

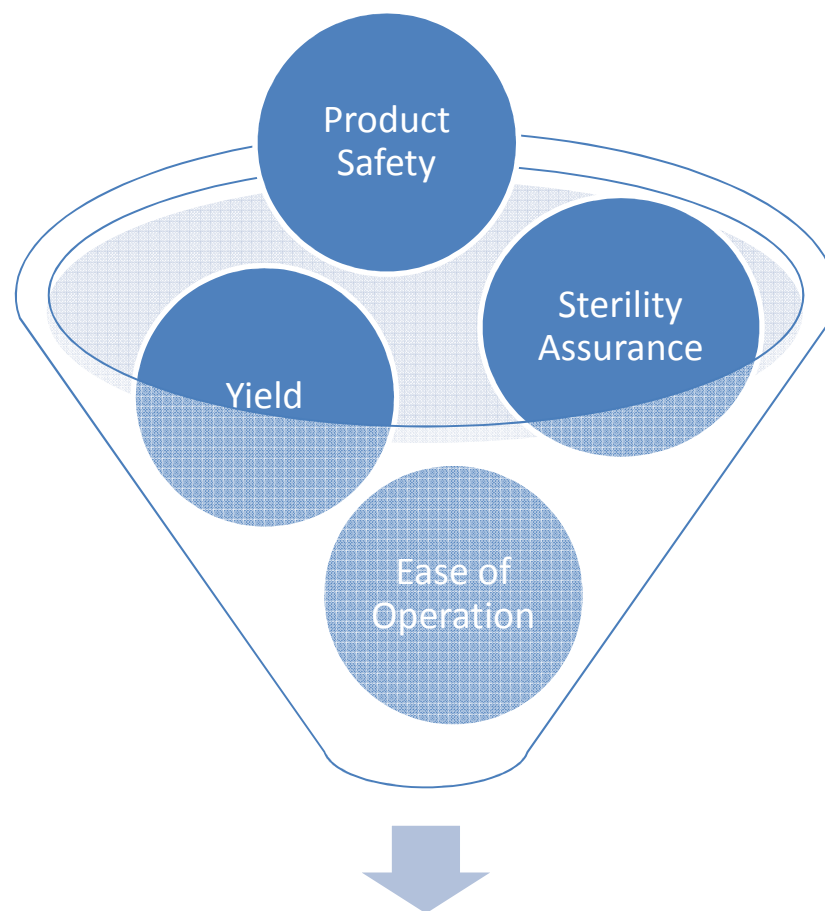
Implementation of Single Use Assemblies for Final Sterile Filling

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- **Sue Walker - Manager Final Fill**
- **Roberto Uchimura – Latin America Technology Manager Filtration and Purification**

Why Single Use Assemblies???

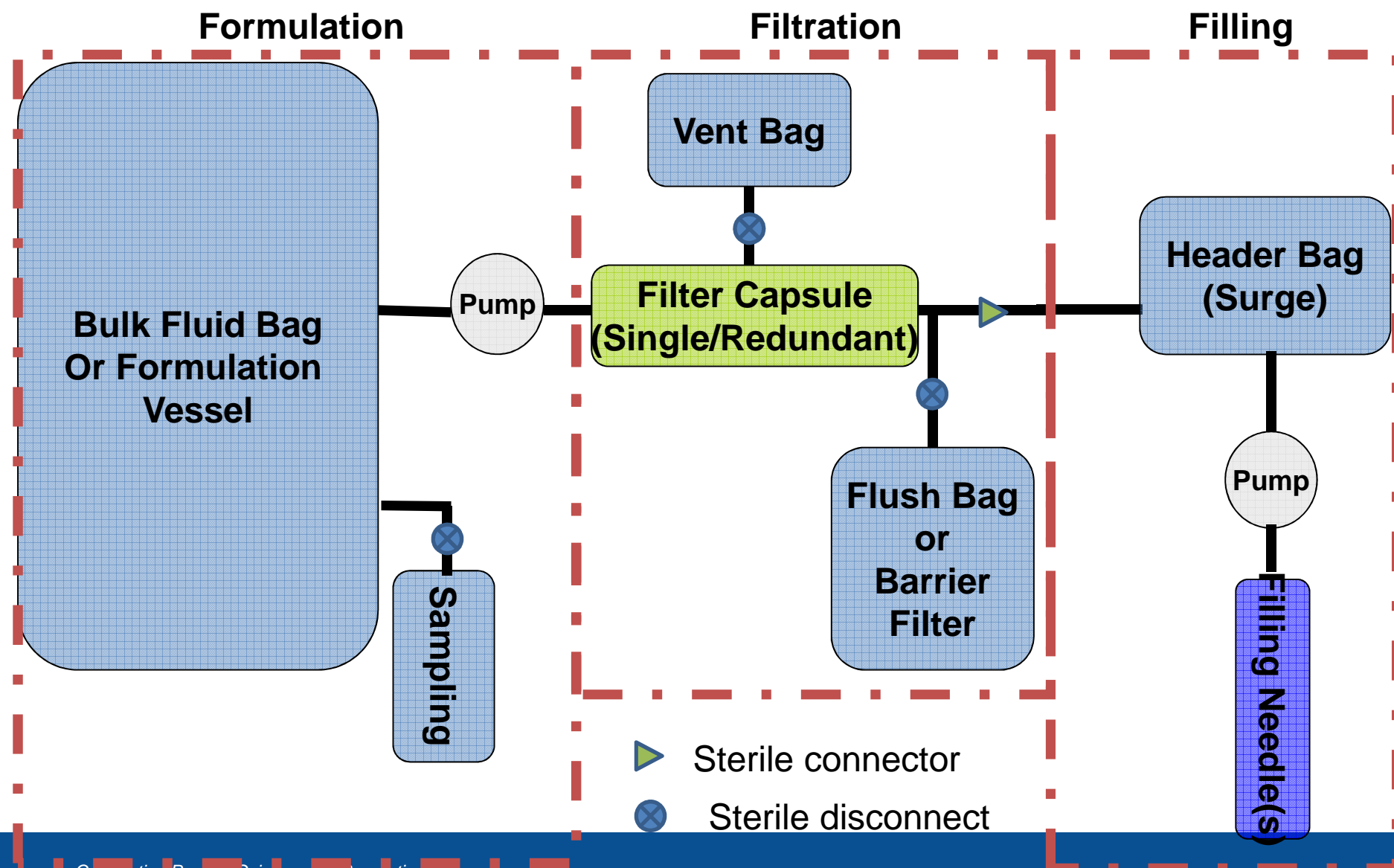
- The benefits of single use include:
 - Reduced risk of contamination
 - Ease of operation
 - Leading to overall time savings
- However the risks may include:
 - Sterility assurance
 - Patient safety
 - Yield loss

How do you mitigate the risk?



Design, Manufacture, & Use

Design of Single Use Assemblies



Project Timing

- Challenge
 - Highly customized product line containing a library of over 2000 qualified components
- Overall project timing: 9 to 18 months
 - Drawing generation and revisions
 - Prototype testing for form, fit, and principal function
 - Final drawings are generated with individual drawing numbers. The drawing is unique for each customer and customer site.

Design Considerations

Design includes:

- Selection of individual components
- How these individual components connect to create an assembly
- How the assembly performs in the process
- And, ultimately how the assembly impacts the final drug product

Plus consideration for component, assembly, and final packaged product qualification

Risk Mitigation through Assembly Design

Guidelines follow Good Engineering Practice – ASTM E2500

- Reduce the number of parts
- Foolproof the assembly design
- Avoid tight tolerances
- Design for ease of assembly and modular products

Integrate specific manufacturing concerns into the assembly design

- Results in a product that is easier to manufacture with excellent overall quality*

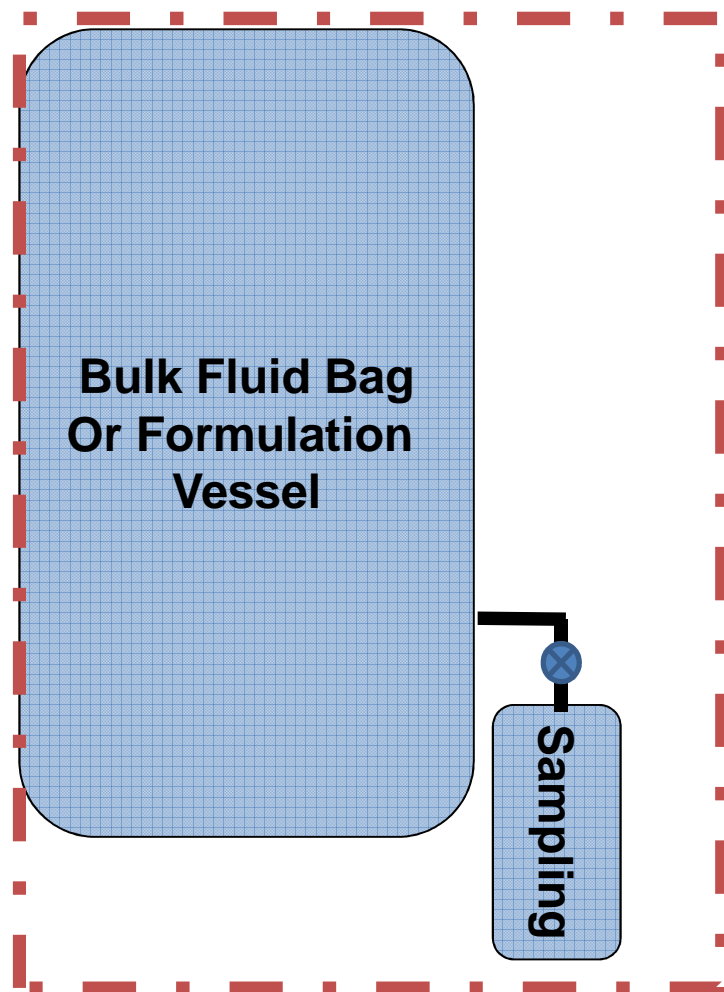
Apply Quality by Design concepts during specification and design

- Critical quality attributes (CQAs)
- Critical process parameters (CPPs)
- Prior production experience

Fit for intended use should not rely solely upon verification after installation

(*) http://www.intel.com/design/quality/mq_dfm.htm

Formulation



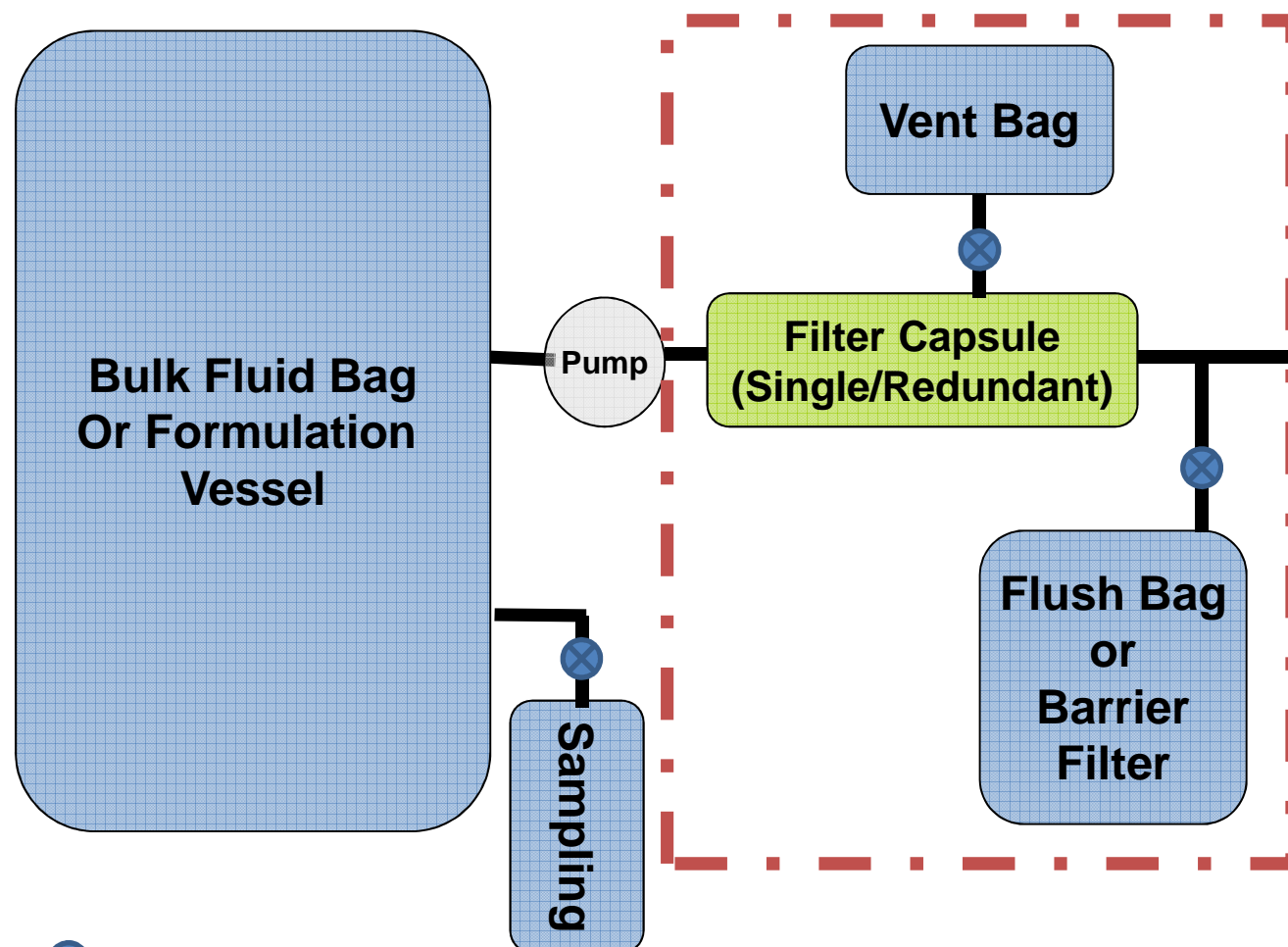
⊗ Sterile disconnect

Key Needs

- Component introduction
- Robust mixing
- Temperature control
- Minimize bioburden
- Representative sampling
- Product Recovery

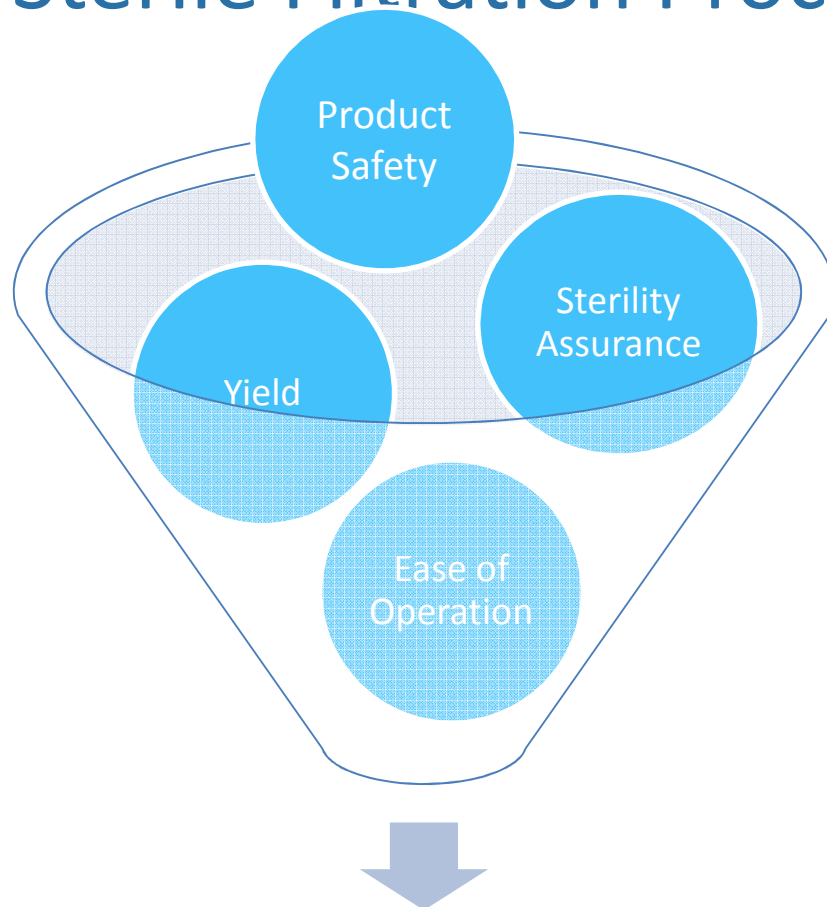
And potentially consider a hybrid system

Filtration



⊗ Sterile disconnect

Sterile Filtration Process Needs



Design Considerations

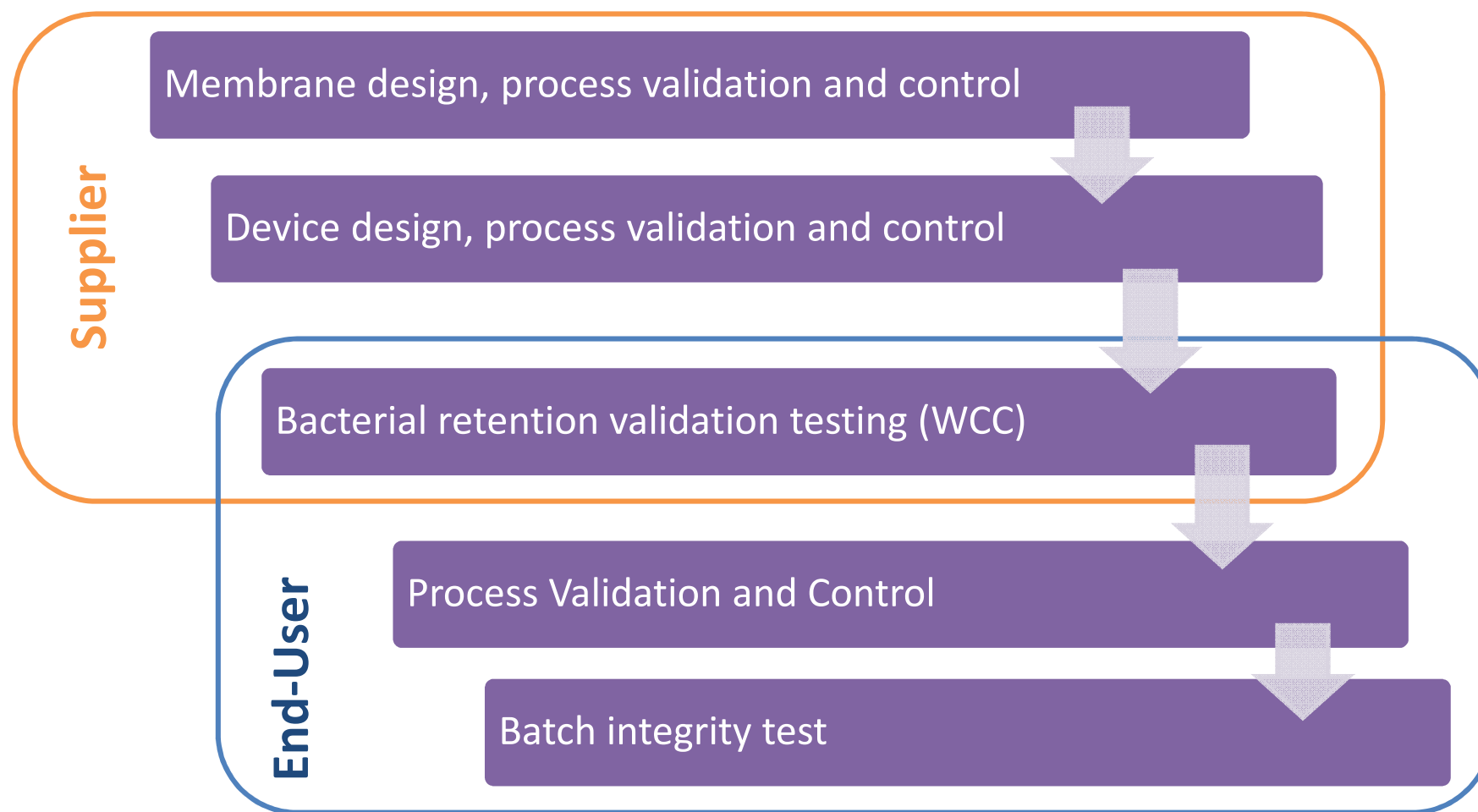
Filter **benefits**

- Robust retention performance
- Well characterized materials
- Multiple device size and connection options
 - Low adsorption membranes
 - Protein
 - Surfactants

■ **Risks** that must be addressed in design and operation

- Downstream sterility
- Filter and system integrity
- Extractables
- Product recovery
- Operator manipulations

Sterilizing Filter Retention Assurance



Device Characteristics

- **Materials**

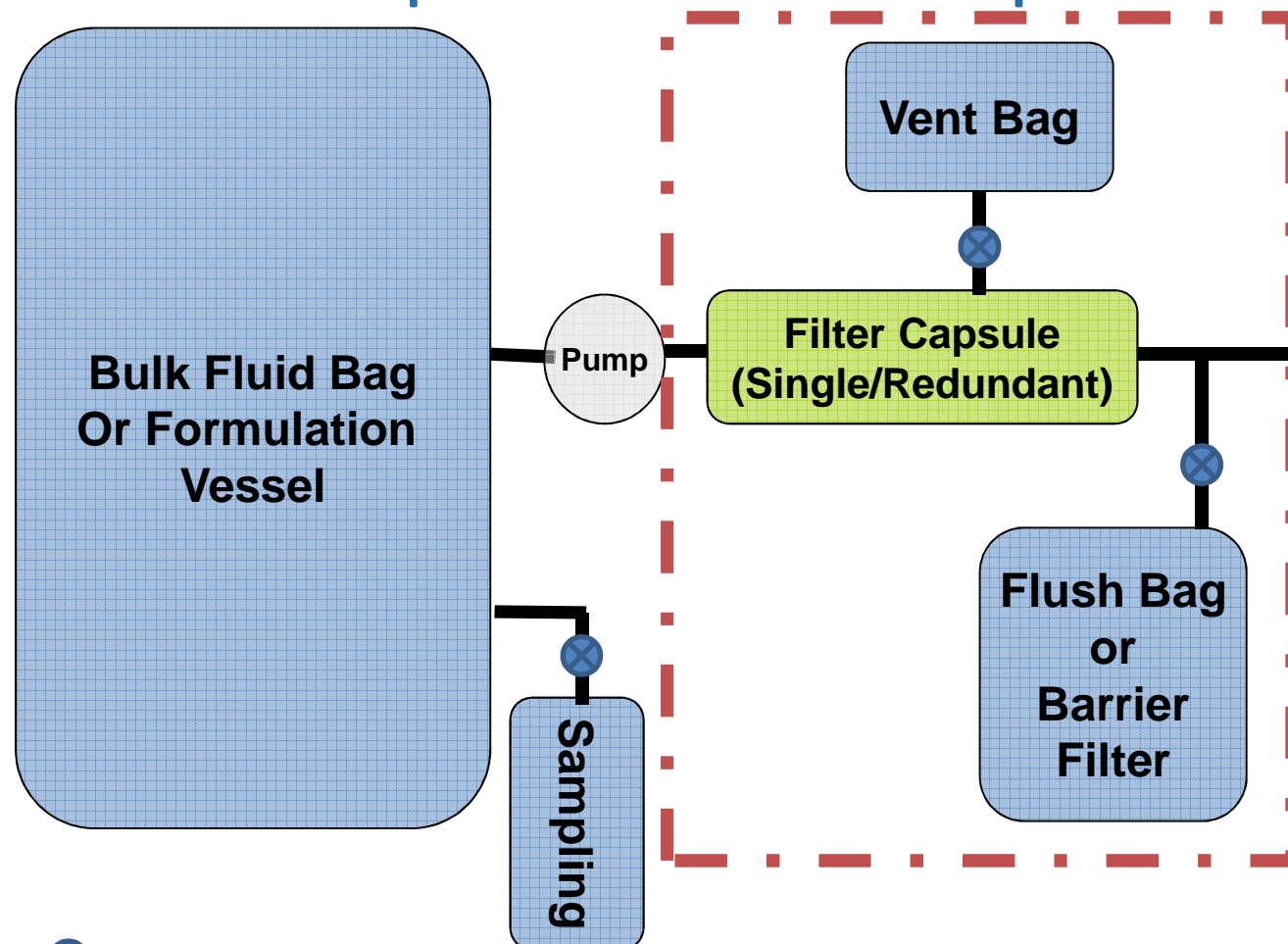
- Sterilization process compatibility
- Predictable extractables/leachables
- Low adsorption

Physical

- Robust connections
- Yield
 - Low hold-up
 - Stacked disk vs. pleated



Filter Capsule Module Options



⊗ Sterile disconnect

Process Design Considerations

Number of filters in system

- Single stage
- Dual stage
- Redundant

Filter integrity testing

- Pre-use testing

Flushing

- Flush bag or barrier filter

Filters in or out of isolator

Product Recovery

- Blow down through filter
- Downstream blow down

Regulatory Guidance – Redundant Filters

FDA Aseptic Processing guidelines, 2004

“Use of redundant sterilizing filters should be considered in many cases”

Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. U.S. Department of Health and Human Services Food and Drug Administration. September 2004. Pharmaceutical CGMPs

EMA Annex 1, 2008

“Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.”

EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1. Manufacture of Sterile Medicinal Products. EUROPEAN COMMISSION. Brussels, 25 November 2008

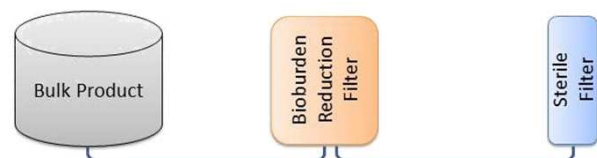
There are a variety of final filter set-ups in use



Single filter:

Sterile Filtration

- Minimum hold-up volume
- Minimum flushing requirements
- Ease of handling and operation
- Lower filter cost
- No back-up in the event of primary filter failure
- Feed bioburden control
- Filter plugging



Dual filter:

Bioburden / Sterile Filtration

- Feed bioburden control
- Very low plugging risk for primary filter
- No back-up in the event of primary filter failure
- Higher hold up
- Higher cost
- Higher system complexity



Sterile – Hold - Sterile Filtration



Redundant Sterile Filtration

- Feed bioburden control
- Very low plugging risk for primary filter
- Potential batch recovery if one filter fails IT
- Higher hold up
- Higher cost
- Highest system complexity

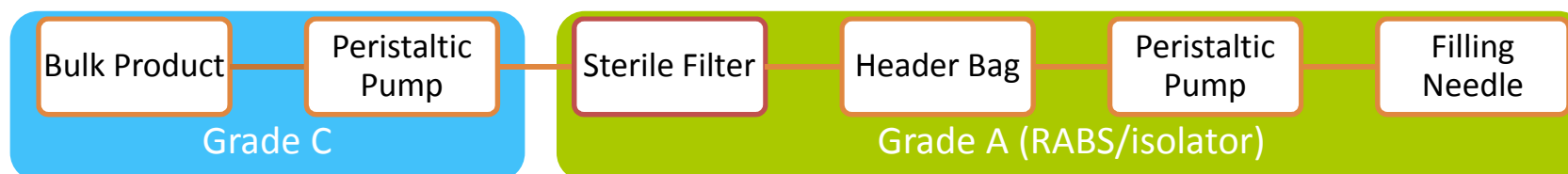
There is no one common filling set up, you design systems that are appropriate for your process based on your risk/benefits considerations

Single v. Dual v. Redundant Risk Considerations

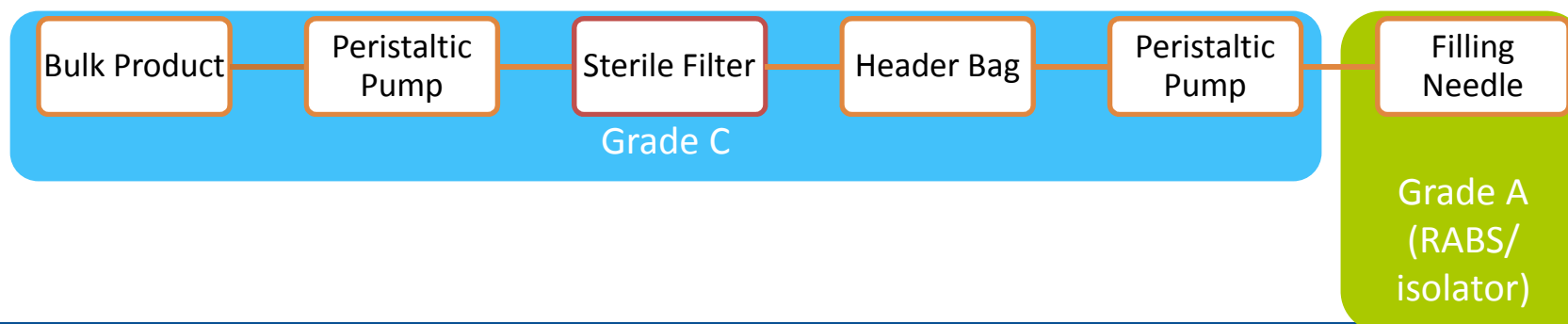
- Product value
 - Batch value if scrapped
 - Re-processing costs if possible
 - Losses due to system hold-up
 - Losses due to adsorption
- Integrity failure history
- Internal Quality or Regulatory Affairs perspective
- Feed bioburden control
 - EU guideline - NMT10 cfu/100ml
- Operations and handling
 - More parts and manipulations = greater risk of contamination

Filter In or Out of the Isolator

- Filter in Grade A / ISO 5 / Class 100
 - **Complete SUS** must be transferred to Grade A

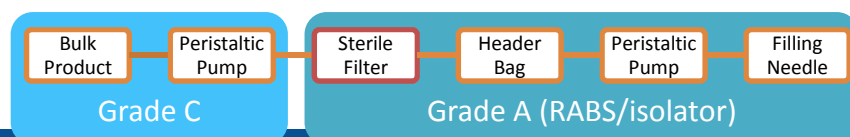
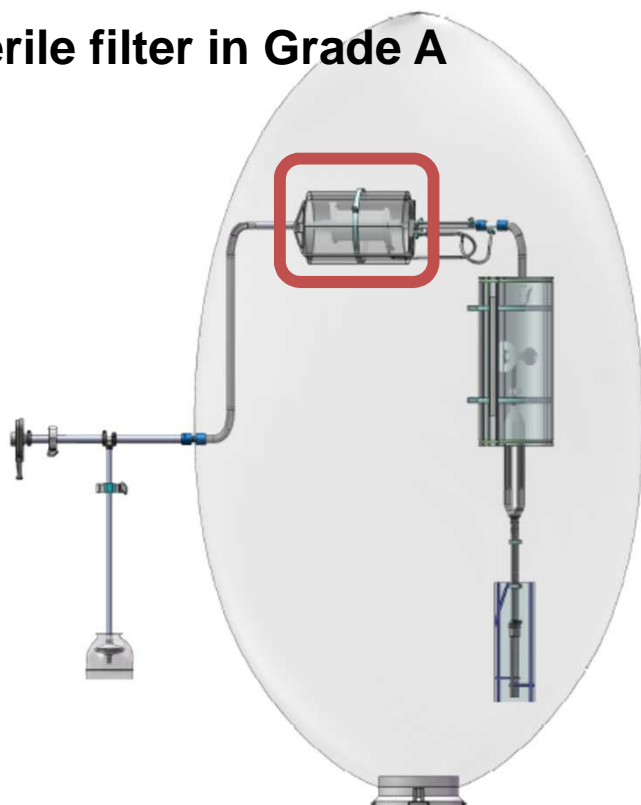


- Filter in Grade C / ISO 7 / Class 10,000
 - **Only filling needles** transferred to Grade A

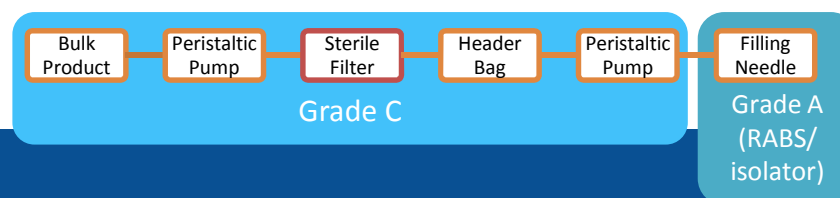
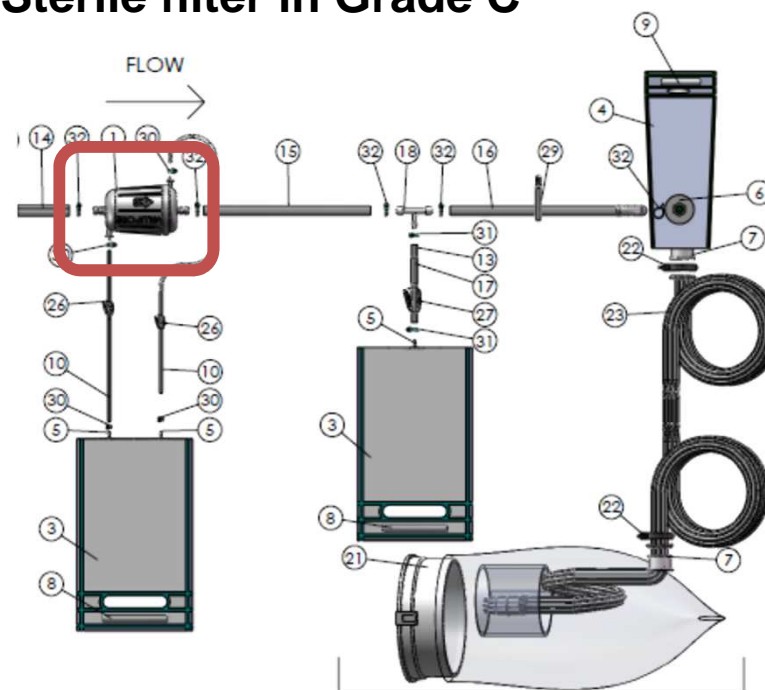


Example of Sterile Filter Placement

Sterile filter in Grade A



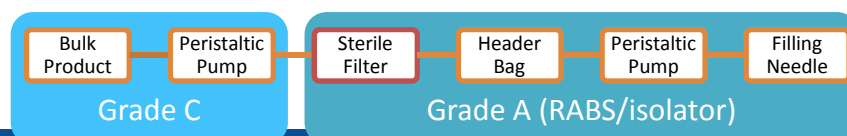
Sterile filter in Grade C



Filter Placement

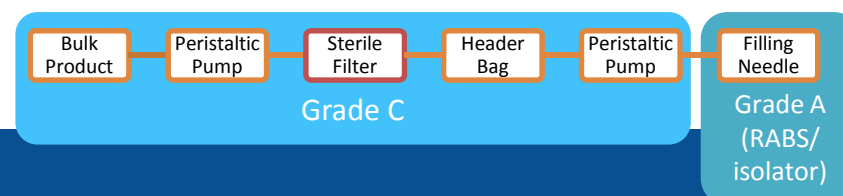
Sterile filter in Grade A

- Low risk to fluid path contamination
 - Open vents
 - Connections
- Sterile environment risk from vented liquid
- Handling challenges
 - Large number of components to transfer
 - Pre-use integrity testing challenge



Sterile filter in Grade C

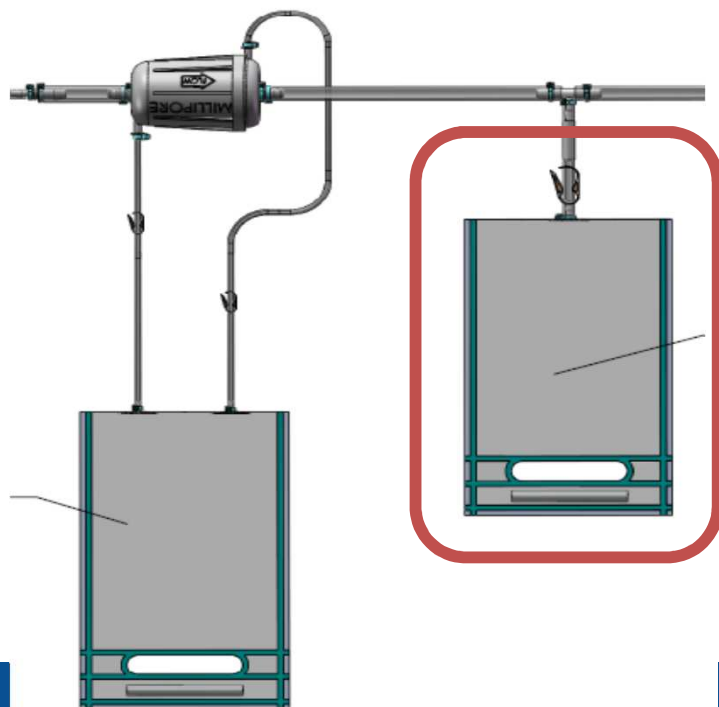
- Easier manipulations
 - Installation
 - Flushing
 - Integrity testing
 - Venting
 - Pump tubing adjustment
- Potential to replace filter if integrity fails
- More potential points for ingress
- Demonstration of assembly integrity more critical



Flushing

Flush bag

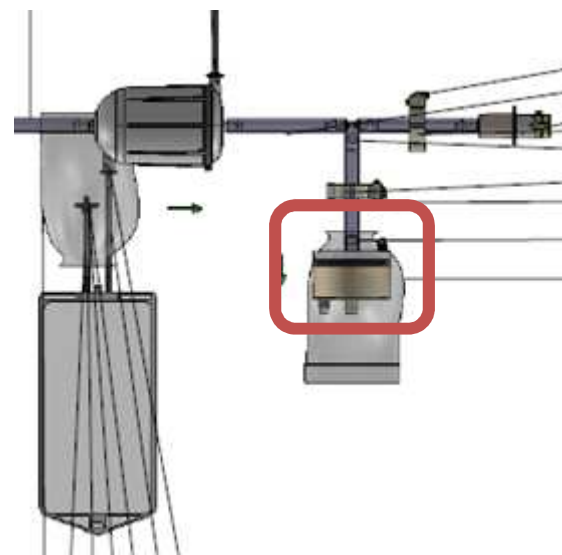
- Minimize materials
- Minimize cost
- Must vent to integrity test
- Flush volume limited
- Bag pressure limit – control critical



Compressing, Mixing, Solvents and Reg

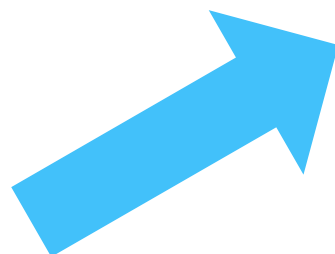
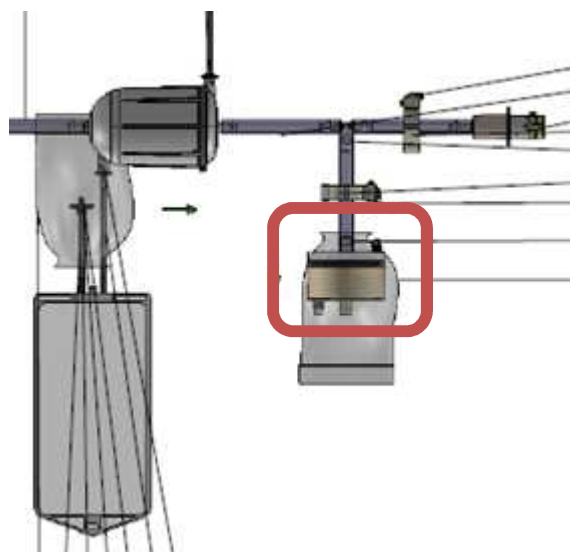
Barrier filter

- Unlimited flush volume
- Facilitate integrity test
- Facilitate blow-down
- Integrity testable
- Need to integrity test (Prior to processing)



Millipak® Barrier Filter

Post sterilization integrity testing is simplified with the **Millipak® Barrier** filter which allows the sterile flow of **liquid** and **gas**



Liquid
Wetting and flushing fluids
evacuate to drain



Gas
Air from integrity test and
blowdown can vent from
same filter

Sterile Filter Integrity Testing

- Post-use test is requirement from all geographies
- Pre-use test for single-use-system is de facto post-sterilization
- FDA expects end-user to define need for pre-use test
- EMA guidance states post-sterilization/pre-use test is required
 - Inconsistent enforcement
 - Filter healing is most common reason given

Regulatory Guidance – Filter Integrity Testing

FDA Aseptic Processing guidelines, 2004

- “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.”

Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. U.S. Department of Health and Human Services Food and Drug Administration. September 2004. Pharmaceutical CGMPs

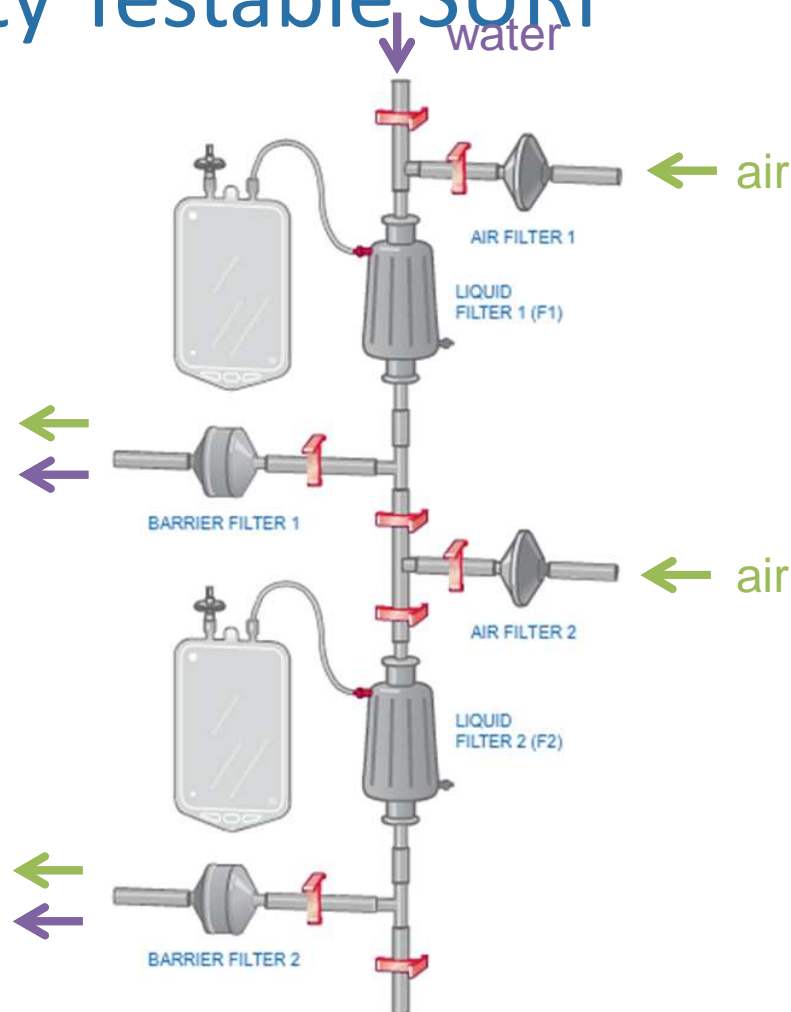
EMA Annex 1, 2008

“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.”

EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1. Manufacture of Sterile Medicinal Products. EUROPEAN COMMISSION. Brussels, 25 November 2008

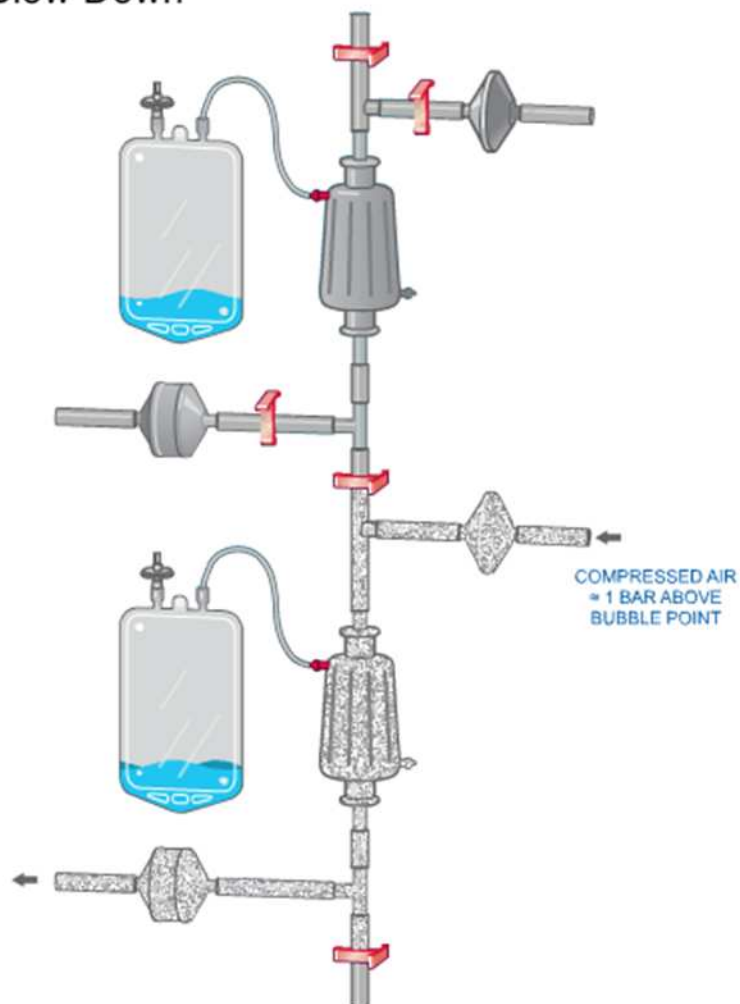
Filter Options: Integrity Testable SURF

- **Practical Challenges of Preuse Test on Sterile System**
- Remove . . .
 - Wetting Liquid
 - Test Gas
- Maintain downstream
 - Sterility
 - Atmospheric pressure (test)



Pre-use Integrity Testing with Barrier Filter

Filter Blow Down



To Test or Not To Test

Pre-use Test

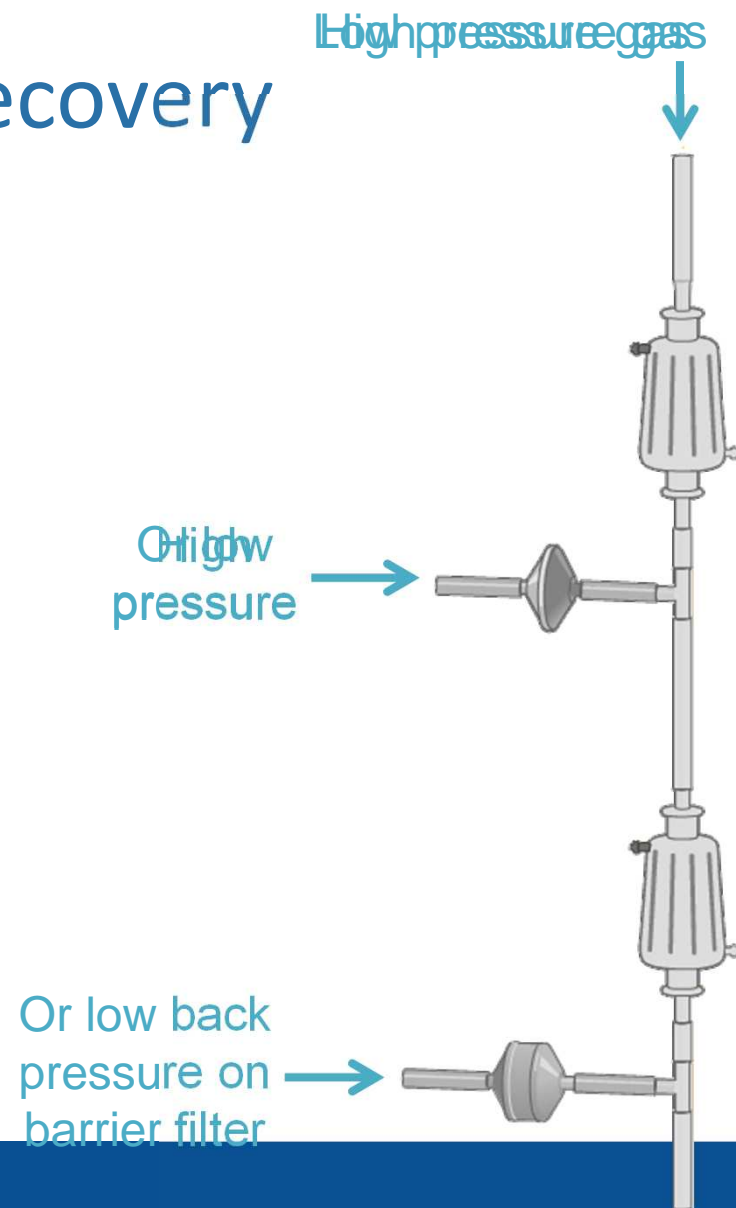
- + Identify filter damage from shipping, handling, installation
- + Protect from enforcement inconsistencies
- Requires manipulations on sterile side of filter
- Contamination introduced during testing would be very difficult to identify

No Pre-use Test

- + Lower risk to downstream sterility
- + Easier operation
- + Testing cost savings
- Filter damage not identified until product is filled
 - Likely loss of batch

Post Process Product Recovery

- During processing the entire system is flooded, including filter upstream and downstream.
- At the end of the process, product volume upstream of the first filter is easily recovered by gas displacement
- But gas will not pass through the wet membrane below the bubble point pressure and so product is held up in the core of the first filter all the way through to the final dispense
- Introducing gas to displace downstream liquid requires either exceeding the bubble point with high pressure upstream, or aseptically introducing gas downstream



Post Process Product Recovery

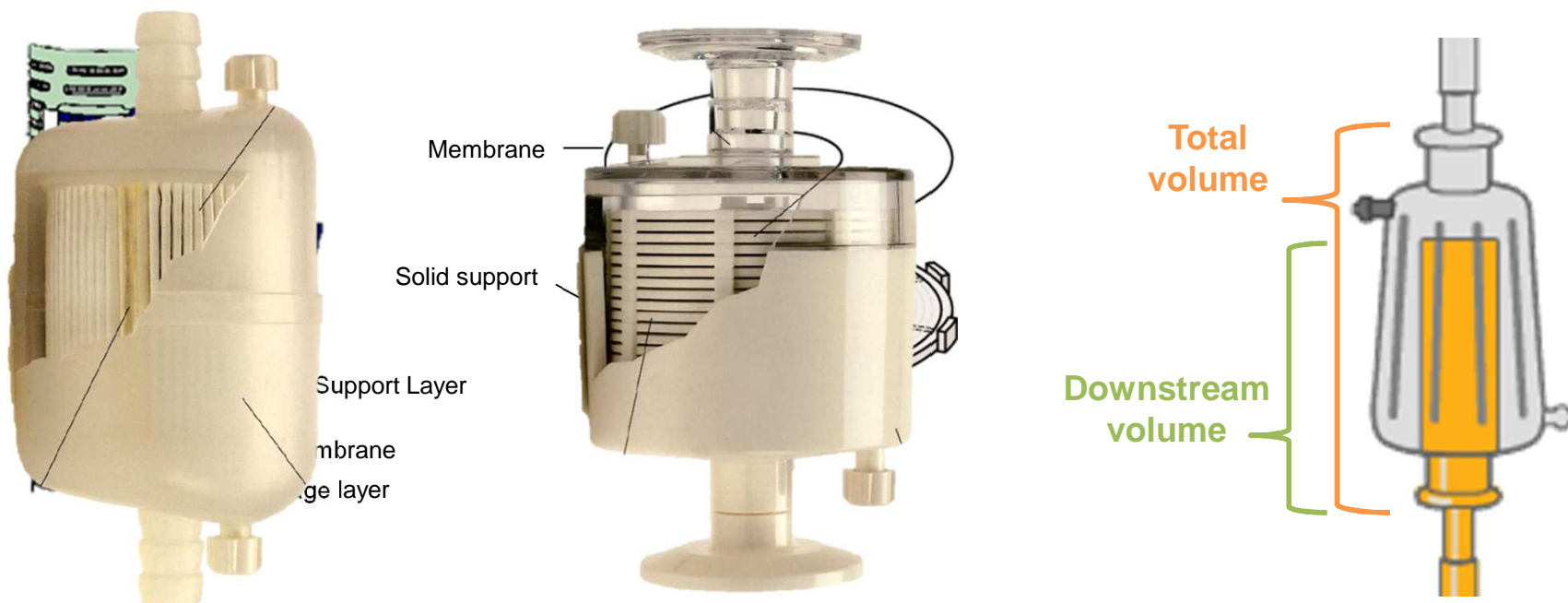
Blow-down through final filter
(Exceed filter bubble point > 50 psi)

- + No added downstream fittings
- + No downstream manipulations
- Requires proper validation
- Risks product foaming
- Downstream component pressure limits

Blow-down after final filter
(Air introduced downstream)

- + Low pressure
- + Low shear/foaming
- + No added filter validation concern
- Requires sterile gas filter
 - That will require testing
- Requires downstream fittings and manipulations

Maximizing yield



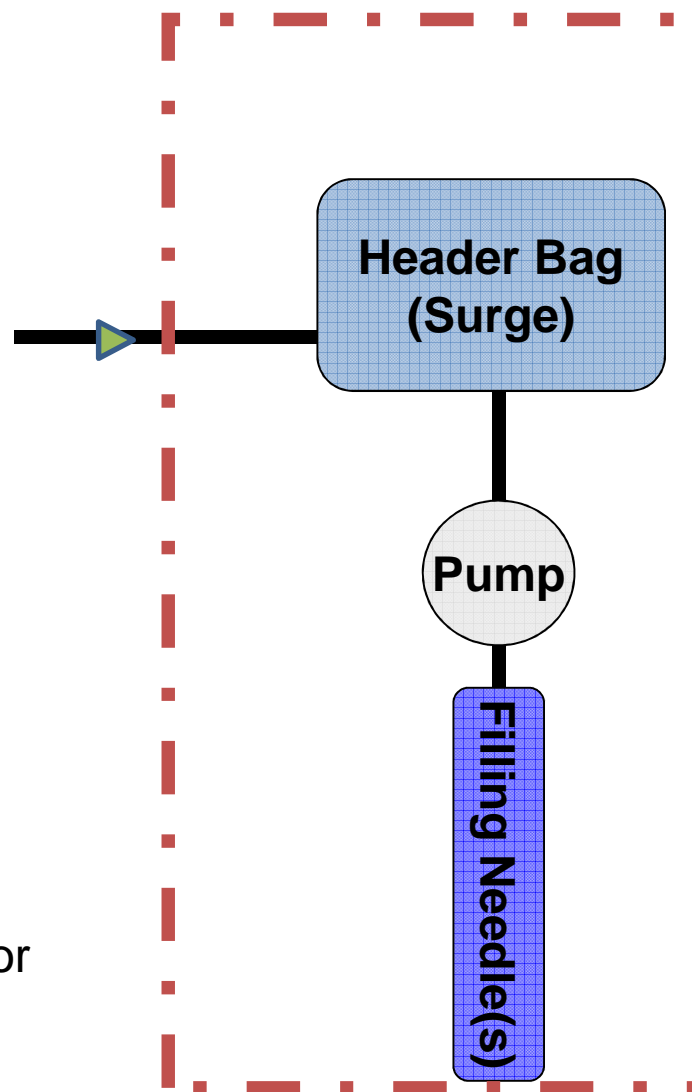
	EFA	Total volume (mL)	Downstream volume (mL)	Hold up volume (mL)
Millipak® 20 filter	100 cm ²	30	4	1
Millipak® 200 filter	1,000 cm ²	130	40	9
Opticap® XL 2 capsule	900 cm ²	225	30	15

Filling

Key Needs

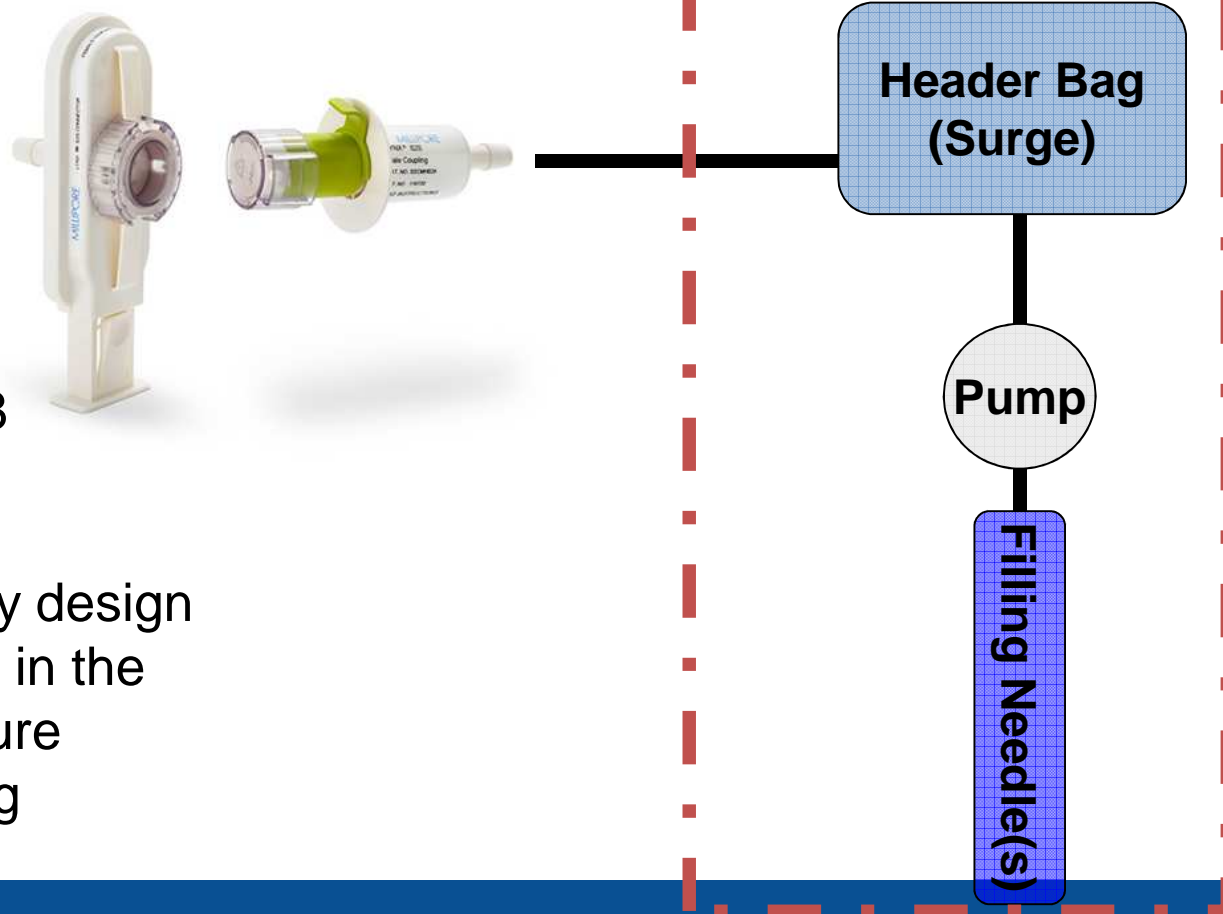
- Sterility Assurance
- Dosing Accuracy
- Product Recovery

► Sterile connector



Making Sterile Connections

- Testing to USP 788
- Sterility validation
- Closed flow path
- Simplifies assembly design
- Increases flexibility in the event of a filter failure
- Isolates header bag

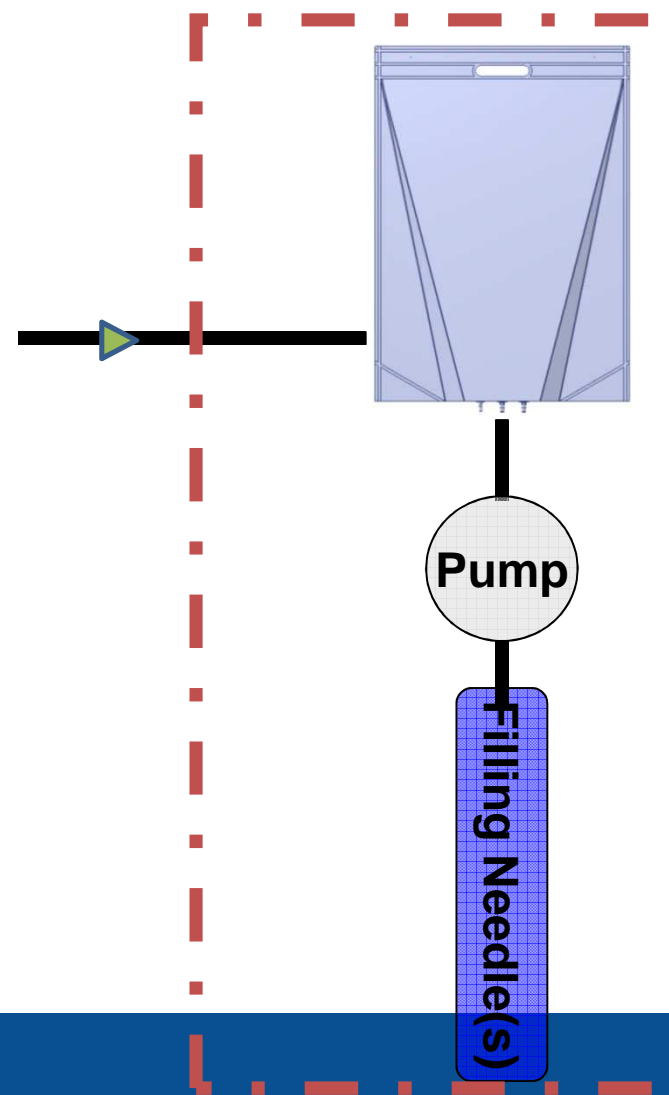


2-D Header (Surge) Bag

- The header bag is used for level control to create constant inlet conditions.
 - Vent filter not required
- Side inlet port and bottom outlet port design for maximum product recovery
- 2-D design allows for restrained plate integrity test prior to manufacturing release

▶ Sterile connector

Filling

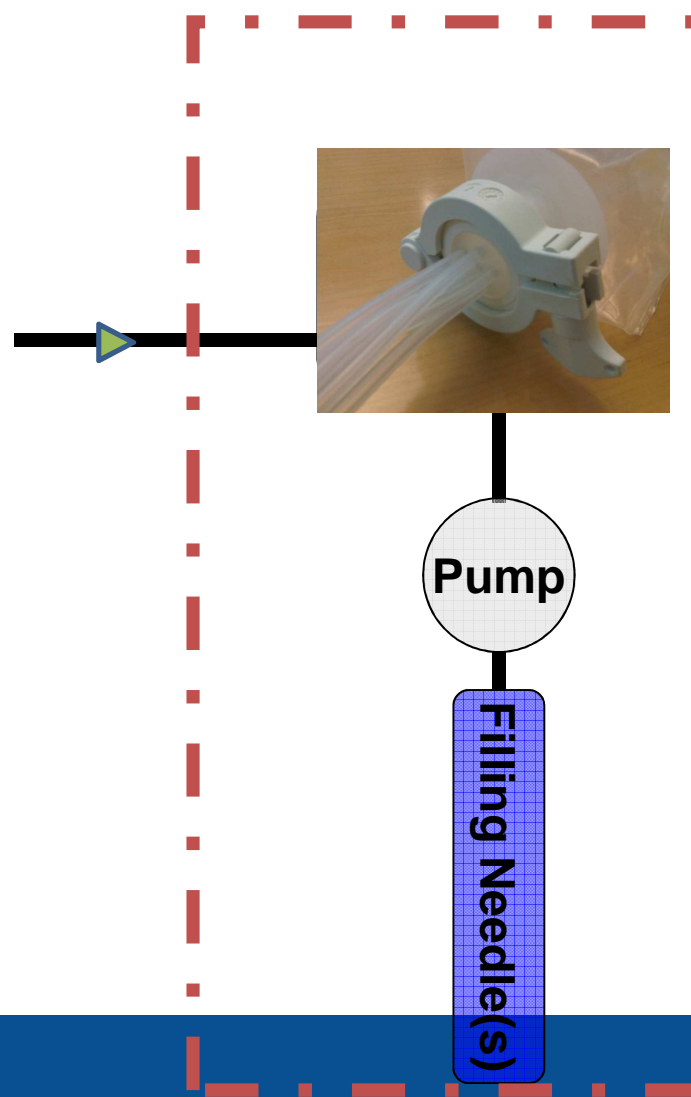


Tubing Manifold

- Overmolded technology
 - Minimizes tubing/fitting connections
 - Decreases air entrainment in lines
 - Provides uniform flow distribution to all filling needles for fill volume accuracy and repeatability
- Available in a range of tubing sizes (ID/OD), lengths, and number of filling needles
- Maximized product recovery when combined with the header bag design

► Sterile connector

Filling



Filling Needles

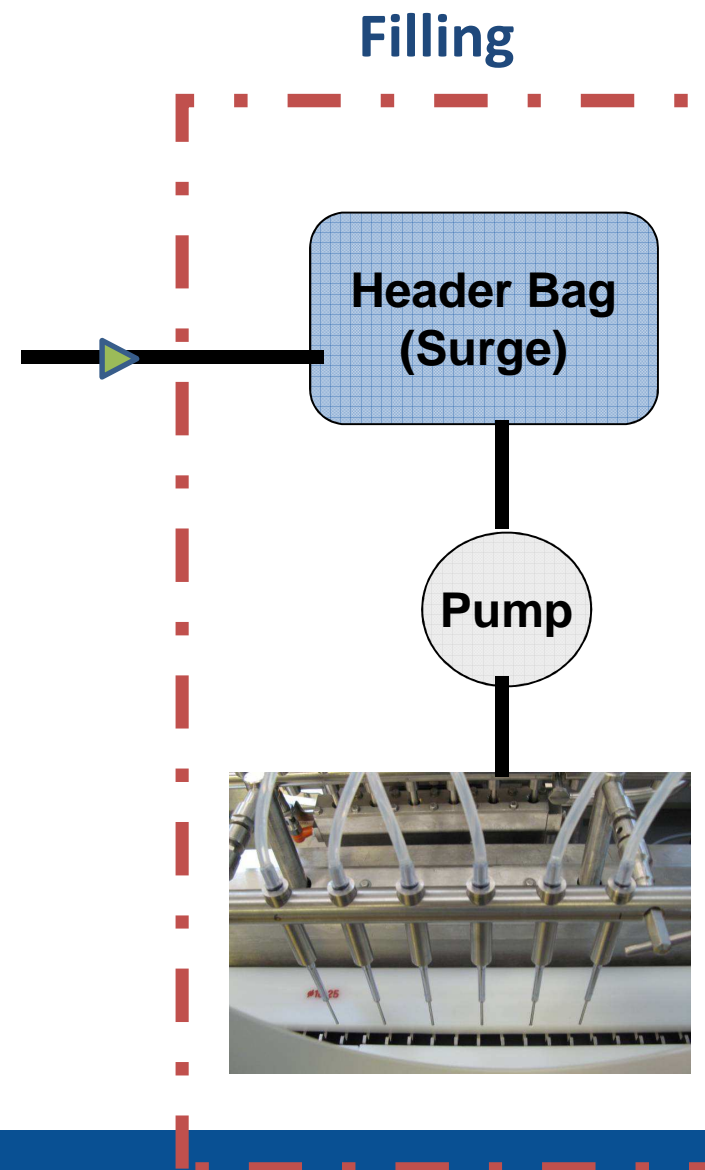
With a peristaltic pump, dosing accuracy is a function of tubing and needle type.

Filling needles are available to meet the equipment manufacturer's requirements in a range of sizes including 1.2mm to 8mm.

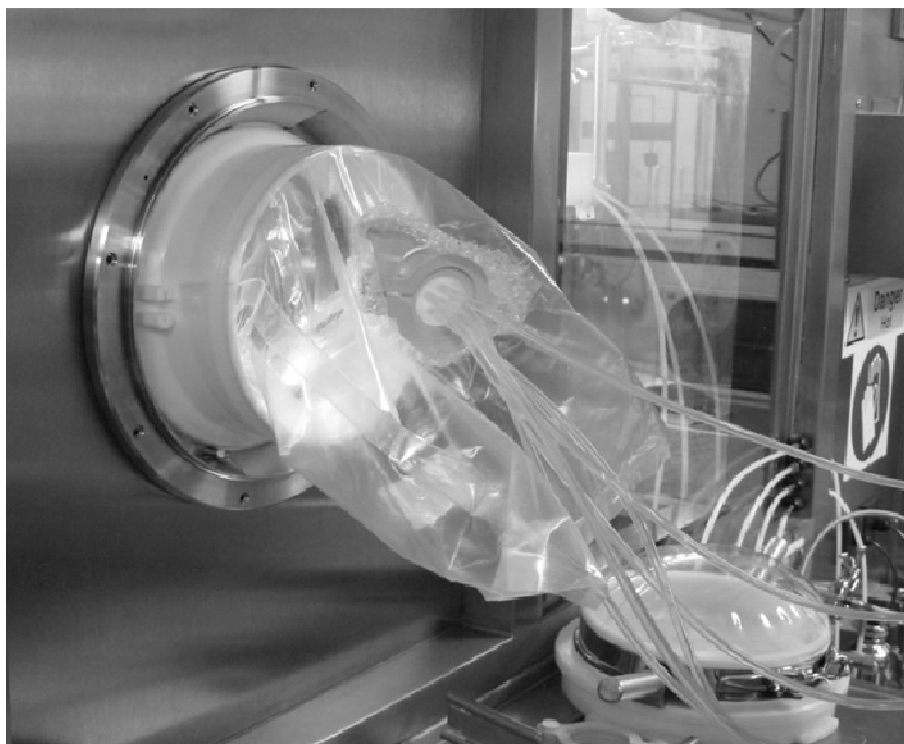
For example:

- Groninger
- Bosch
- Others (including plastic)

► Sterile connector



Isolator Interface with Getinge DPTE® Beta Bag



Ability to interface with an isolator while maintaining sterility

Thank you!

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