Advancements on implementation of single use technology in vaccine manufacturing

October 25th, 2013

DCVMN Meeting
Rio de Janeiro, Brazil

Outline

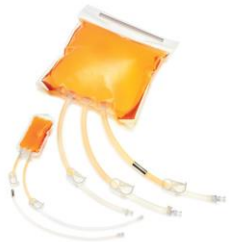
Overview of single use products

Applications of single use technology in vaccine manufacturing

Validation of single use systems

Overview of SU Products

- SU products
  - Single use containers or bags for storage and sampling
  - Filter assemblies with tubing (silicone and /or C-Flex)
  - Non-sterile and sterile connectors
  - Disposable mixing system for solution preparation and formulation
  - Final filtration assemblies for final filling
  - Single use systems



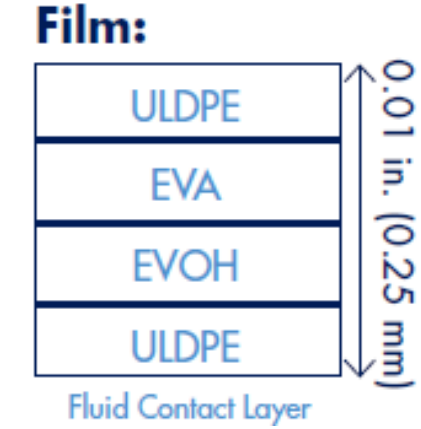
Film Technology

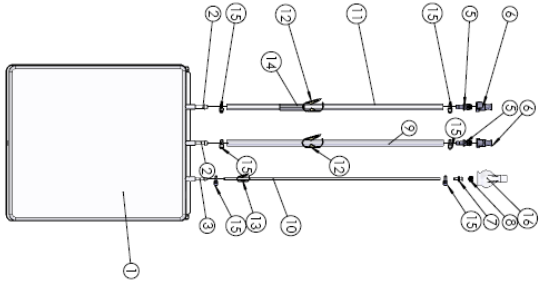
Typical 2D Bag Subassemblies

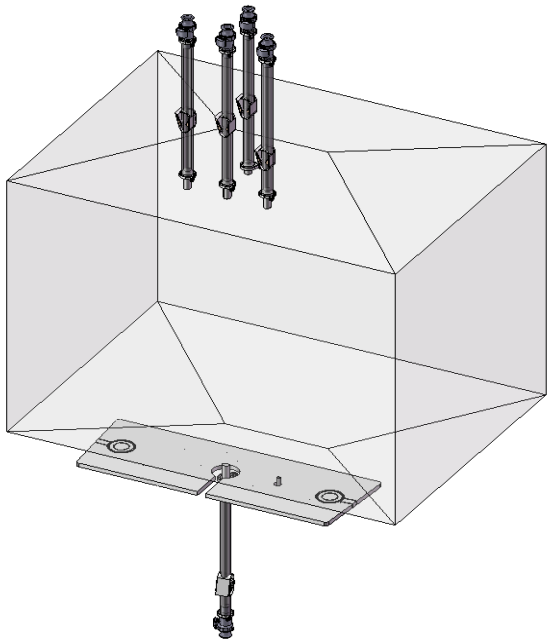
- 50mL to 50L

Typical 3D Bag Subassemblies

- 100L to 3500L for any bins
- Hand free filling available







Sterile connectors
Description & functionality

What it is:

Single-use sterile connector made with

1 female coupling + 1 male coupling part

What it does:

An operator independent, sterile connection between

γ-sterilized assembly + γ-sterilized assembly

γ-sterilized assembly + Autoclaved assembly

Autoclaved assembly + Autoclaved assembly

… in any environment !

Note : γ is Gamma

SU mixing systems and mix bags

Wide range of sizes (10/50/100/200/500/1000 L)

- Levitating, magnetically driven impeller
- Configurable bag assemblies

Electronic drive unit and motor

- Portable & removable
- Interchangeable
- Multiple carrier options
- PE, SS, Jacketed SS, Load Cells
- Stable & Mobile

Sampling system

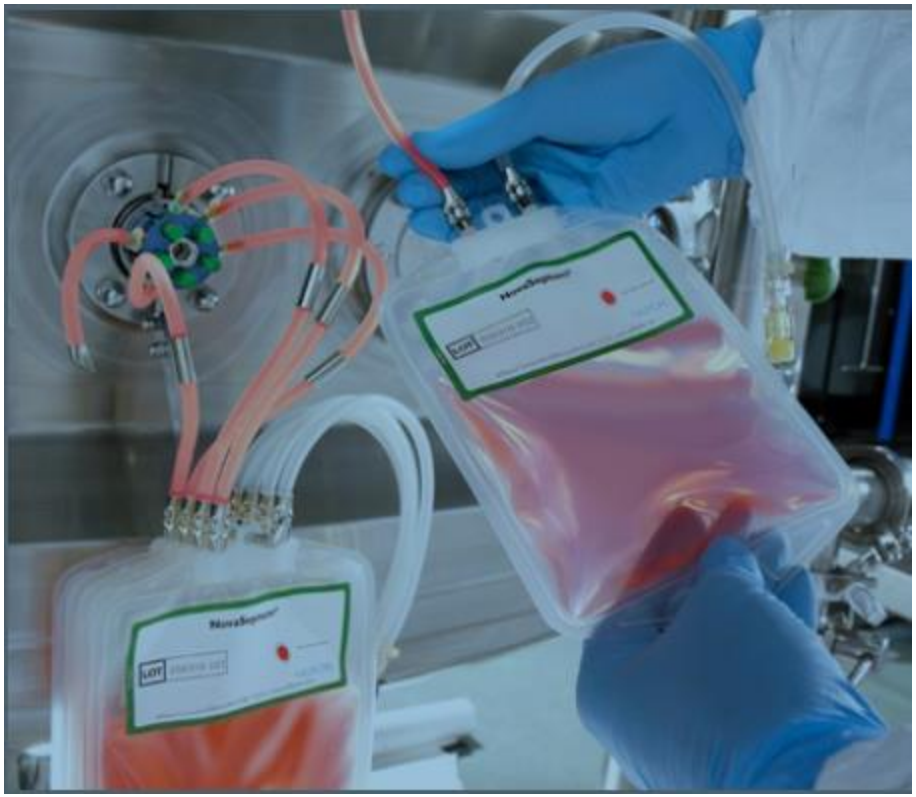
Increased sampling productivity, while reducing set-up, cleaning and flushing time

Traditional Sampling Method

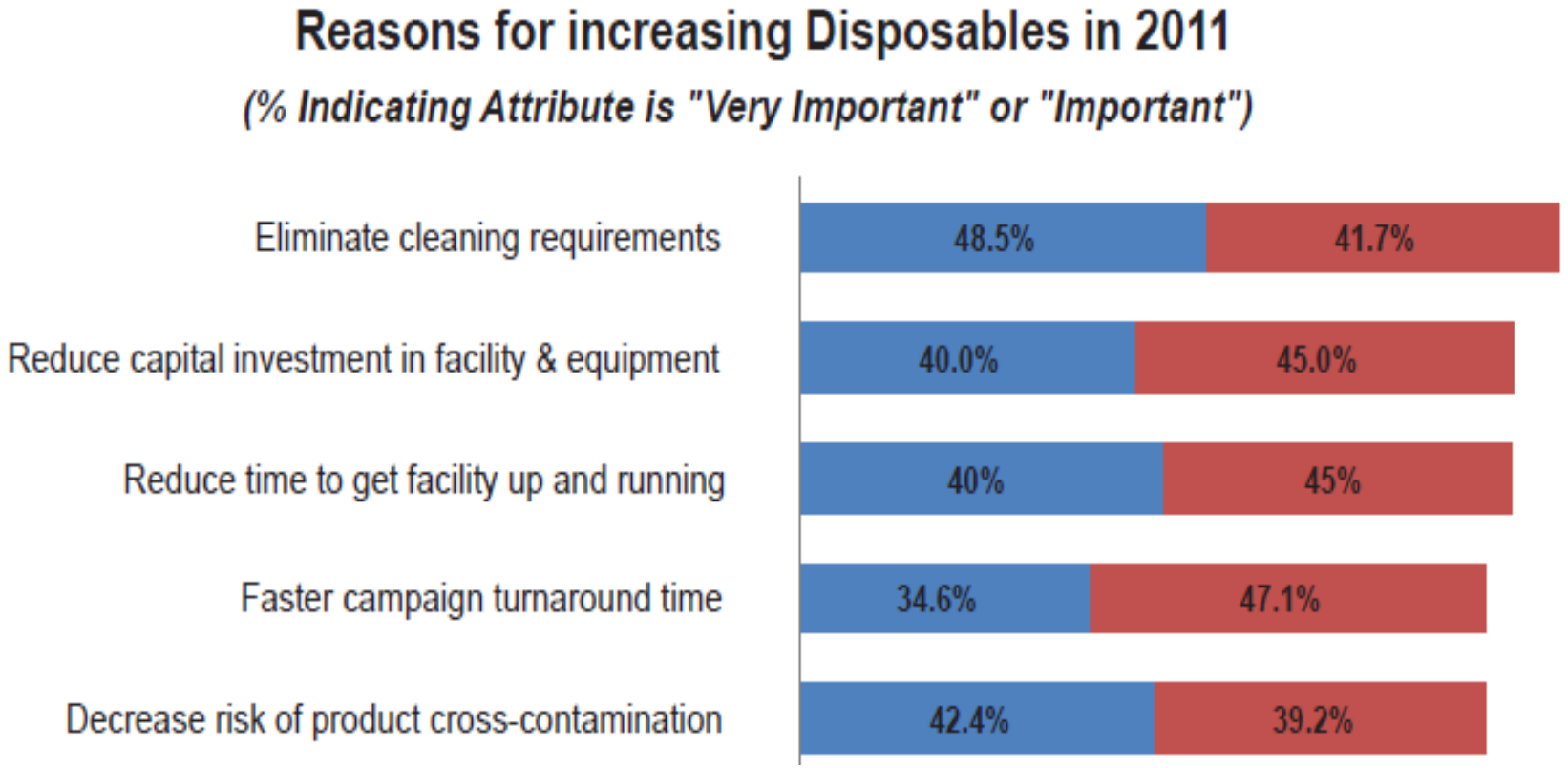
- Lengthy CIP/SIP with each sample
- Additional steps over and over again

Sampling with Millipore

- Only one SIP
- Push to sample
- Separate & crimp
- One to 45 samples at once
- Unlimited possibilities



Increasing Use of Single-use systems



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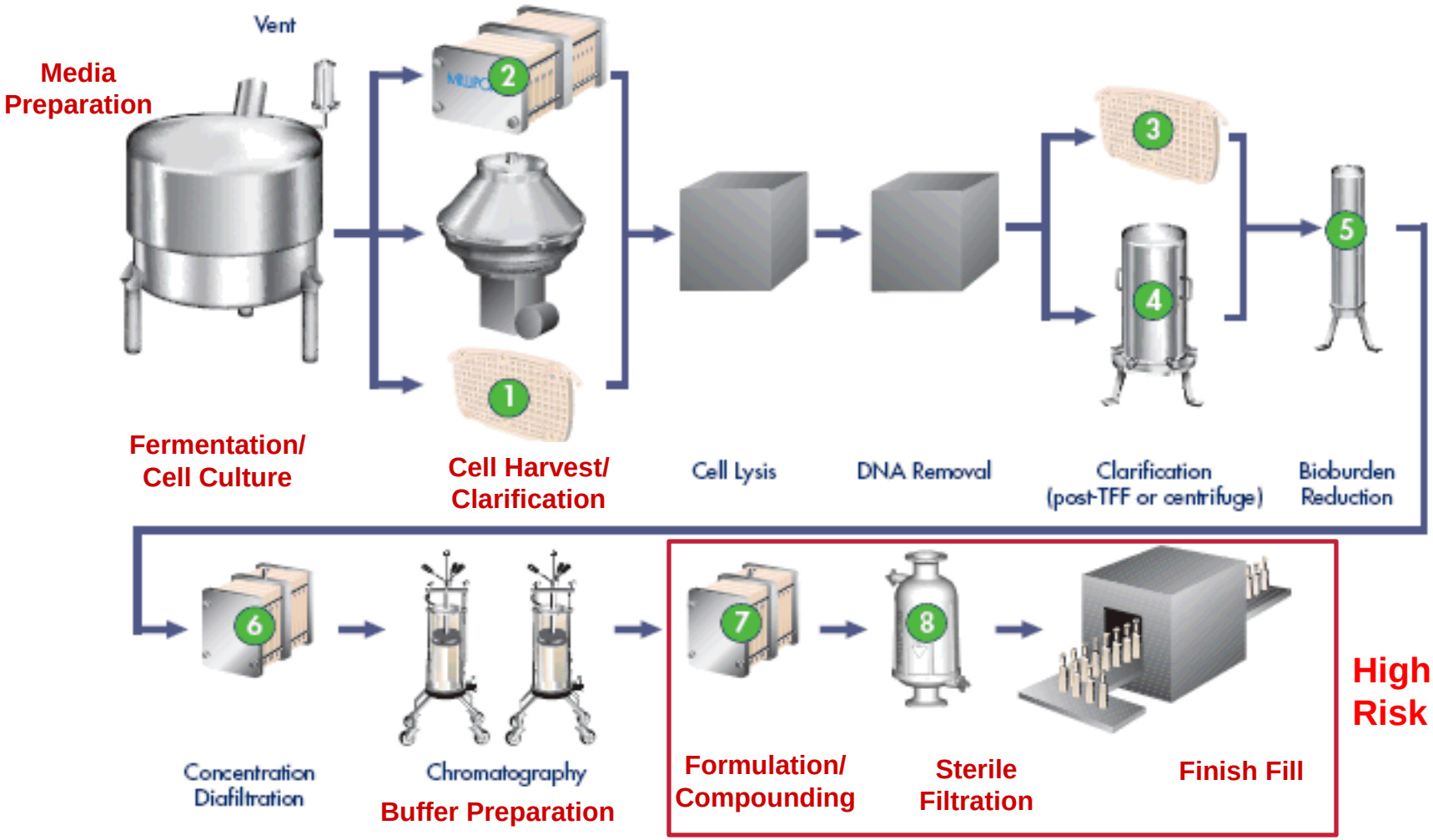
Single use technology in Vaccine Manufacturing

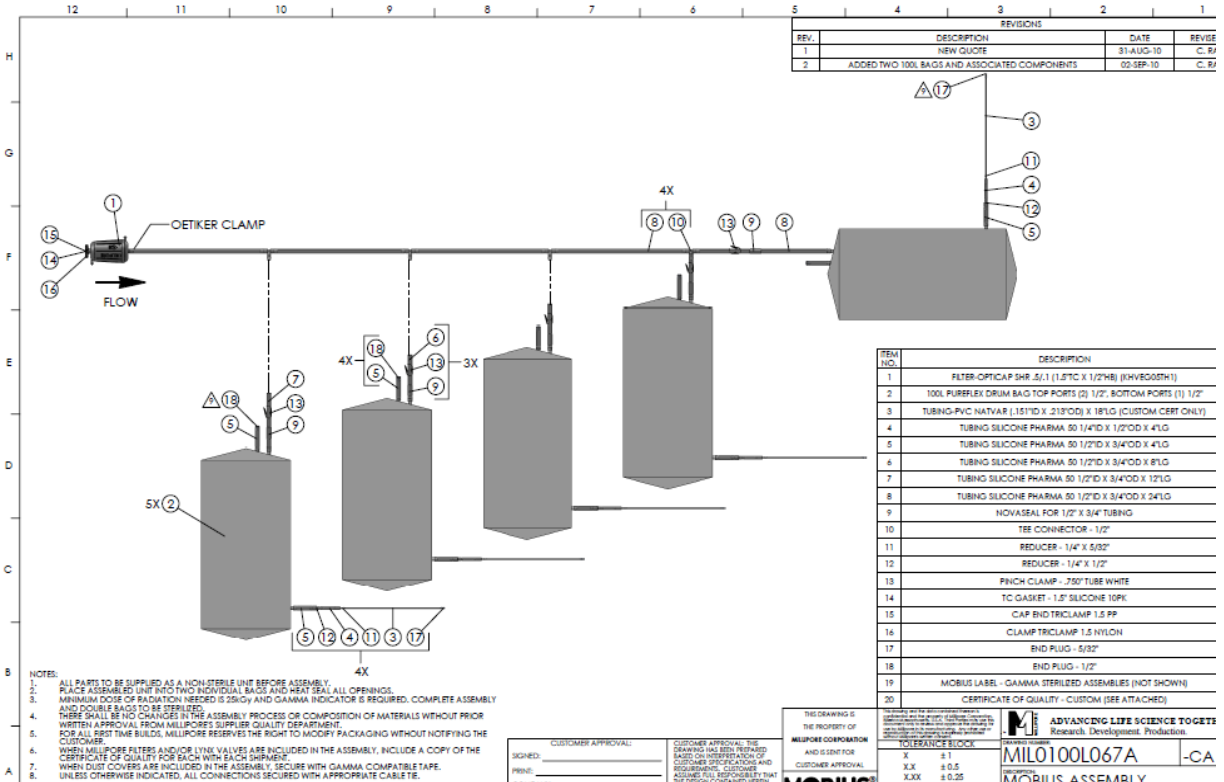


Media/Buffer Preparation

Use of disposable mixing systems with liners or bags.

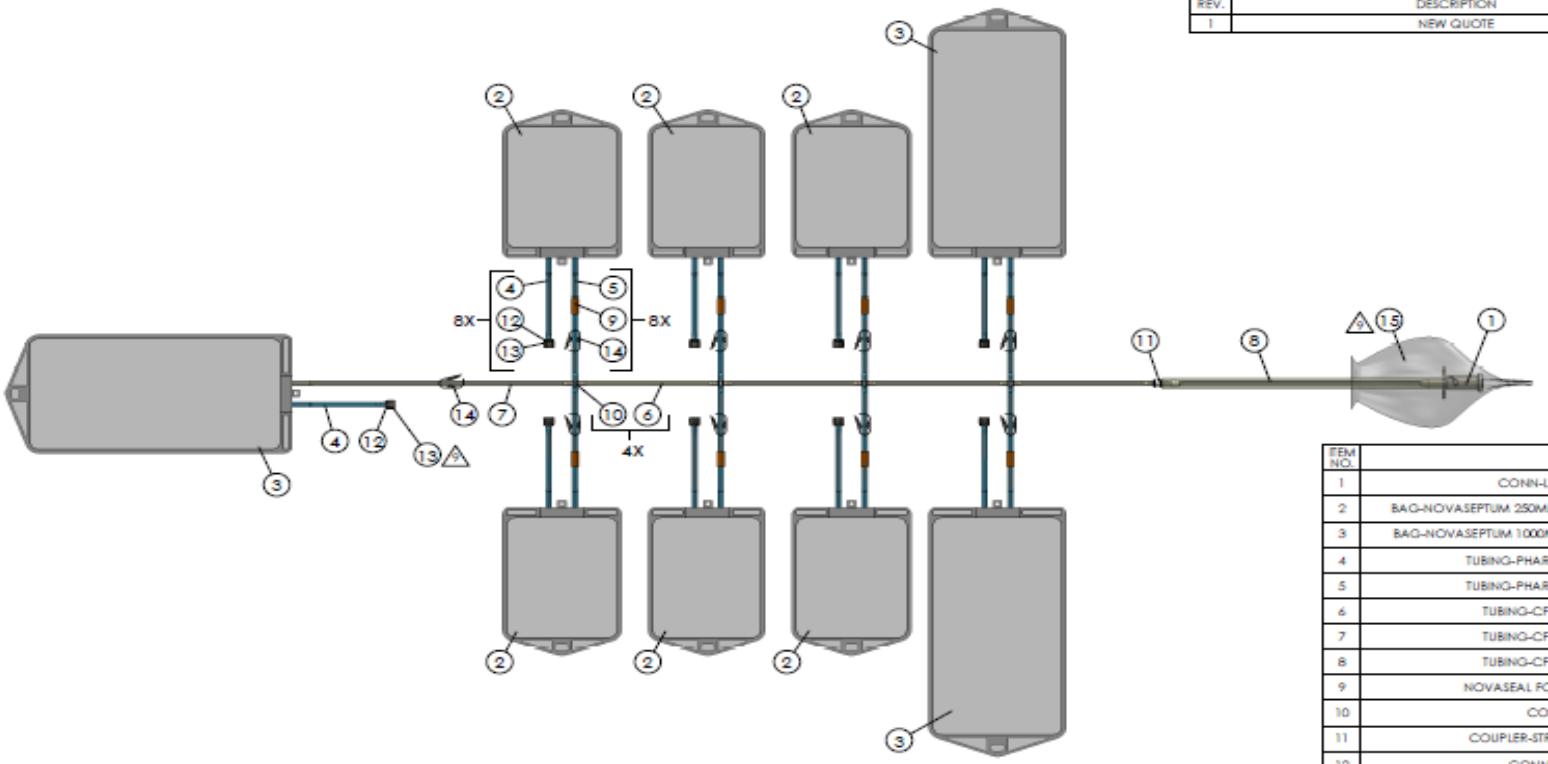
Bag with filter assemblies

Media addition assemblies



Transfer lines and manifolds

Sterile sampling from SST bioreactors



REVISIONS

REV.	DESCRIPTION	DATE	REVISED BY
1	NEW QUOTE	12-MAY-11	C. RAYE

ITEM NO.	DESCRIPTION	LG	QTY.
1	CONN-LYNX ST 1/4"HB X 3/4"TC		1
2	BAG-NOVASEPTUM 250ML (5.12"W X 7.3"H) END-PORTED (2 X 1/8")		6
3	BAG-NOVASEPTUM 1000ML (6"W X 12.3"H) END-PORTED (2 X 1/8")		3
4	TUBING-PHARMA 65 (3mm ID X 6mm OD)	4	9
5	TUBING-PHARMA 65 (3mm ID X 6mm OD)	6	8
6	TUBING-CFLEX 374 (1/8"ID X 1/4"OD)	6	4
7	TUBING-CFLEX 374 (1/8"ID X 1/4"OD)	12	1
8	TUBING-CFLEX 374 (1/4"ID X 1/2"OD)	12	1
9	NOVASEAL FOR 3MMID X 6MMOD TUBING		8
10	COUPLER-CROSS 1/8"		4
11	COUPLER-STRAIGHT REDUCER 1/4" X 1/8"		1
12	CONN-LUER FEMALE 1/8"HB		9
13	CAP-LUER MALE KYNAR		9
14	CLAMP-PINCH 1/2" (6MM-1/8"OD TO 3/8"OD TUBE)		9
15	DUST COVER 6" X 6"		1
16	CERTIFICATE OF QUALITY - SILVER (NOT SHOWN)		3
17	LABEL - GAMMA STERILIZED ASSEMBLIES (NOT SHOWN)		3

NOTES:
1. ALL PARTS TO BE SUPPLIED AS A NON-STERILE UNIT BEFORE ASSEMBLY.
2. PLACE ASSEMBLED UNIT INTO TWO INDIVIDUAL BAGS AND HEAT SEAL ALL OPENINGS.
3. MINIMUM DOSE OF RADIATION NEEDED IS 25kGy AND GAMMA INDICATOR IS REQUIRED. COMPLETE ASSEMBLY AND DOUBLE BAGS TO BE STERILIZED.
4. THERE SHALL BE NO CHANGES IN THE ASSEMBLY PROCESS OR COMPOSITION OF MATERIALS WITHOUT PRIOR WRITTEN APPROVAL FROM MILLIPORE'S SUPPLIER QUALITY DEPARTMENT.
5. FOR ALL FIRST TIME BUILDS, MILLIPORE RESERVES THE RIGHT TO MODIFY PACKAGING WITHOUT NOTIFYING THE CUSTOMER.
6. WHEN MILLIPORE FILTERS AND/OR LYNX VALVES ARE INCLUDED IN THE ASSEMBLY, INCLUDE A COPY OF THE CERTIFICATE OF QUALITY FOR EACH WITH EACH SHIPMENT.
7. WHEN DUST COVERS ARE INCLUDED IN THE ASSEMBLY, SECURE WITH GAMMA COMPATIBLE TAPE.
8. UNLESS OTHERWISE INDICATED, ALL CONNECTIONS SECURED WITH APPROPRIATE OETIKER CLAMP.

⚠ ITEMS 13 AND 15 EXCLUDED FROM INTEGRITY TEST.

CUSTOMER APPROVAL:
SIGNED:
PRINT:
COMPANY:
DATE:

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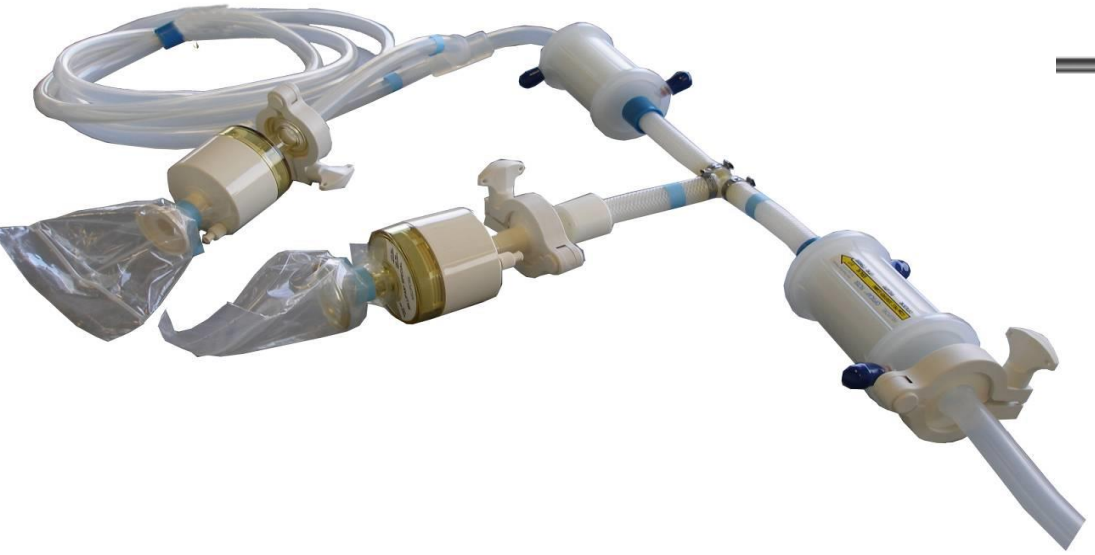
MOBIUS® by MILLIPORE

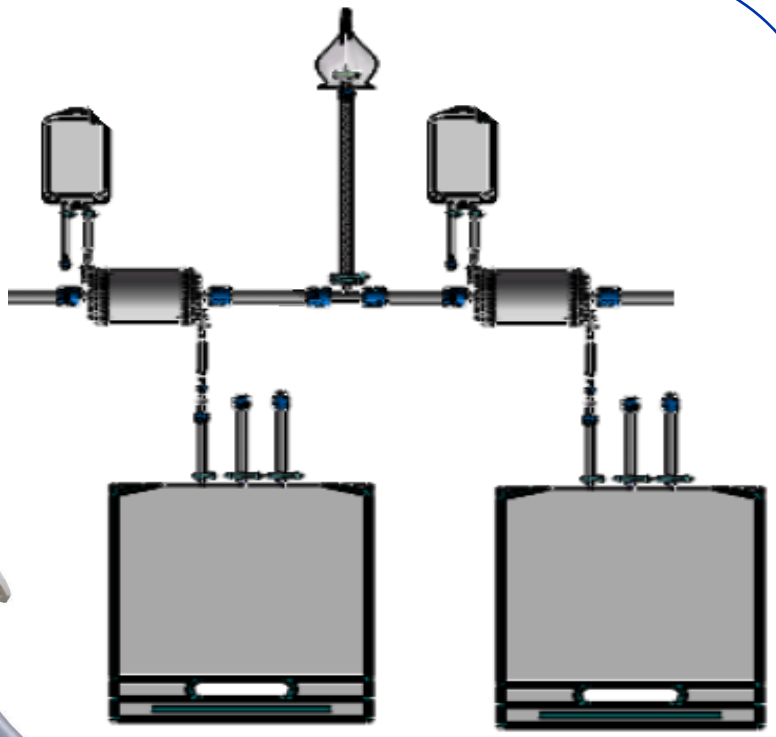
TOLERANCE BLOCK
X ± 1
X.X ± 0.5
X.XX ± 0.25
X.XXX ± 0.125
∠ ± 5°
ALL DIMENSIONS IN INCHES

ADVANCING LIFE SCIENCE TOGETHER®
Research. Development. Production.

DRAWING NUMBER: MCA0001L959A -CA REV: 1
DESCRIPTION: MOBIUS ASSEMBLY
DRAWN BY: C. RAYE | SHEET SIZE: B | SCALE: NTS | LOCATION: L | DATE: 12-MAY-11 | SHEET: 1 of 1

Sterile Filtration



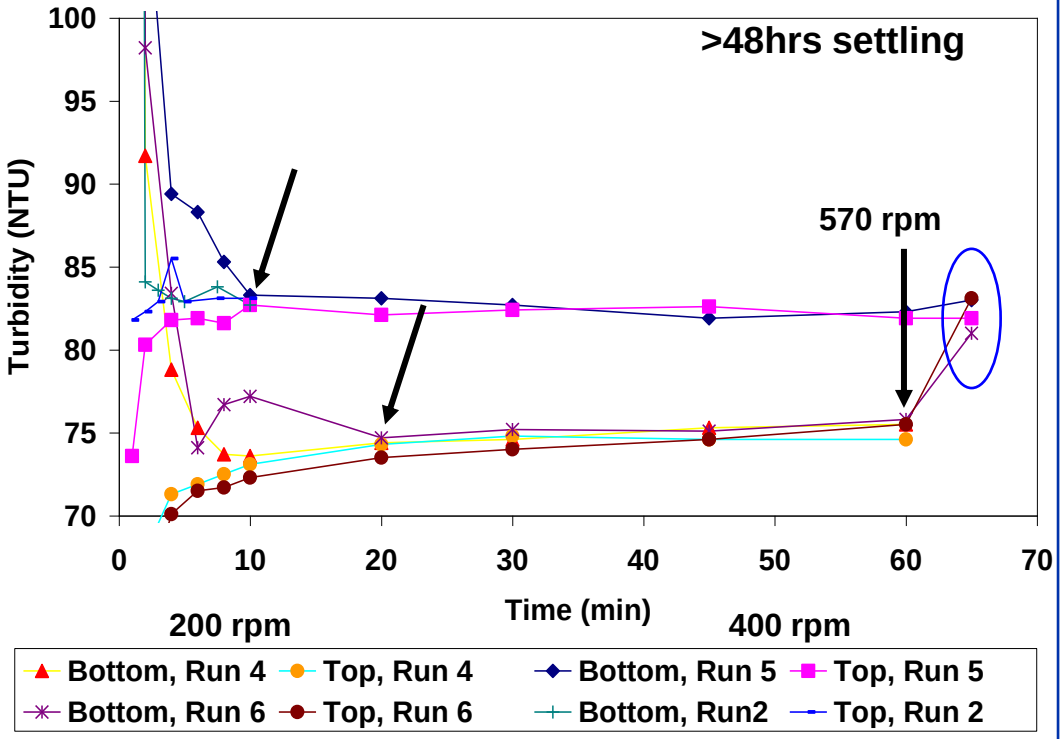


- Sterilizing filters for air filtration during integrity testing
- Flush bags and bags on vent/drain (operator safety)
- Gamma-irradiated single-use assembly (efficiency)
- Optimized hardware (ease of use)

Formulation and bulk preparation

Mixing, transfer and storage

Aseptic Alum Mixing Using Disposable Mixer



Final Formulation Filling Challenges

Limited Flexibility

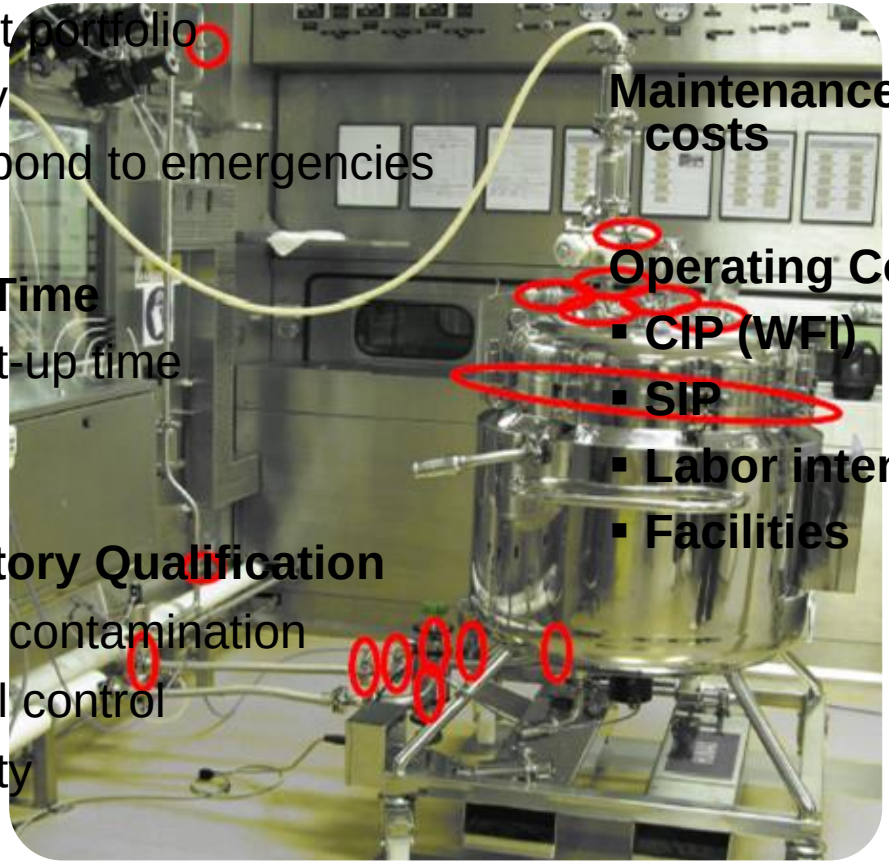
- Varied product portfolio
- Fixed capacity
- Unable to respond to emergencies

Long Change-out Time

- Equipment set-up time
- CIP/SIP

Increasing Regulatory Qualification

- Product cross contamination
- Environmental control
- Operator safety



High capital equipment

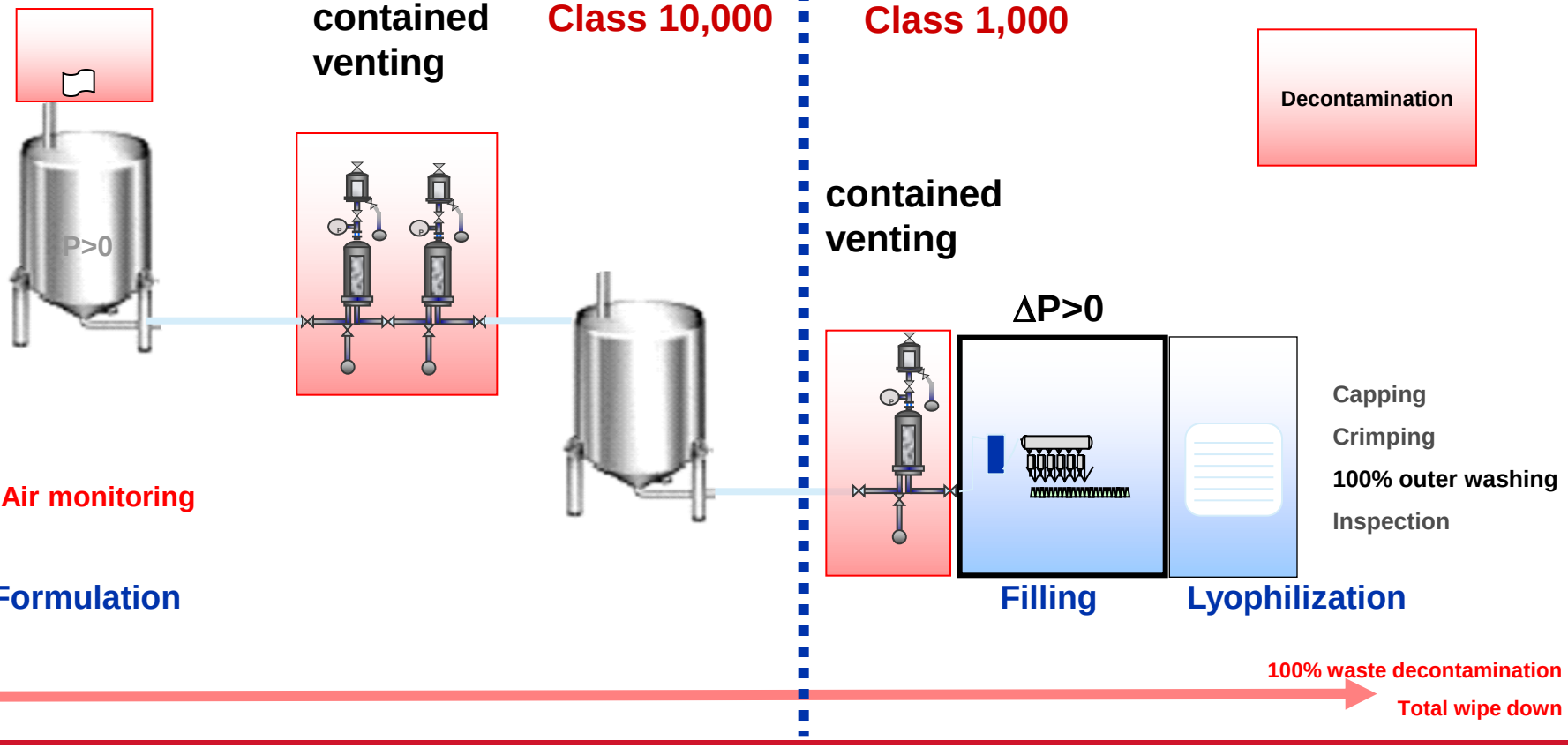
Maintenance and spare parts costs

Operating Costs

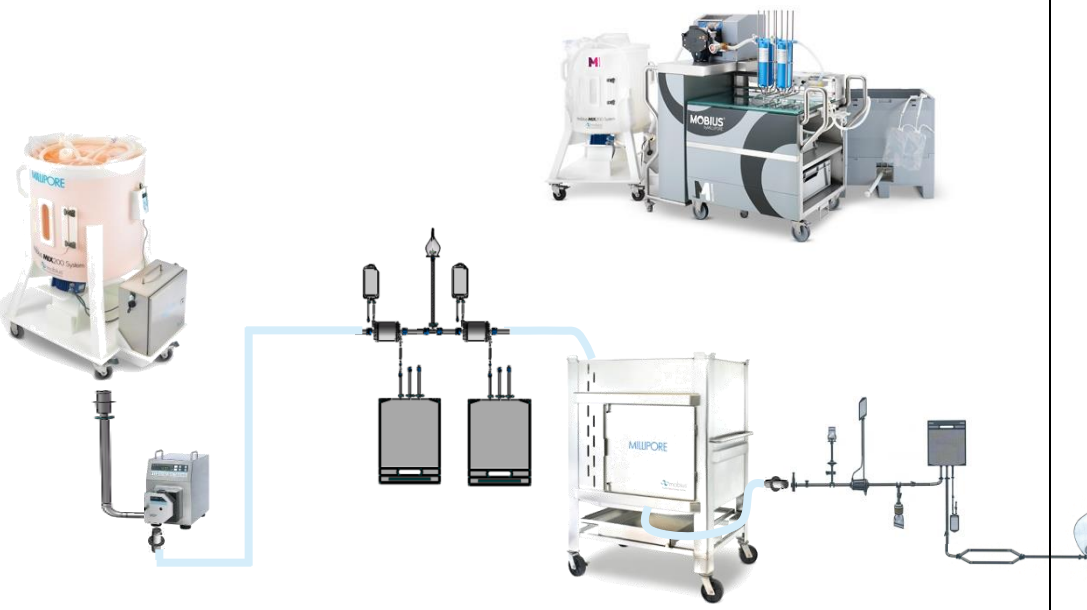
- **CIP (WFI)**
- **SIP**
- **Labor intensive**
- **Facilities**

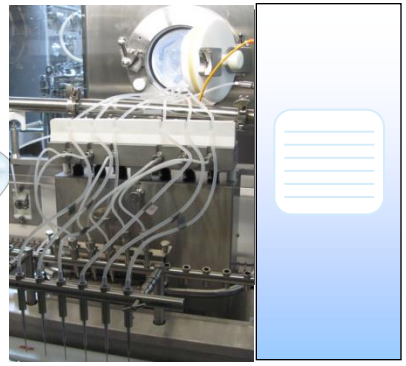
Vaccine Formulation & Filling

Highest level of product integrity and personnel protection



Changing the Paradigm
-Single-use Finish & Fill for vaccines





Capping

Crimping

100% vial washing

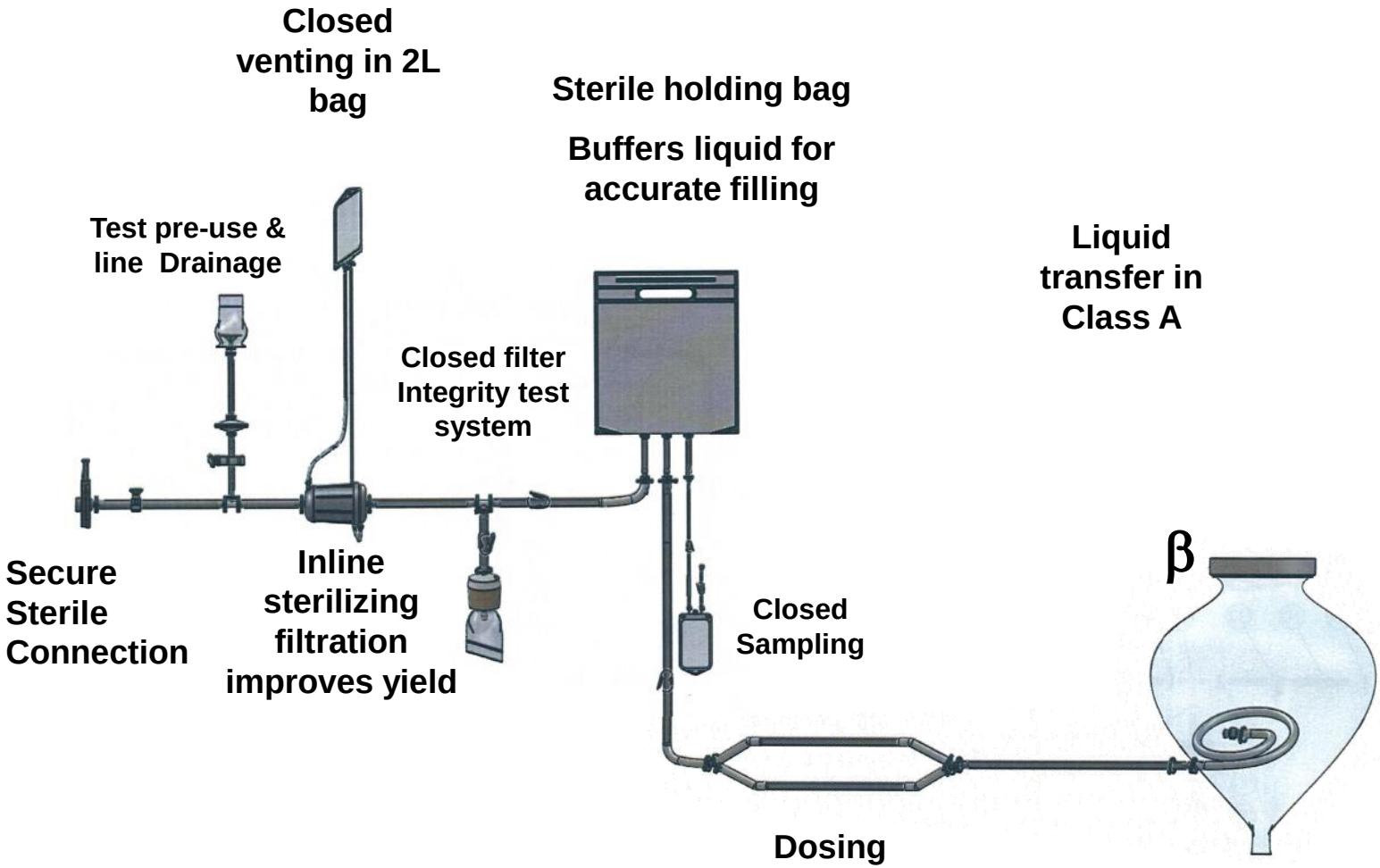
inspection

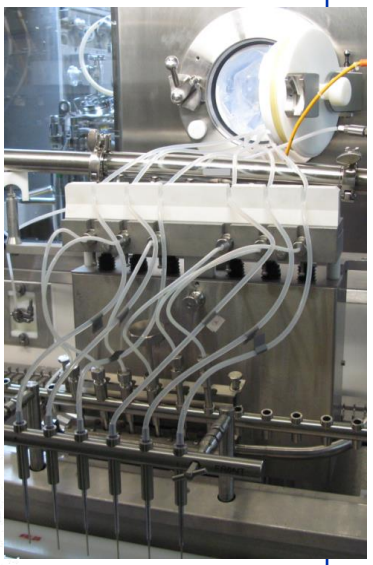
100% waste decontamination

Total wipe down

Design Considerations

Typical Final Filling Assembly: Good Design





Example: Final Formulation & Fill Finish Assembly

100L MIX Bag

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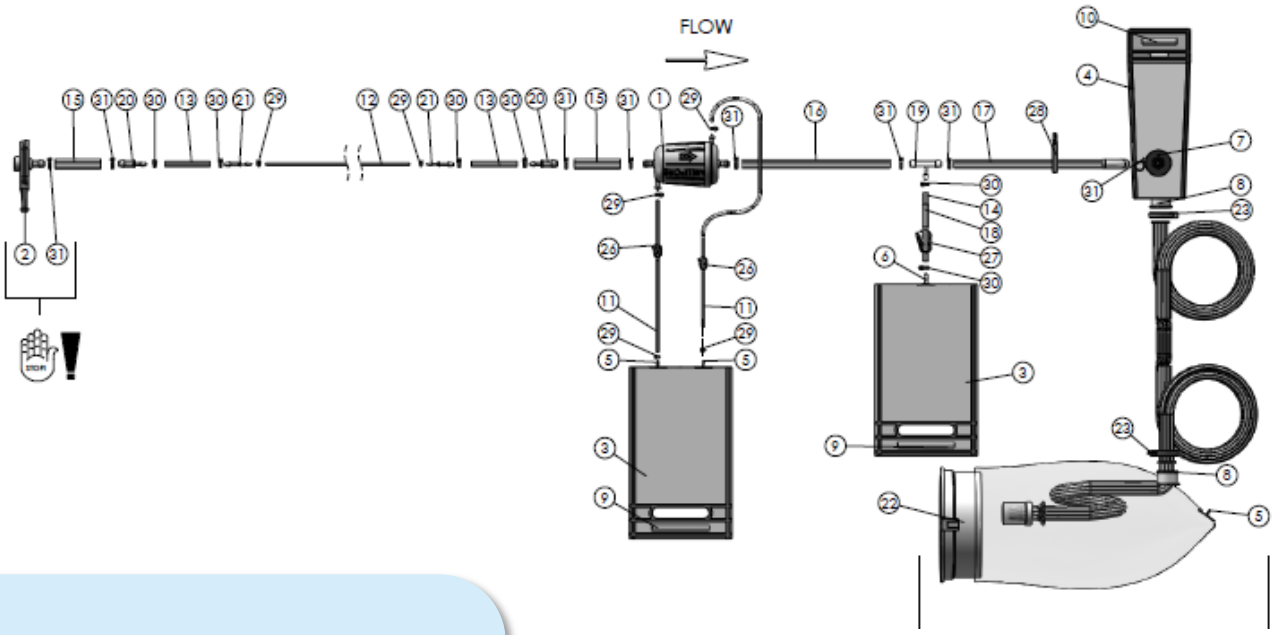
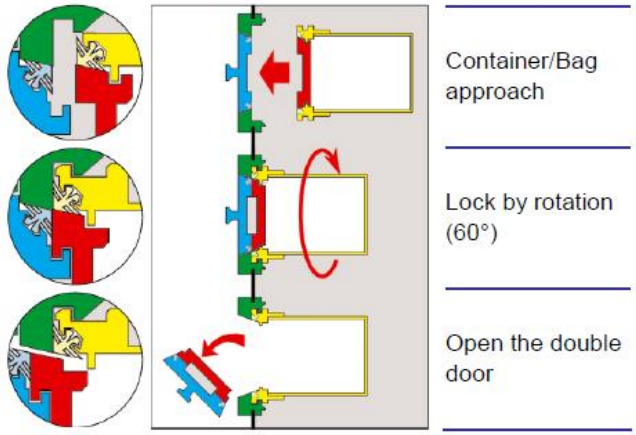
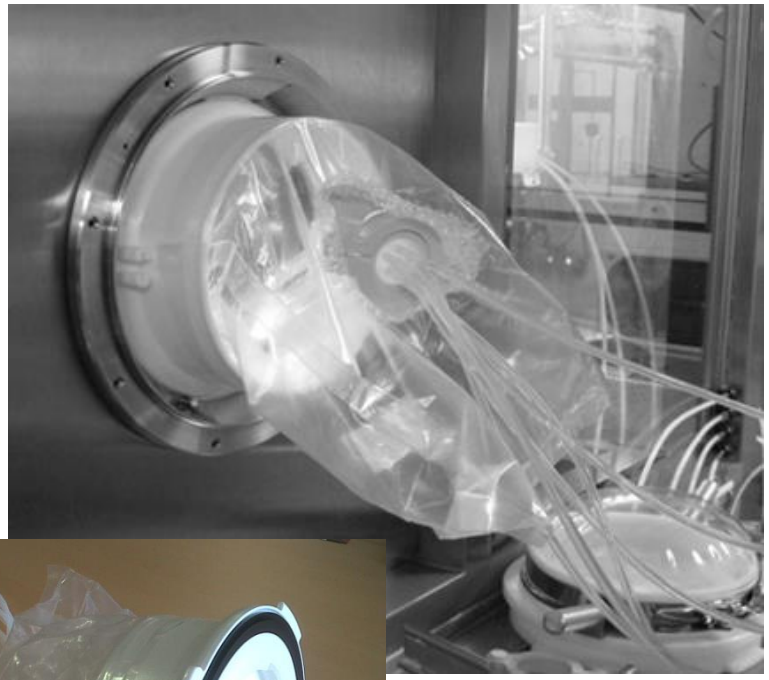


Batch size: 100 L
Max. contact: 24 hours
Process temperature: RT
Product: Small molecule
Dosage: 1 mL syringe/daily

Sterile Transfer across a sterile barrier





Case study: Single-Use Benefits

	Traditional	SU Solution
Clean and set-up	14 Hrs	<1 Hr
Cleaning validation	Extensive	Zero
Filling time	24 hrs	10 hrs
Average vials/hr	3,000	10,000
Aseptic connections	50	0
Operator Training	2 weeks	2 days
Equipment utilization	35%	82%
CAMPAIGN FILL TIME	36 Hrs	12 Hrs

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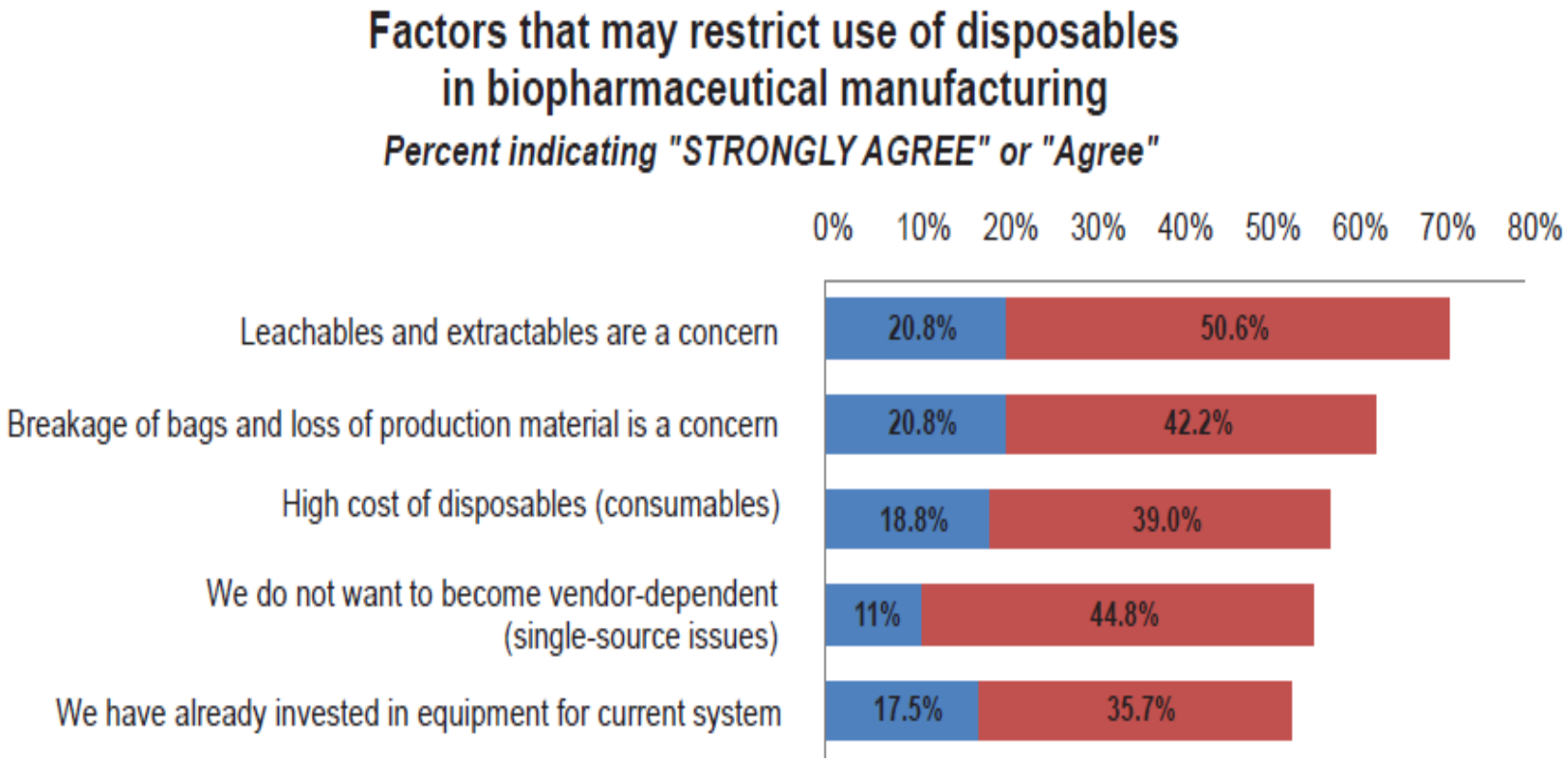
Applications of single use technology in vaccine manufacturing

Validation of single use systems

Potential challenges with adoption of single use



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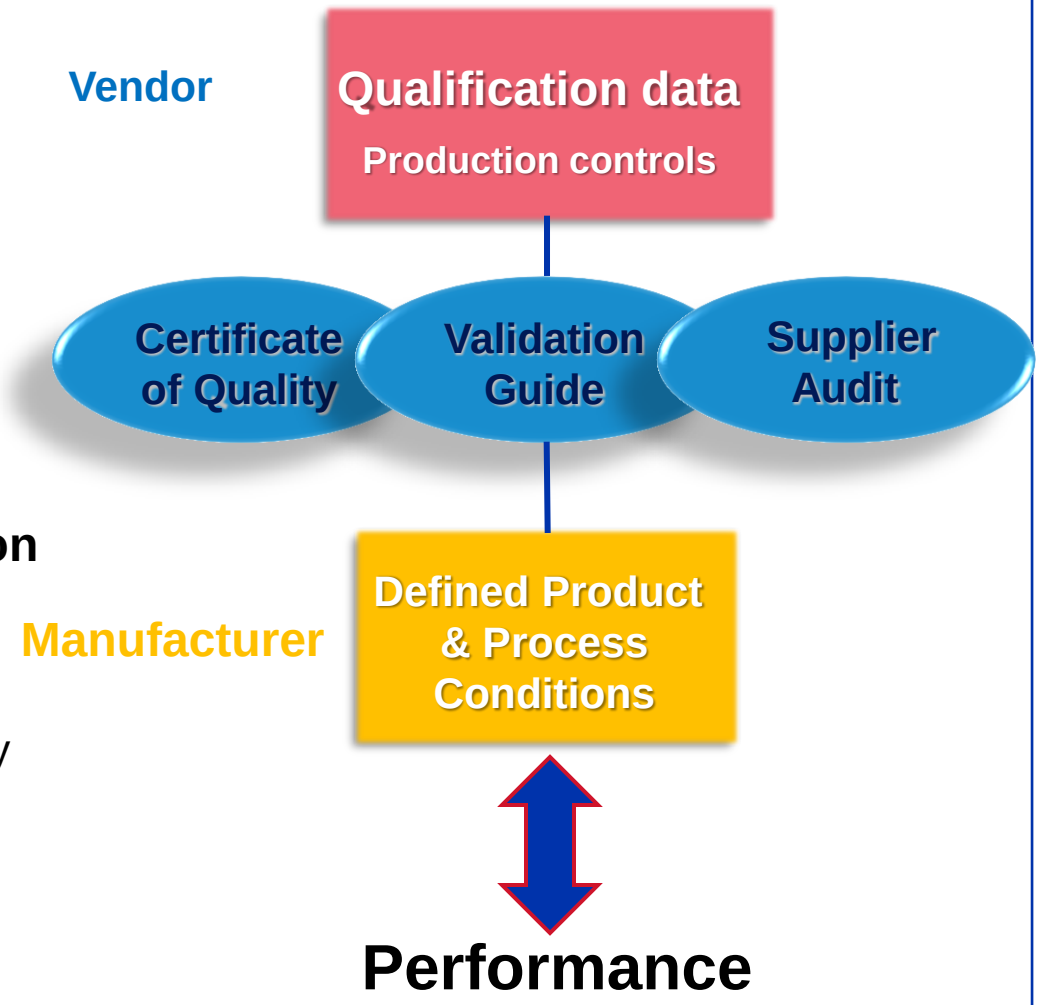
Validation considerations

Incorporate QbD by selecting well qualified and safe materials (vendor selection)

- Components connections
- Integrity
- Sterilisation
- Packaging
- Shelf life
- Sterility



Risk assessment and qualification

- Chemical compatibility
- Extractable and leachable
- Impact on vaccine safety and efficacy
- Bioburden and endotoxin
- Stability studies

E&L PDA Definitions

Extractables

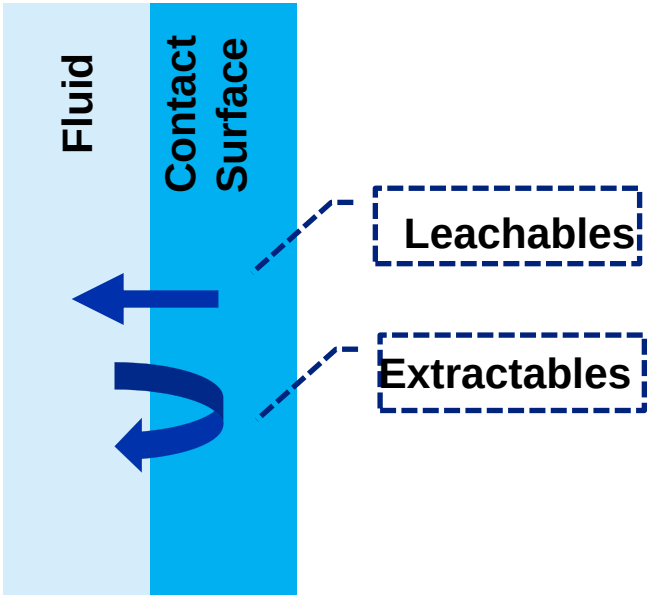
"Any chemical component that is removed from a material by the application of an artificial or exaggerated force (e.g., solvent, temperature or time)."

Determined under "worst-case" conditions following the Model Stream approach.

Leachables

"A chemical component that migrates from a contact surface into a drug product or process fluid during storage or normal use conditions."

Determined with the product under normal processing/storage conditions.



PDA® Technical report N° 26, 2008

Regulatory Agencies Expectations

*"Where there is **relevant risk**, the drug sponsor may have to **determine toxicity based on maximum dosage of potential leachables based on extractables data.”***

***“If there is no relevant risk** associated with the (material in question), **vendor data can be cross referenced** and a detailed justification for the applicability of these data and a justification for no additional testing should be submitted."*

Destry M. Sillivan - Senior Regulatory Review Officer, CBER
IBC's 7th International Single Use Applications for Biopharmaceutical Manufacturing Conference, la Jolla, CA, June 14, 2010

Example: Final Formulation & Fill Finish Assembly

100L MIX Bag

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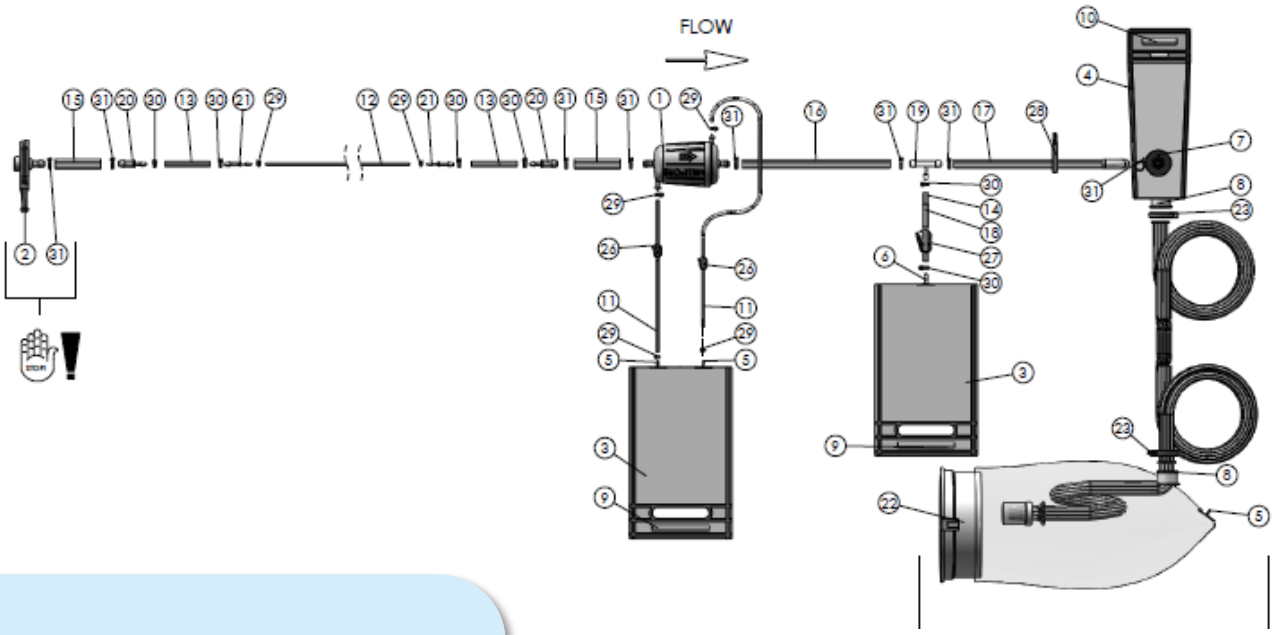

Batch size: 100 L
Max. contact: 24 hours
Process temperature: RT
Product: Small molecule
Dosage: 1 mL syringe/daily

Example: Collection of Vendor EXT Data

Component	TOC (mg C)
100L Mixer Bag	15.4
2L Bag	1.0
Connectors	0.36
Tubing	26.7
Tubing Manifold	47.1
Filter Capsule with Sterilizing Grade Membrane	30.1
TOTAL	**120.7**
Concentration of total extractables (mg/L = ug/ml)	**3.01**

Bags Film
Vendor data

Connectors: Component
Vendor data

Tubing: Component
Vendor data

Filter: Val. Guide

Points to Note on the Analysis / Approach

Did not require

- **An in-house or consultant toxicologist**
- **The single-use system to be made and supplied**
- **The single-use system to be tested**
- **Specific analytical testing**
- **Parallels with container closure approach**
- **Anything other than a review of publically available documentation on extractables and leachables**

HOWEVER it did rely on

- **A qualified informed and experienced vendor**
- **An agreed final draft design**
- **An assigned person in the organization to be responsible**
- **A realistic timeline**
- **A multidisciplinary group in the organization**

Risk Assessment Approach to identify Critical and Specific Service Needs

VENDOR

Process and Manufacturing

Product and Patient Knowledge

Internal Procedure and Controls

Risk Tolerence

Past Experience

Material/Component Knowledge

Assembly Qualification and Design

Manufacturing and Controls

Assembly handling best practices

Experience across many customer processes

Packaging Testing

Shelf Life

Sterilization Validation

Summary

- Use of single use technologies can quickly help increase operational flexibility and manufacturing capacity.
- Implementation of single use technologies is a multi-stage collaborative process between vendor and customer
- Great vendor support is critical to successful implementation and validation of SUS

Thank you !!!