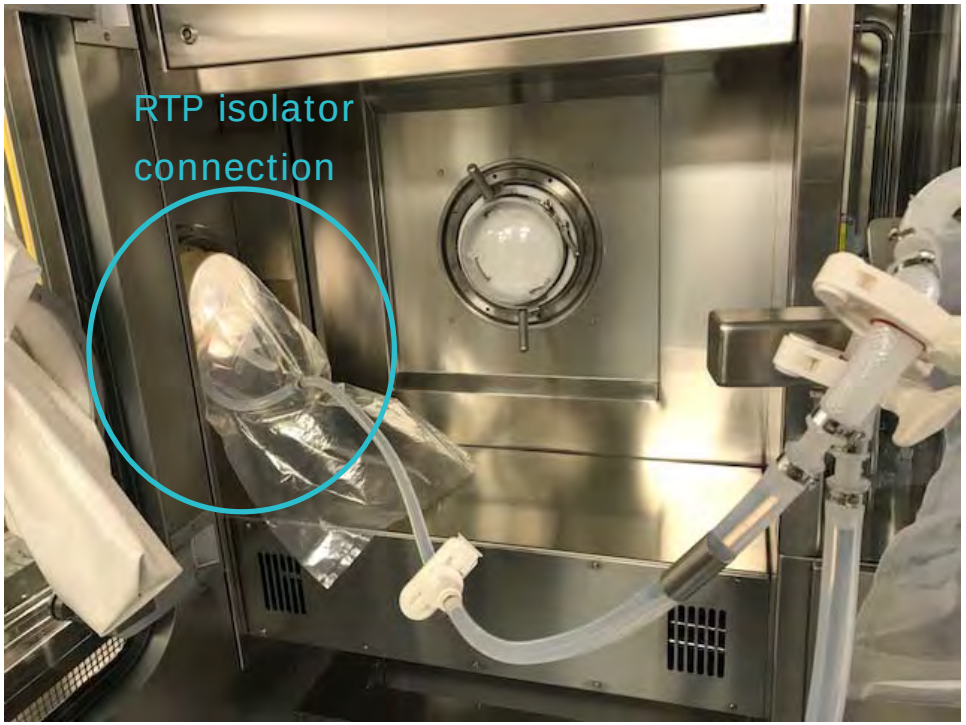
Case Study

Single-use Redundant Filtration Assembly



Merck Healthcare final filling site in Italy, Bari

Case Study – Merck Healthcare Final Fill (Italy/Bari)

Why Implement Single-Use Technology?

Process Flexibility

- Pre-formulated drug product pooling in a **closed system** (very low bioburden)
- Flexible **batch size**
- Filter **membrane flexibility** (dimension and material)
- **Peristaltic pumps** for filling process
- Process **scalability** from small to high batch sizes (platform concept to reduce process development effort)

Time Flexibility

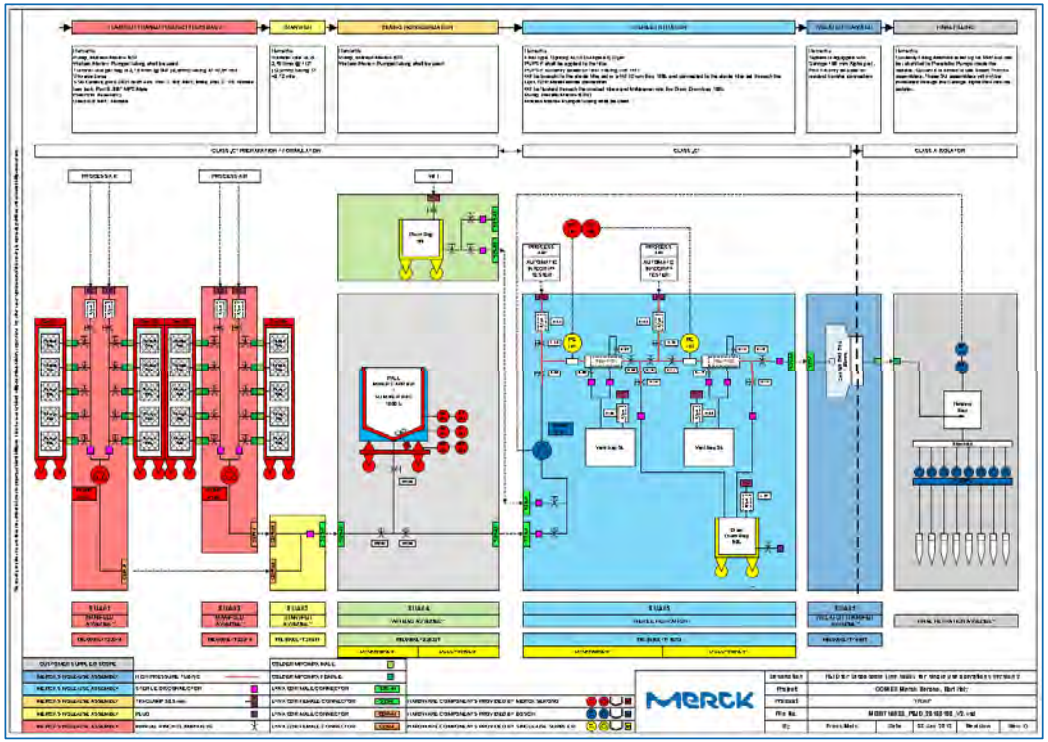
- **4-6 months (pre-Covid19) to design and receive** sterile customized assemblies at site
- **Plug and play** system for routine manufacturing
- **Less stainless steel equipment preparation**
- Limited changes to the stainless steel line to integrate SUS
- **No cleaning validation**

Cost Flexibility

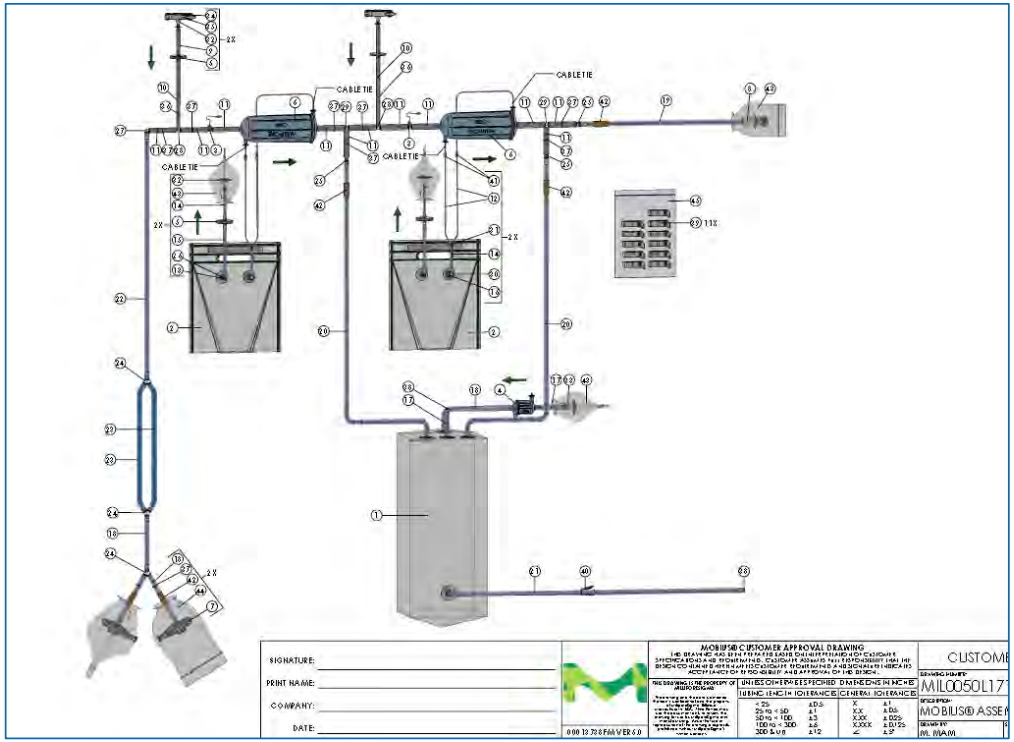
- **Less CAPEX** investments
- **Less machine set-up** and activity hours
- Increased line **capacity**
- Higher consumables direct costs compared to stainless steel equipment
- Business continuity in case of worldwide pandemic (Covid-19 situation)

Your Single-Use System Process

Lots of Components, Connections, Assemblies



Process template (pooling, filtration, filling),
Merck Healthcare (Italy, Bari)



Drawing redundant filtration assembly,
Merck Healthcare (Italy, Bari)

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Integrity Assurance

More than a test

Supplier

- Best handling practices
- Visual inspection to confirm the design

- Best practices for installation
- Point of use integrity/leak test

- Visual verification

Components → **Bag and assembly manufacture** → **Packaging and shipping** → **Receipt and unpacking** → **Pre-use stage** → **Post-use stage**

- Tear resistant and superior bond strength bag film
- Sterile connector integrity test

- Quality by design
- Automated bag bonding
- Visual inspection
- Integrity/leak test

- Define packaging instructions
- Shelf life validation
- Shipping validation

End-user

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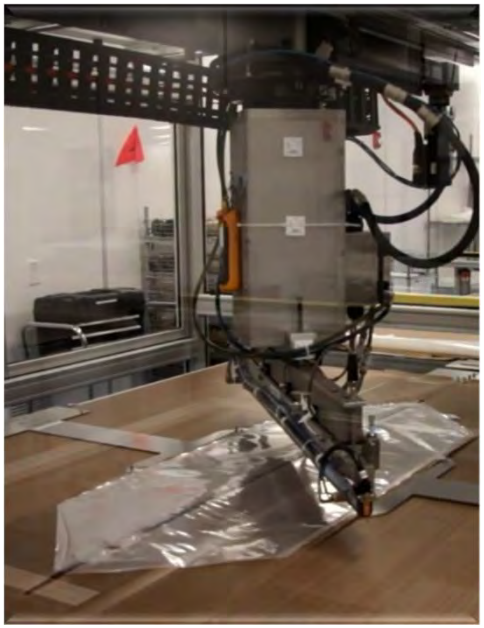
Manufacturing and Control

Do you know what your supplier does?



Bag manufacturing

- Automation
- Validated process
- In-process leak test

Assembly

- Standard operating procedures
- Operator training
- In-process controls

Release testing

- Visual inspection
- Final product leak testing
- Fluid path water extract testing (particles, endotoxin)

Leak / integrity testing

- Various methods depending on application and sensitivity

Release Test

Leak Test vs Integrity Test

Increasing Level of Risk-Reduction

Decreasing Defect Detection Size Limit

Leak Test

Detects **gross leaks** in a system

System Volume	Approximate Detection Limit
Tubing Assemblies	50 µm
1 – 9 L	150 µm
10 – 999 L	1000 µm
>1,000 L	2000 µm

Integrity Test

Helium Integrity Test

Detects **defects of a known size** that have a **correlation to a known parameter** using a specific test methodology such as aerosolized or liquid bacterial ingress.

System Volume	Validated Detection Limit
Tubing Assemblies	20 µm
Up to 50 L	20 µm

System Volume	Validated Detection Limit
Tubing Assemblies	2 µm
Up to 50L	2 µm

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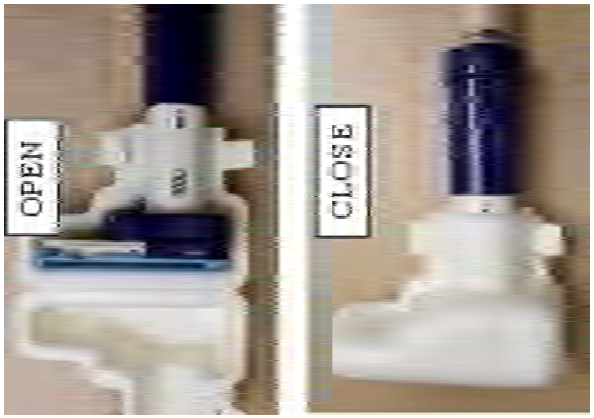
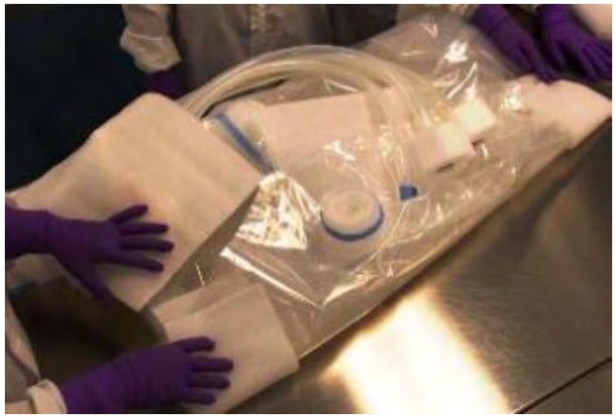
Packaging Design

Ensure Integrity During Shipment



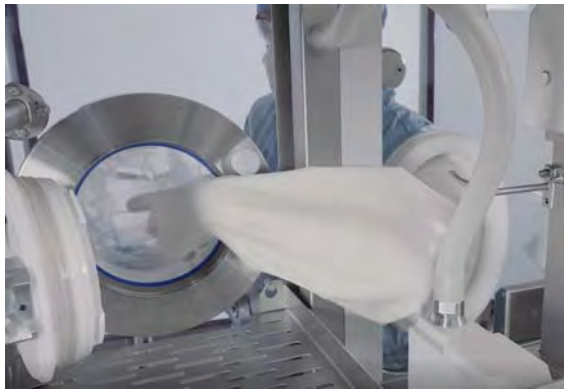


- **Protect** rigid components
- **Qualified packaging material** (shelf life, low particle load, outgassing)
- Ensure that **easy unpacking** is possible
- **Vacuum in packaging** bags to avoid movement of components
- **Shipping validation** (e.g. ISTA 2A)

New Handling Procedures for End-User

Proper Installation of SUS is Key to Maintain Integrity

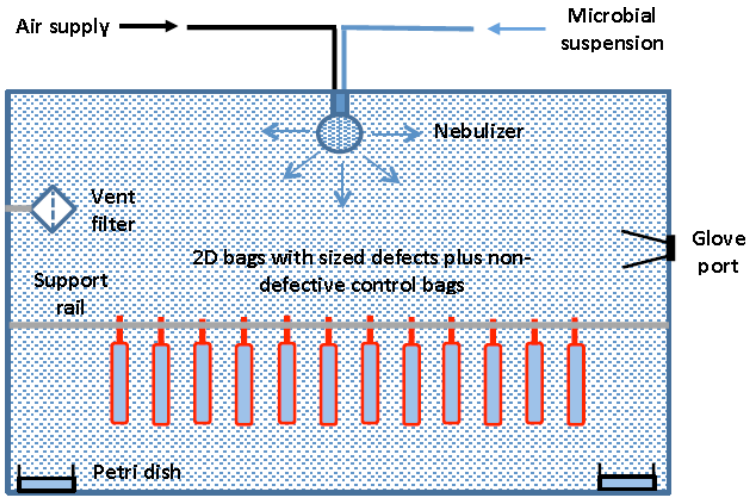
Outside Isolator

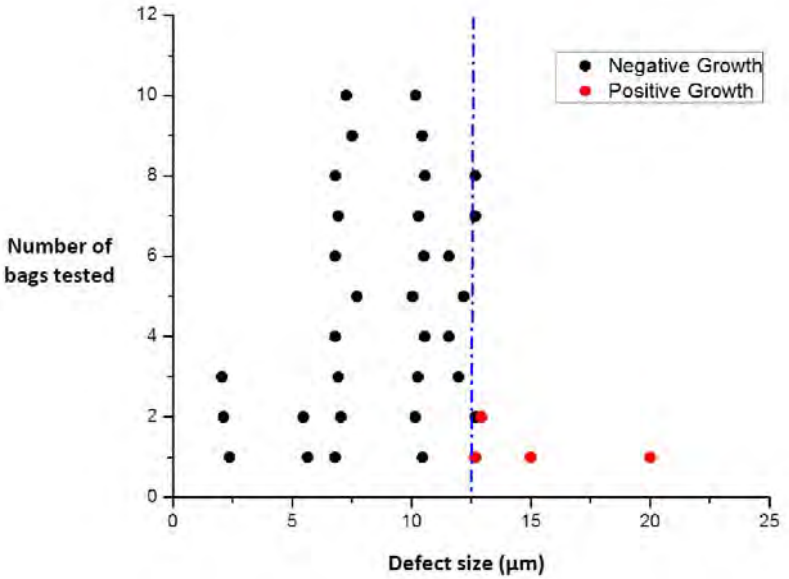


Inside Isolator

Single-Use System Integrity Test

Correlation Between Leak Size and Bacterial Ingress





Aerosol Challenge Test

- Bags with known defect sizes (filled with TSB)
- Microbial aerosol concentration 10^6 cfu/ml
- 60 mins

Incubation

- 30-35 °C
- 14 days

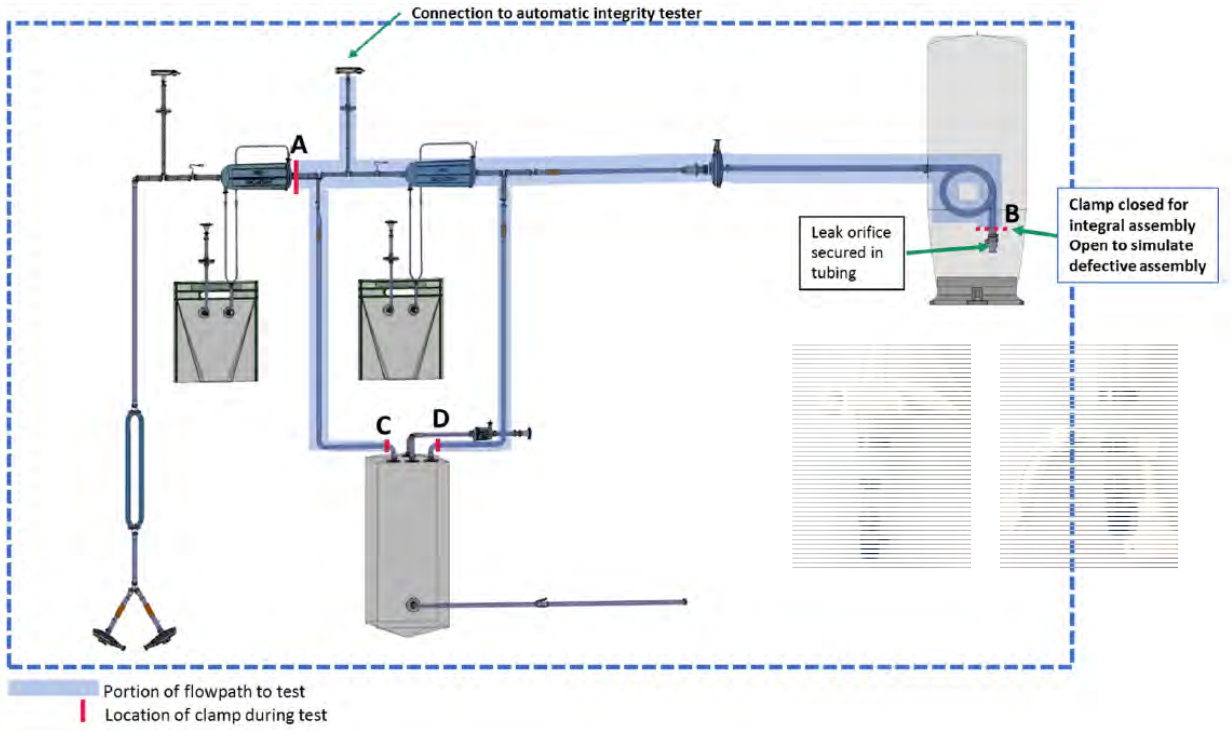
Result

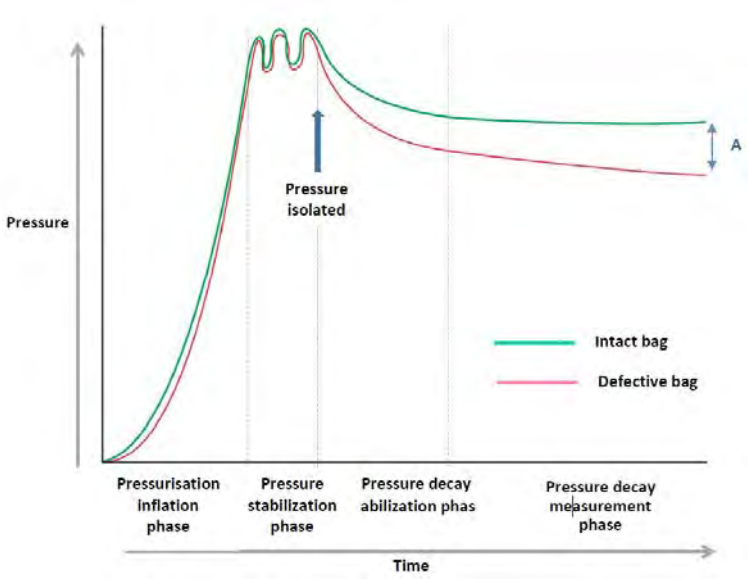
- Growth present in bags with **defects 12.65 µm or greater**

BPSA Technical Guide, Design, Control, and Monitoring of Single-use Systems for Integrity Assurance, 2017

Single-Use System Integrity Test

Pressure Decay Test Sensitivity ≥ 10µm Defect Size





BPSA Technical Guide, Design, Control, and Monitoring of Single-use Systems for Integrity Assurance, 2017

Nicola Rutigliani, Merck, SUT in Aseptic Drug Product Manufacturing, ECA Conference, 2021

Annex 1 Draft and Closed Systems

“Determined and Captured in Contamination Control Strategy”

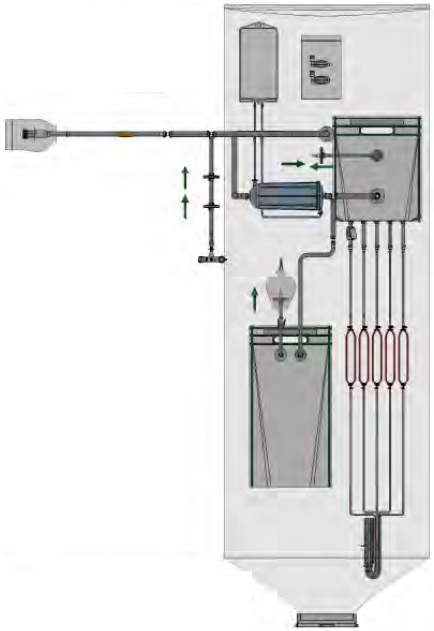
8.118 It is critical to **ensure the sterility of all product contact surfaces of closed systems** used for aseptic processing. The design and selection of any closed system used for aseptic processing should **ensure maintenance of sterility**. **Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic connectors or fusion systems)**.

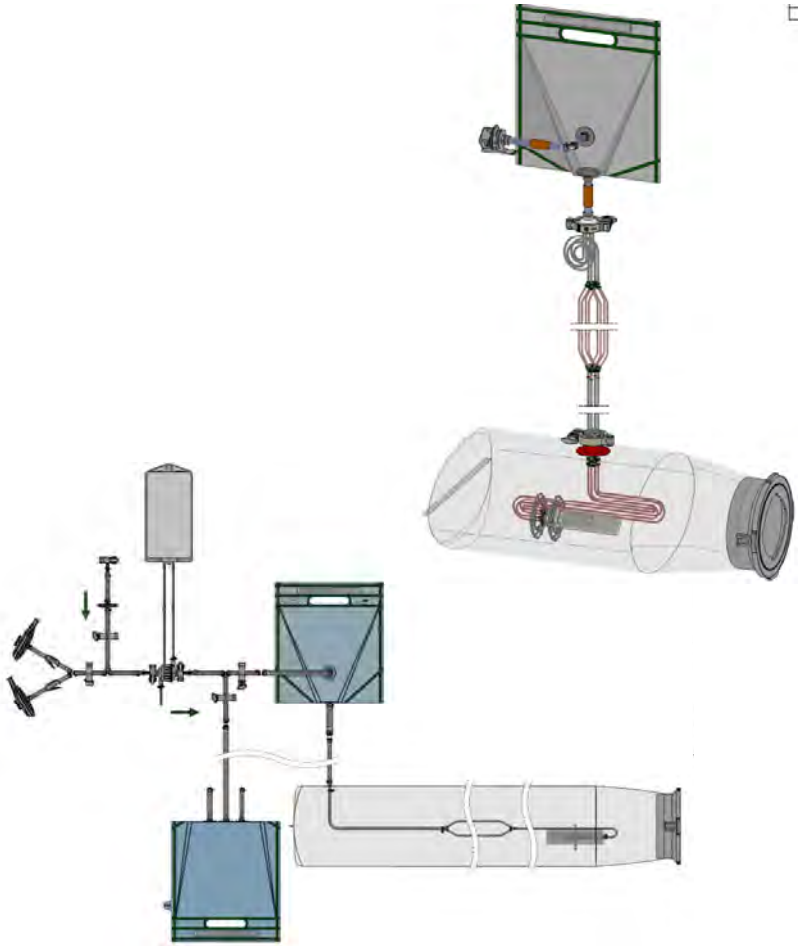
8.119 **Appropriate measures should be in place to ensure the integrity of components used in aseptic connections**. The means by which this is achieved **should be determined and captured in the CCS**. Appropriate **system integrity tests should be considered when there is a risk of compromising product sterility**. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

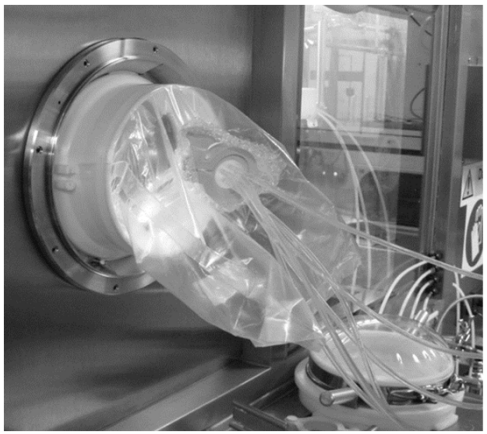
8.120 The background in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in a Grade A zone. **If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used**.

Isolator Interface with Getinge DPTE® Beta Bag

Ability to Interface with an Isolator While Maintaining Sterility

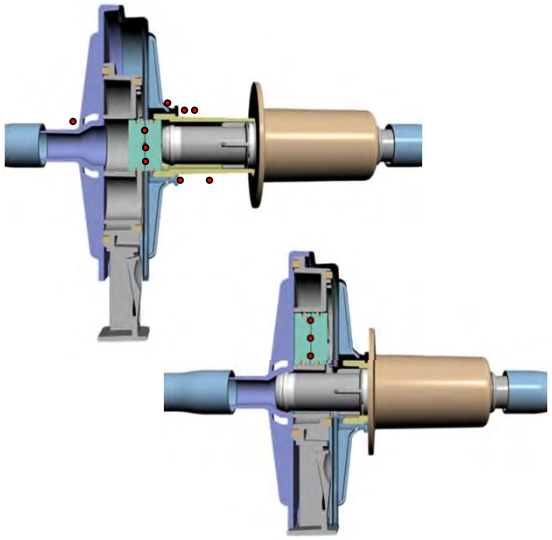






Sterile Connection Device

Reduce Complexity and Maintain Flexibility of the SUS



Brevundimonas diminuta aerosol

Design

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

Handling

- Quick and easy
- Avoid operator mistakes

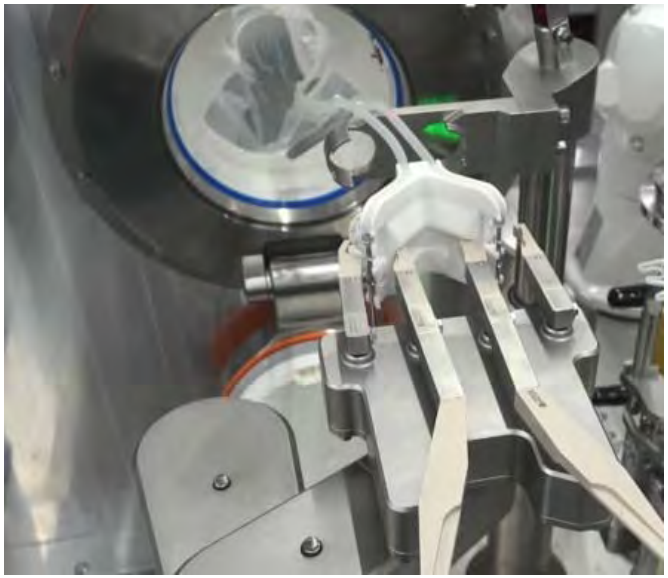
Validation

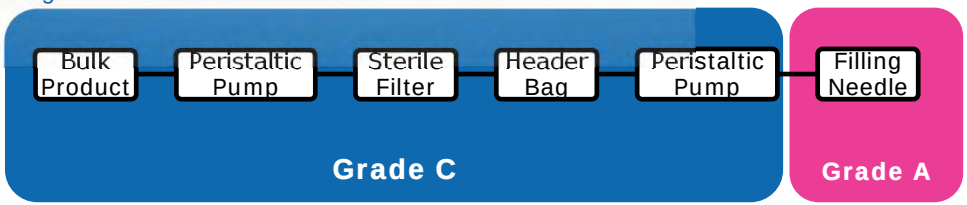
- Aerosolized microbial challenge test
- Media fill

Trend “Gloveless Isolator”

Avoid Human Intervention Inside the Isolator

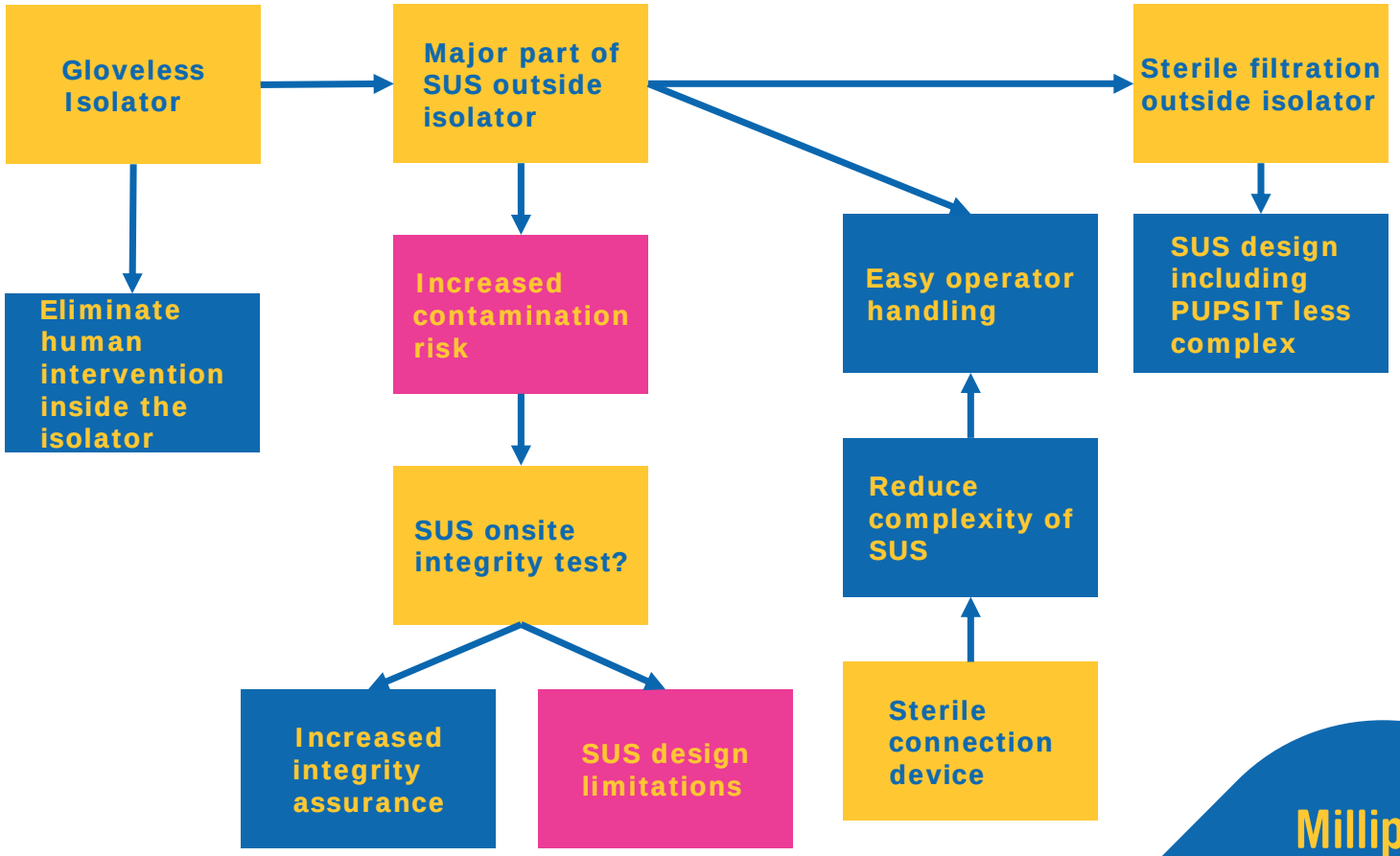
Photo courtesy of Groninger





Contamination Control Strategy (CCS)

Brainstorming



At the end, the drug must be sterile

- There is no one filter set-up fits all applications
- Industry trends and challenges need to be reflected in regulatory guidance
- A robust contamination control strategy is a partnership between suppliers and drug manufacturers

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