Validation considerations for single use components in vaccine process

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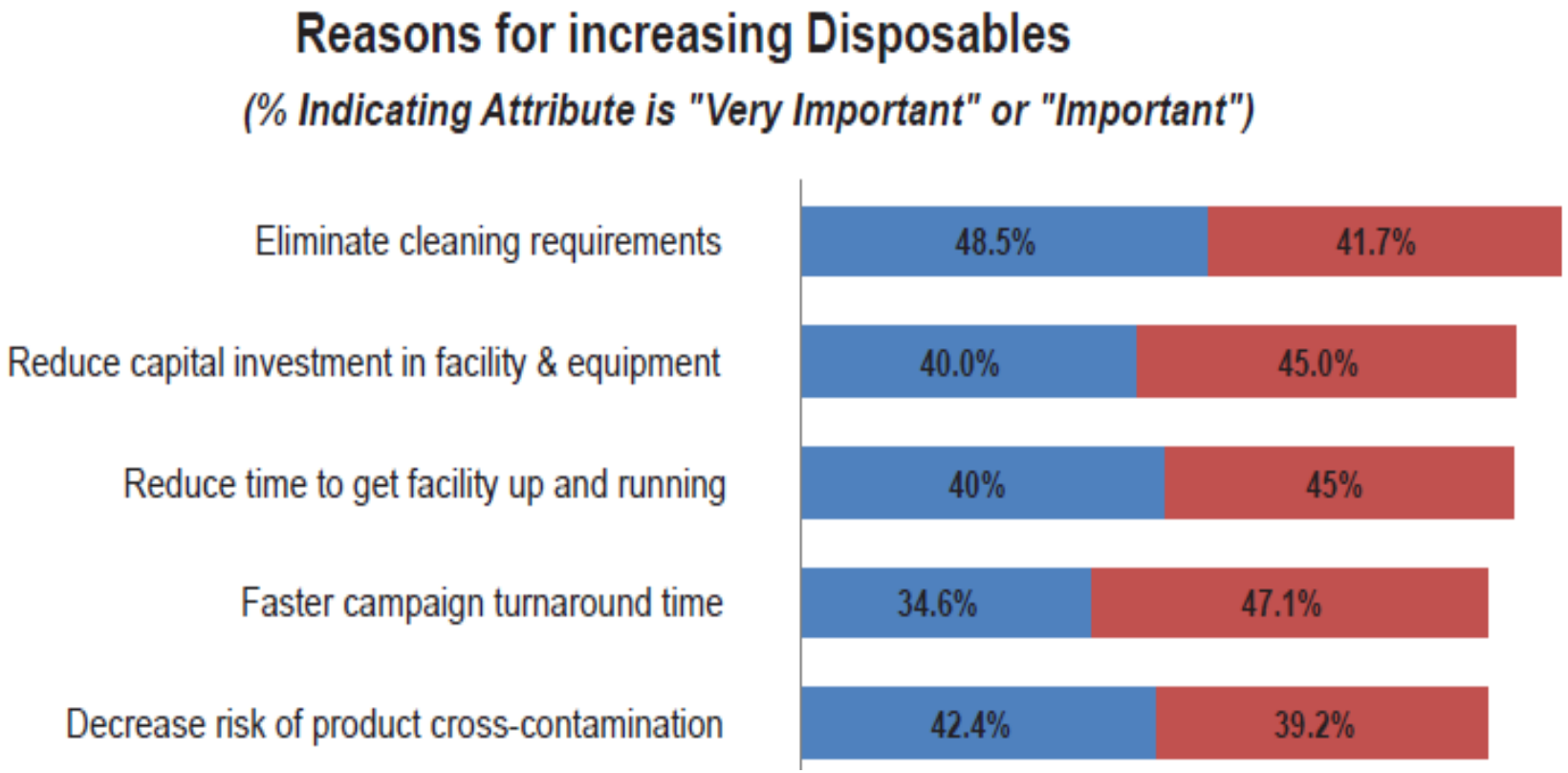
Agenda

1. Overview of single use technology
2. Applications of single use in vaccine manufacturing
3. Considerations of single use systems implementation
4. Validation considerations
5. Summary

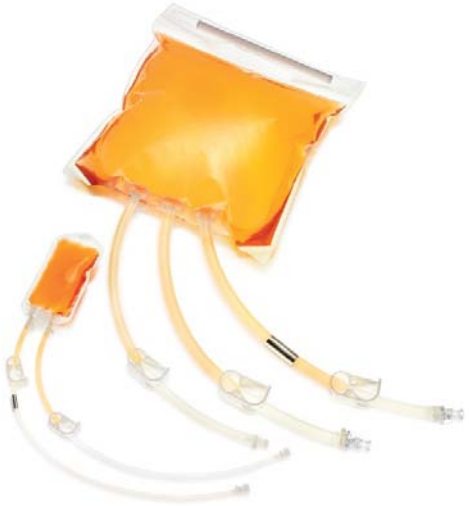
Increasing Use of Single-use systems



Source: *8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production , April 2011*

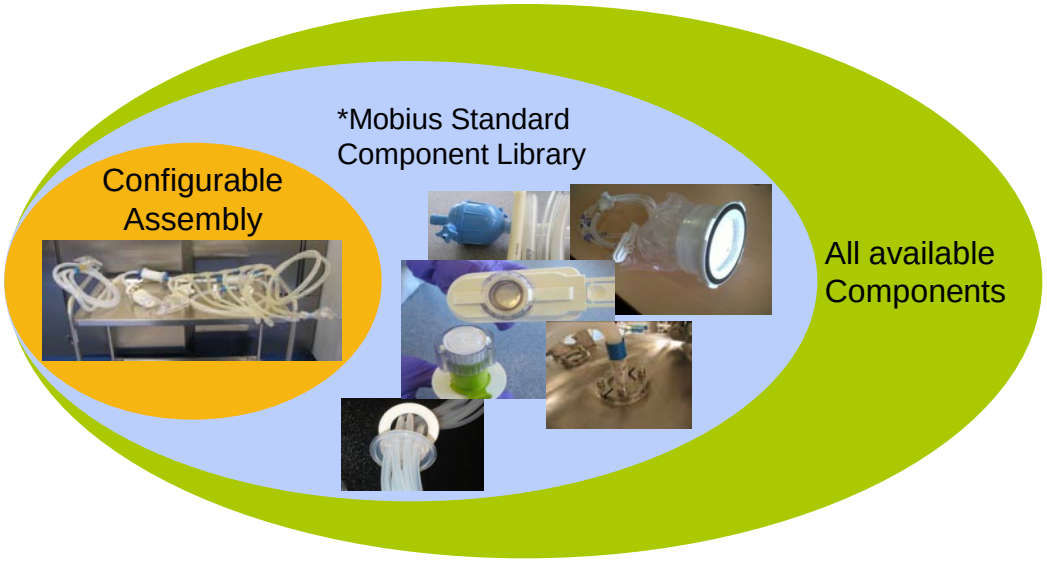
Single-use Components

- Container / bag film
- Product contact components
  - Connectors
  - Filters
  - Aseptic / sterile connectors and disconnectors
  - Tubing
- Non-fluid path components
  - Tubing clamps



Single-use Assemblies

- Self contained & pre-assembled plastic fluid path
- Usually provided gamma irradiated & ready to use
- Uses a combination of standard components:
  - bags, tubing, connectors, filters, mixers, transfer containers, filling system, sampling bag for QC testing
- Single-use assemblies can be customized to meet defined application



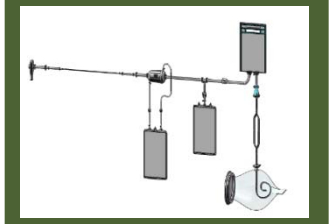
Single-use Systems

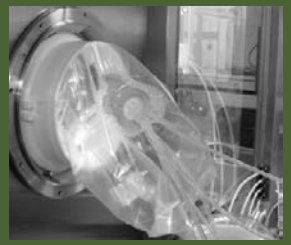
Sterile Connectors and Disconnectors

Assemblies, Support Containers and Mixers

Systems

Final Formulation and Filling Solutions

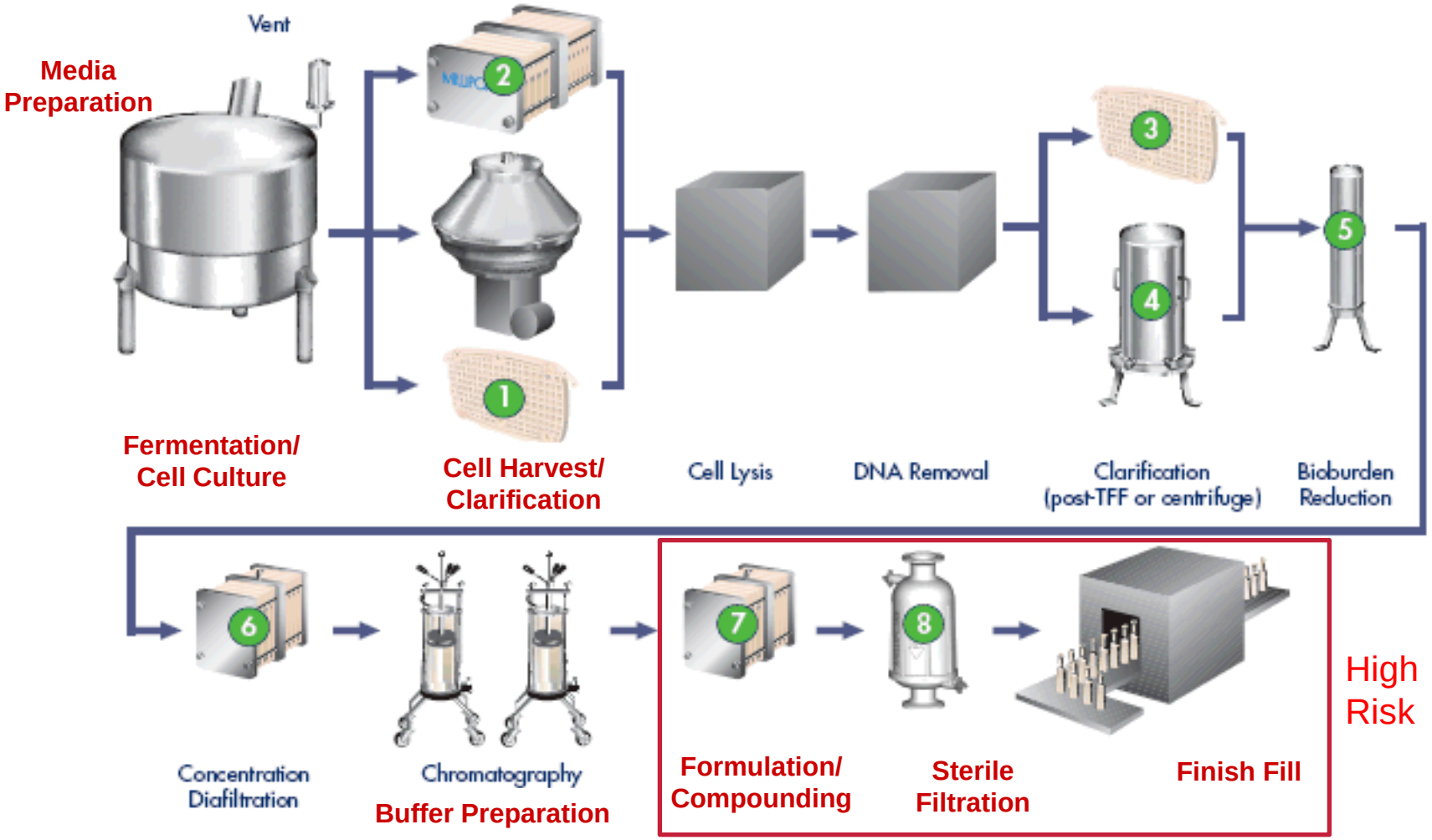




These products require components that need to be assembled

Applications of single use in vaccine manufacturing

Single use technology-
Where in Vaccine Process



Final Formulation Filling Challenges

Limited Flexibility

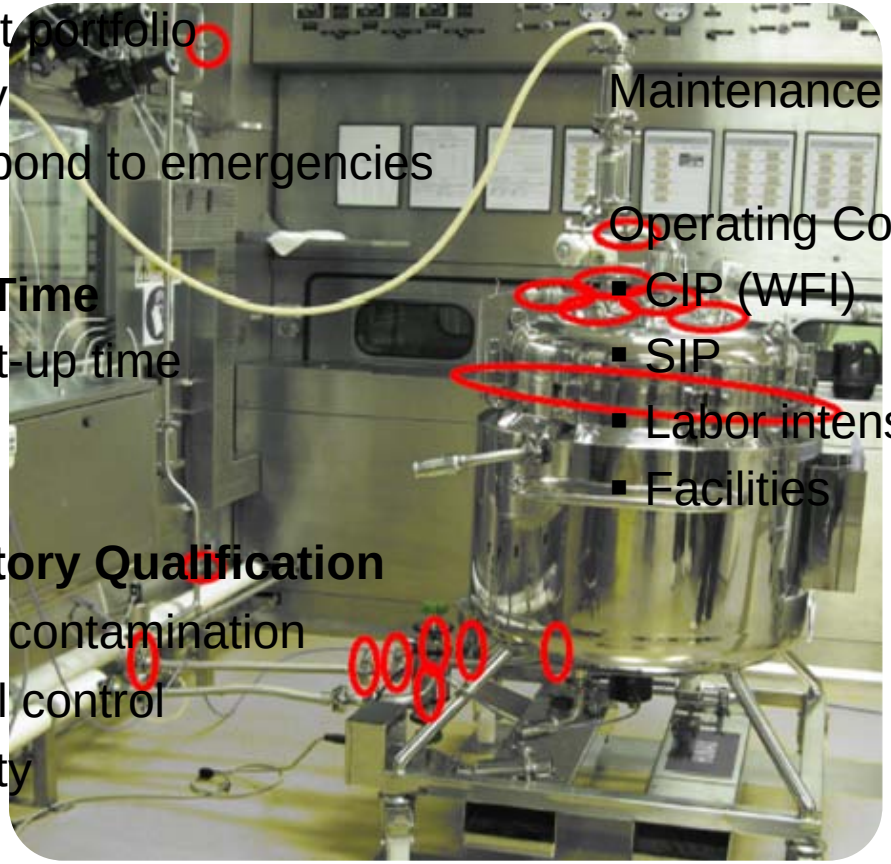
- Varied product portfolio
- Fixed capacity
- Unable to respond to emergencies

Long Change-out Time

- Equipment set-up time
- CIP/SIP

Increasing Regulatory Qualification

- Product cross contamination
- Environmental control
- Operator safety



High capital equipment

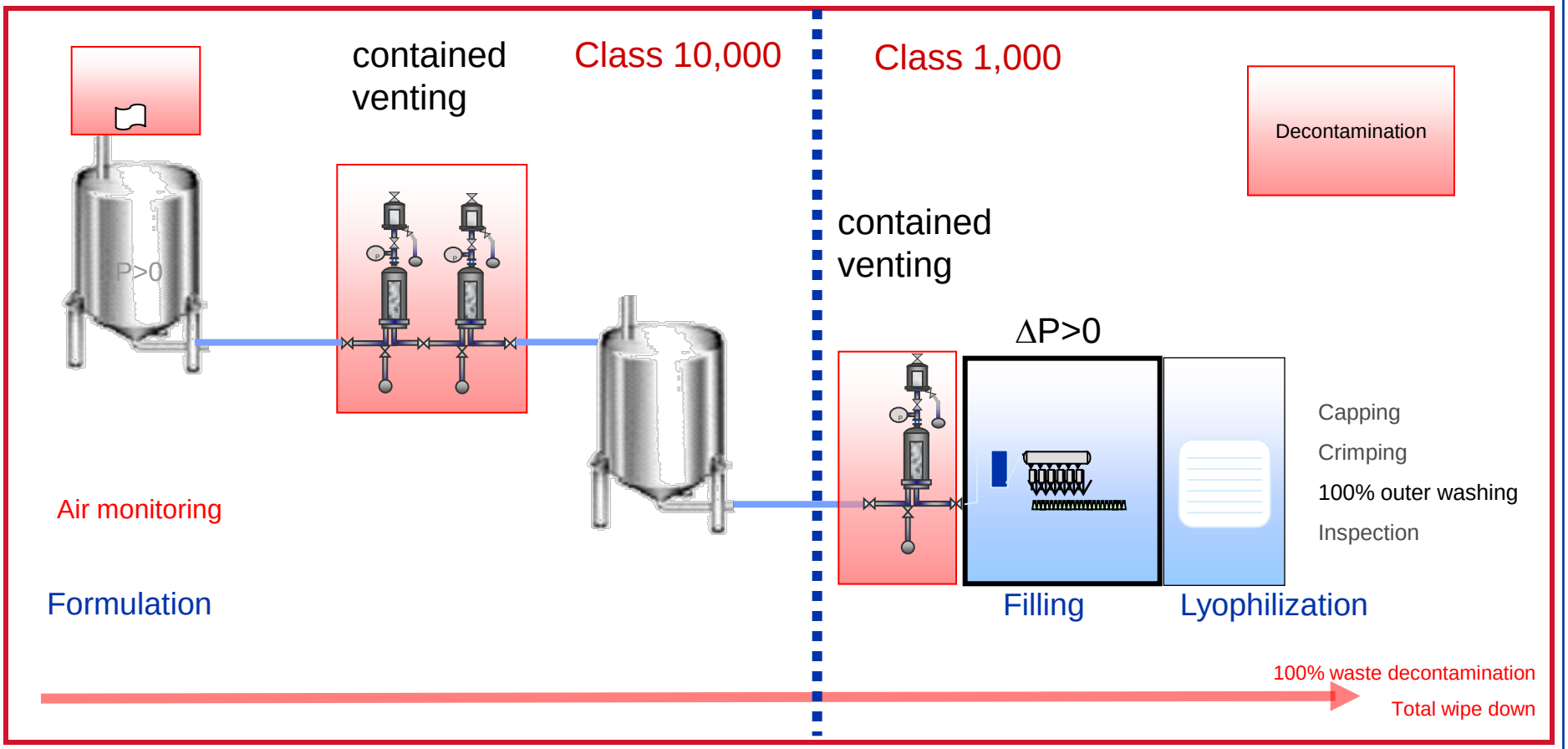
Maintenance and spare parts costs

Operating Costs

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

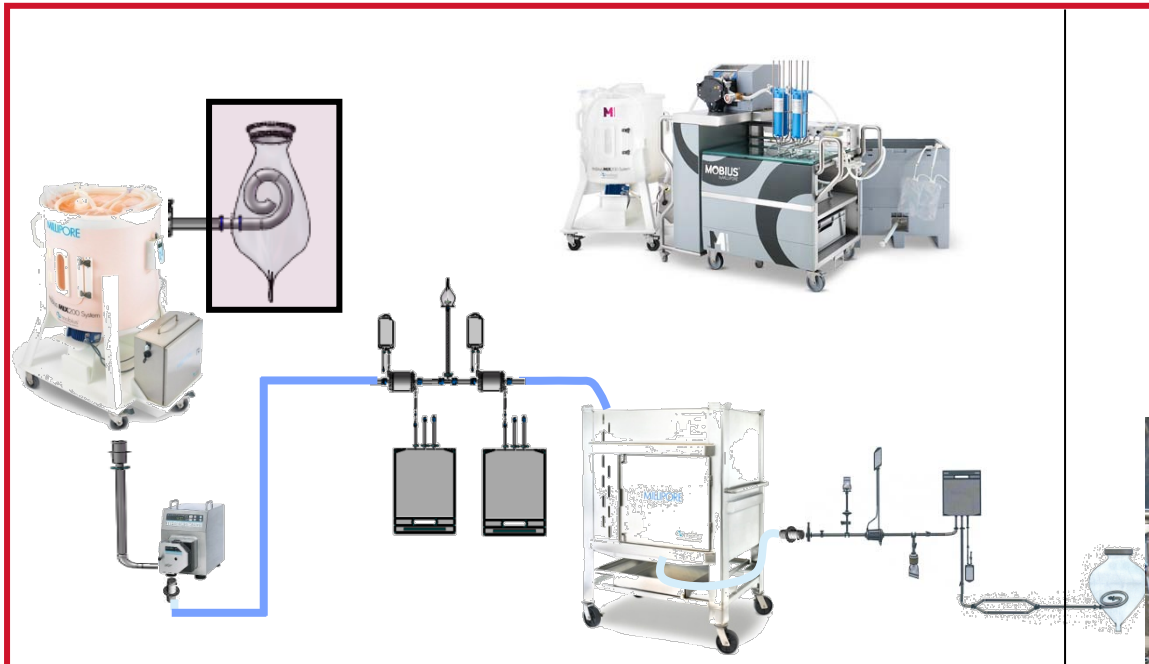
Vaccine Formulation & Filling

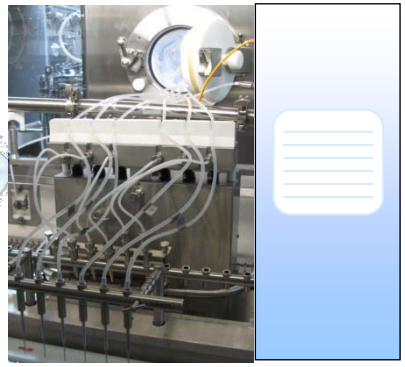
Highest level of product integrity and personnel protection



Single-use Finish & Fill for vaccines

Example: H1N1 Pandemic Influenza Vaccine





Capping

Crimping

100% vial washing

inspection

100% waste decontamination

Total wipe down

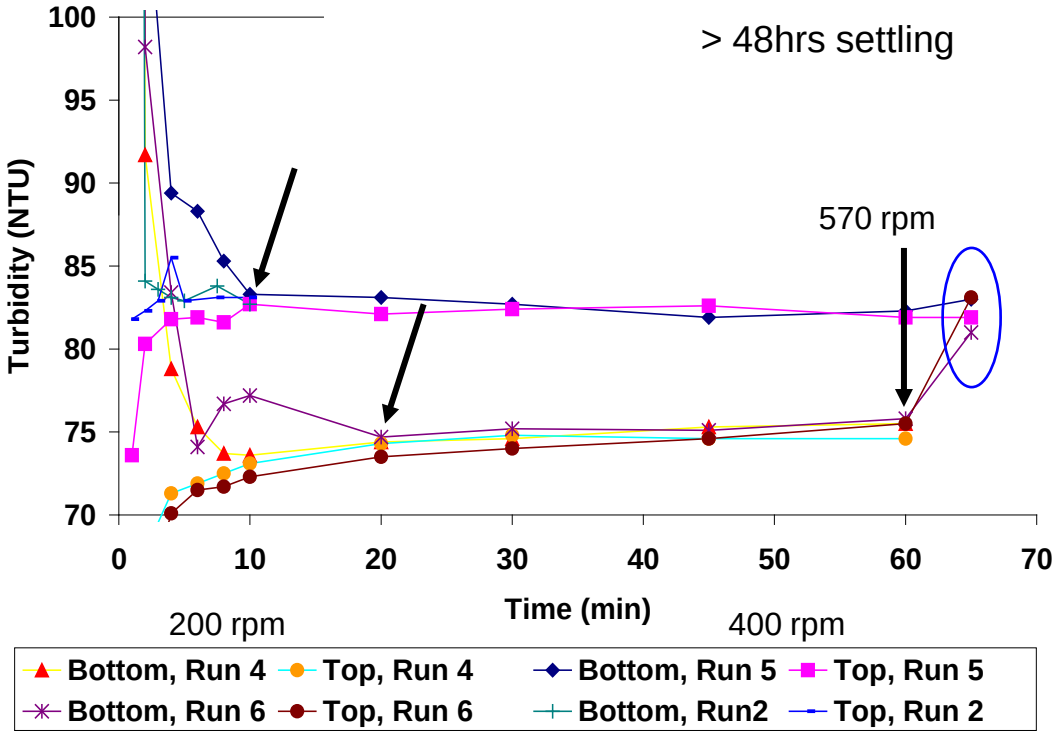
Formulation and bulk preparation

Example: Trivalent Oral Polio Vaccine

Mixing, transfer and storage

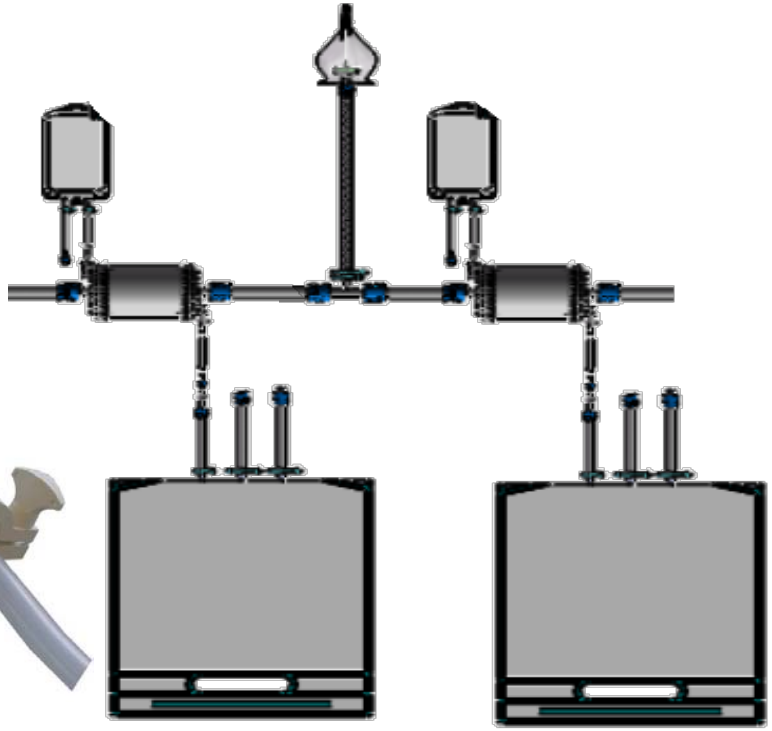
Aseptic mixing and formulation using disposable mixer

Example: Mixing of Alum for use as adjuvant



Sterile Filtration using single use assembly

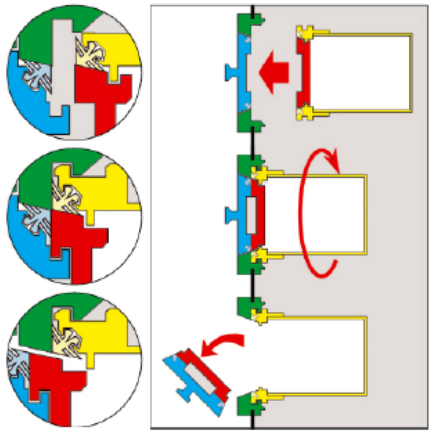
Example: Pneumococcal conjugate vaccine



- 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)

Sterile Transfer across a sterile barrier

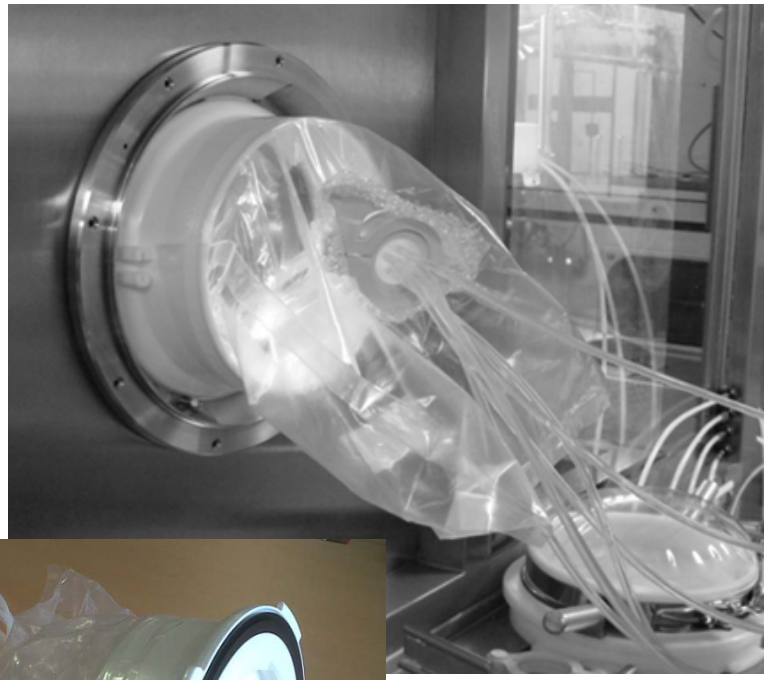
Knowhow is essential and key to success



Container/Bag approach

Lock by rotation (60°)

Open the double door

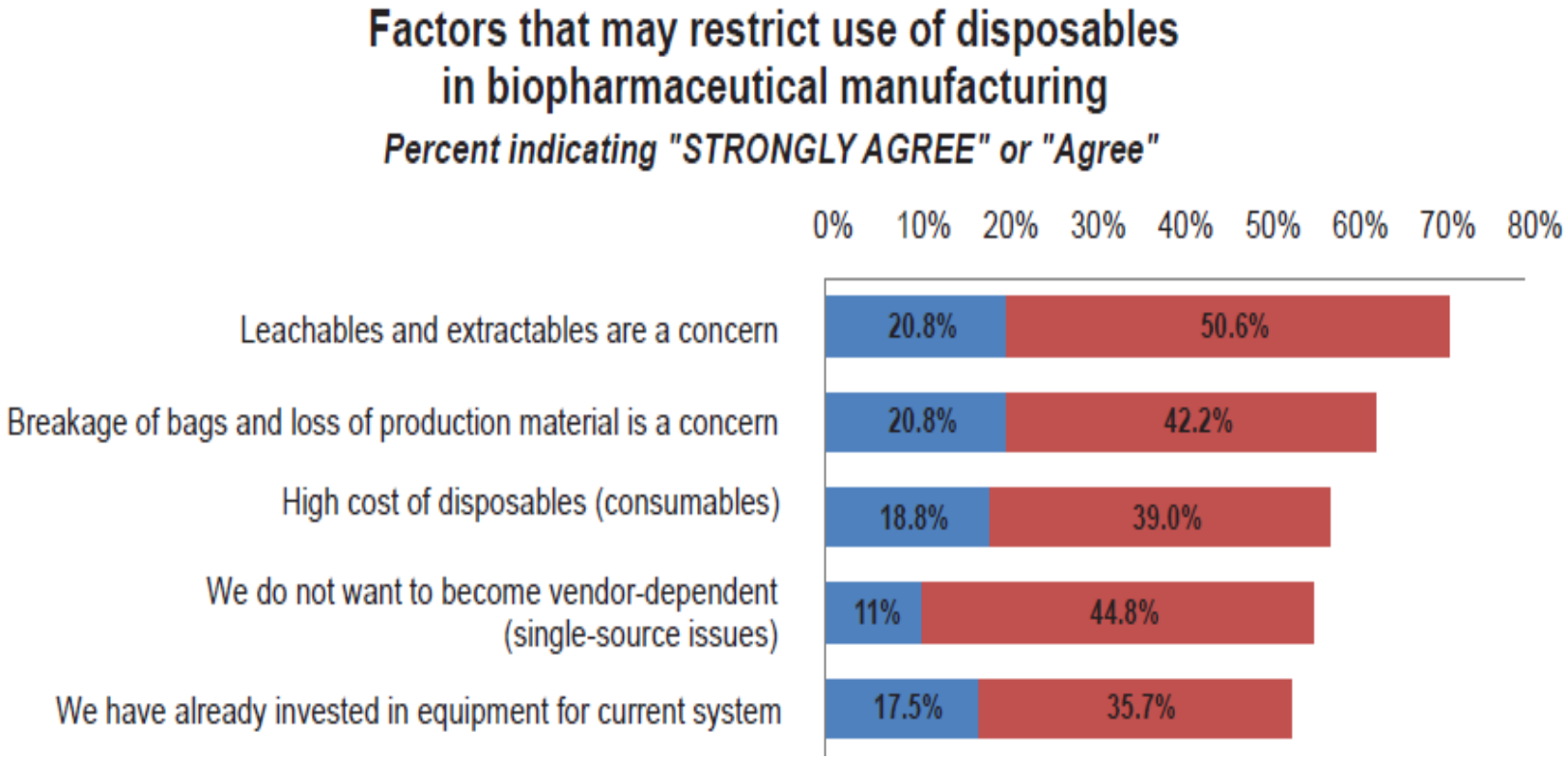


Case study: Single-Use Benefits

	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

Considerations for single use implementation in vaccine process

Potential challenges with adoption of single use



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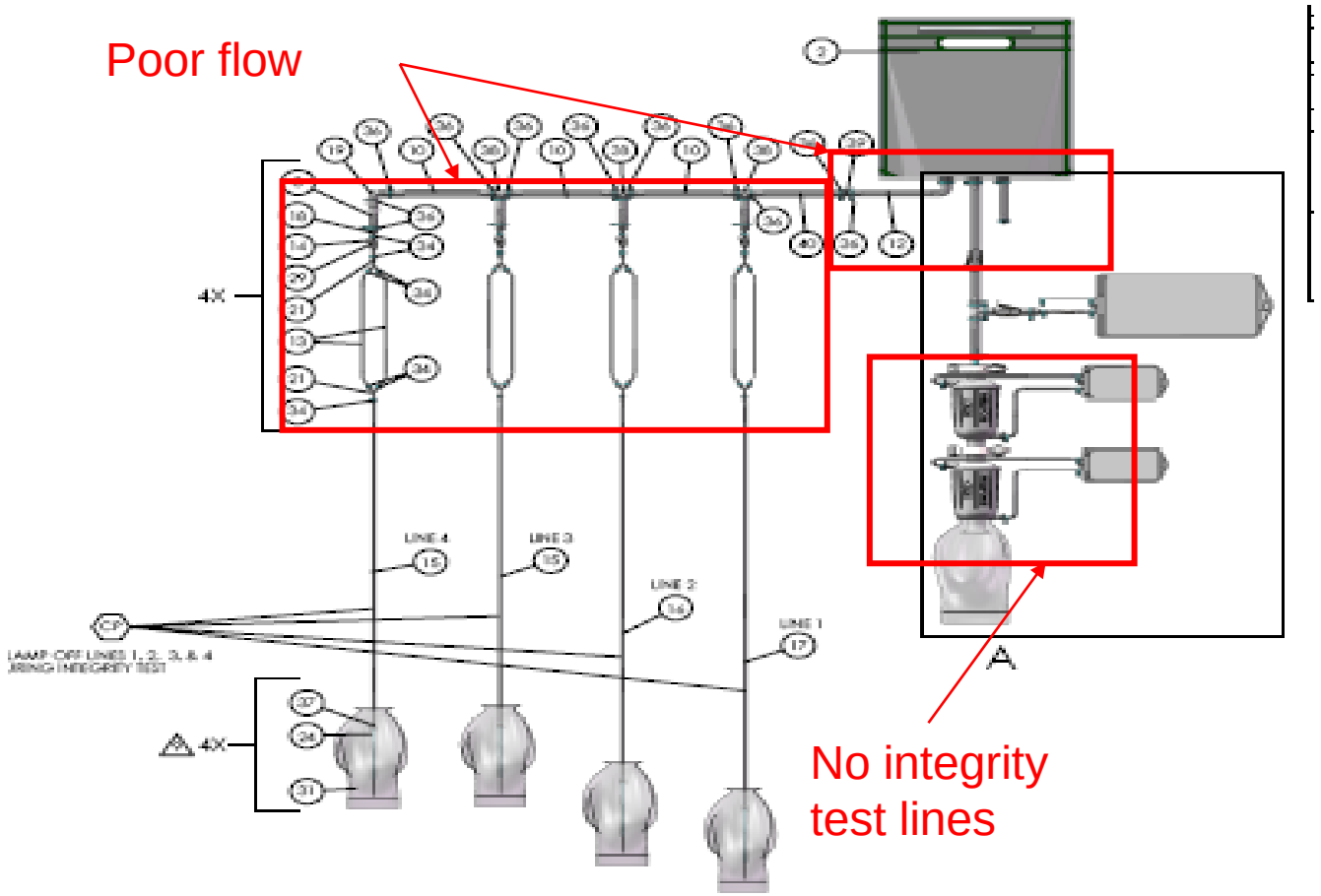
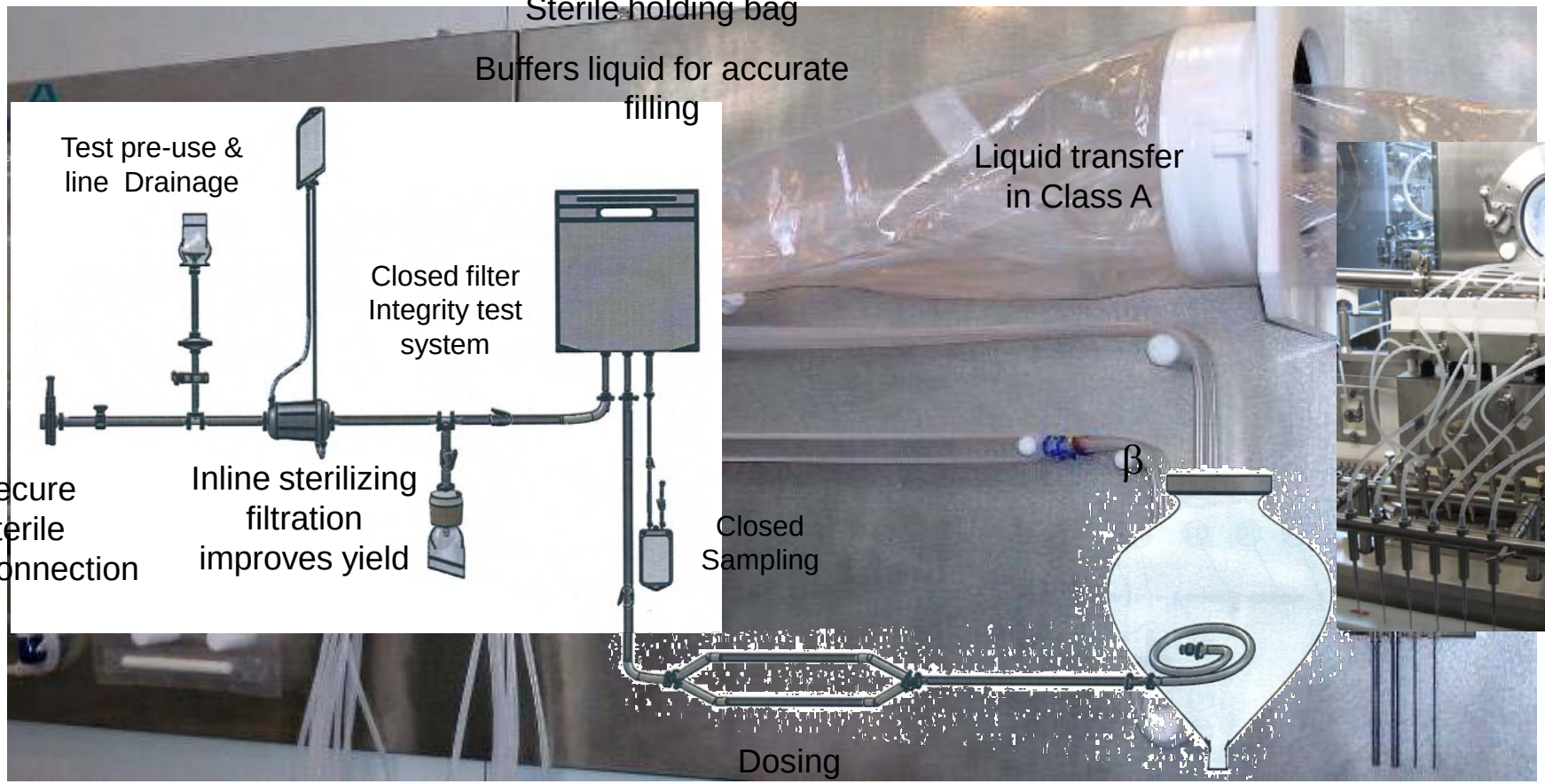
Design Considerations

Typical Final Filling Assembly: Bad Design



Design Considerations

Typical Final Filling Assembly: Good Design



Validation Considerations

Regulatory Agencies Expectations

"Where there is relevant risk, the vaccine 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."

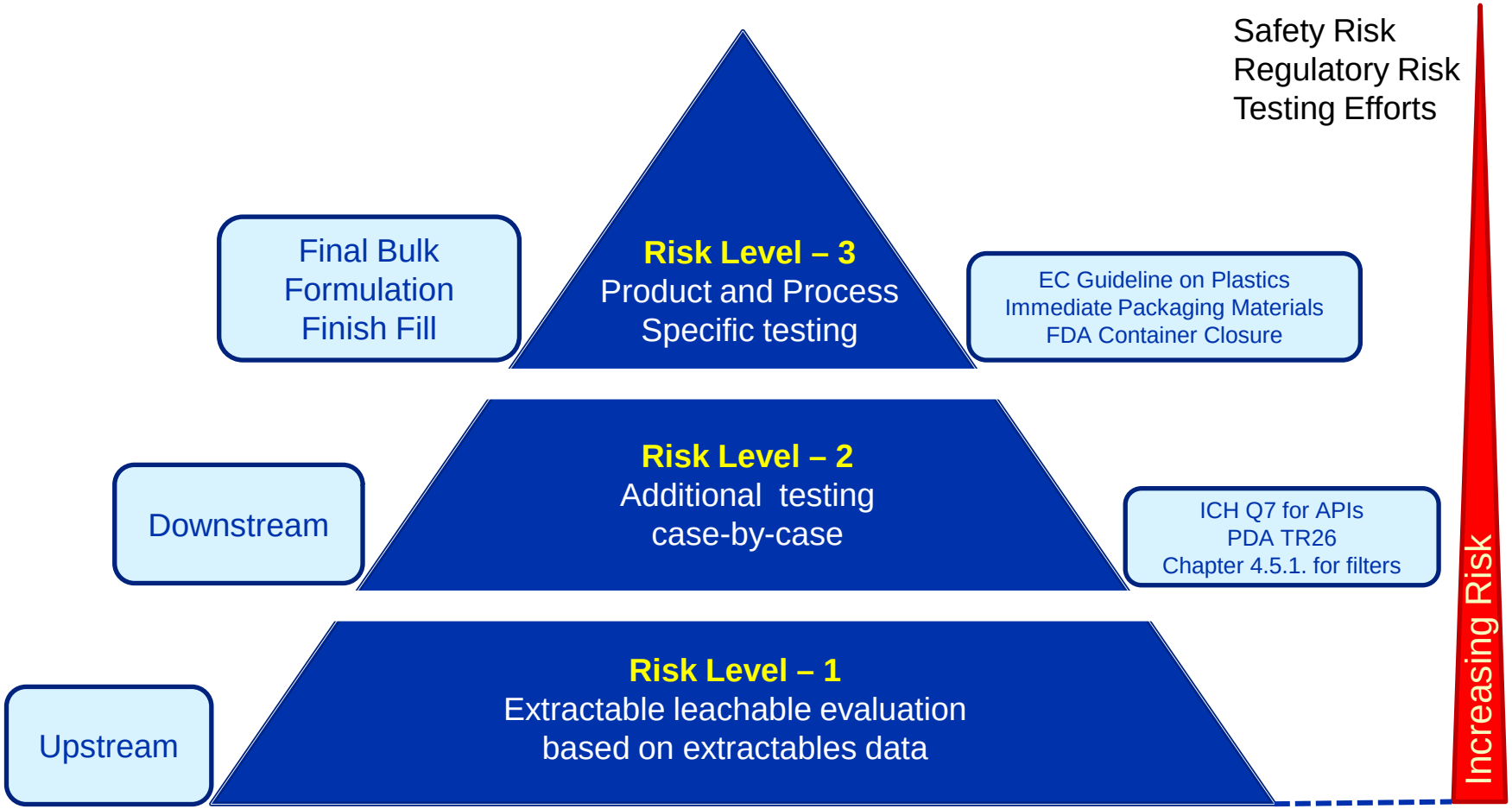
Source: Destry M. Sillivan - Senior Regulatory Review Officer, CBER
IBC's 7th International Single Use Applications for Biopharmaceutical Manufacturing Conference, la Jolla, CA, June 14, 2010

Single Use Validation Considerations

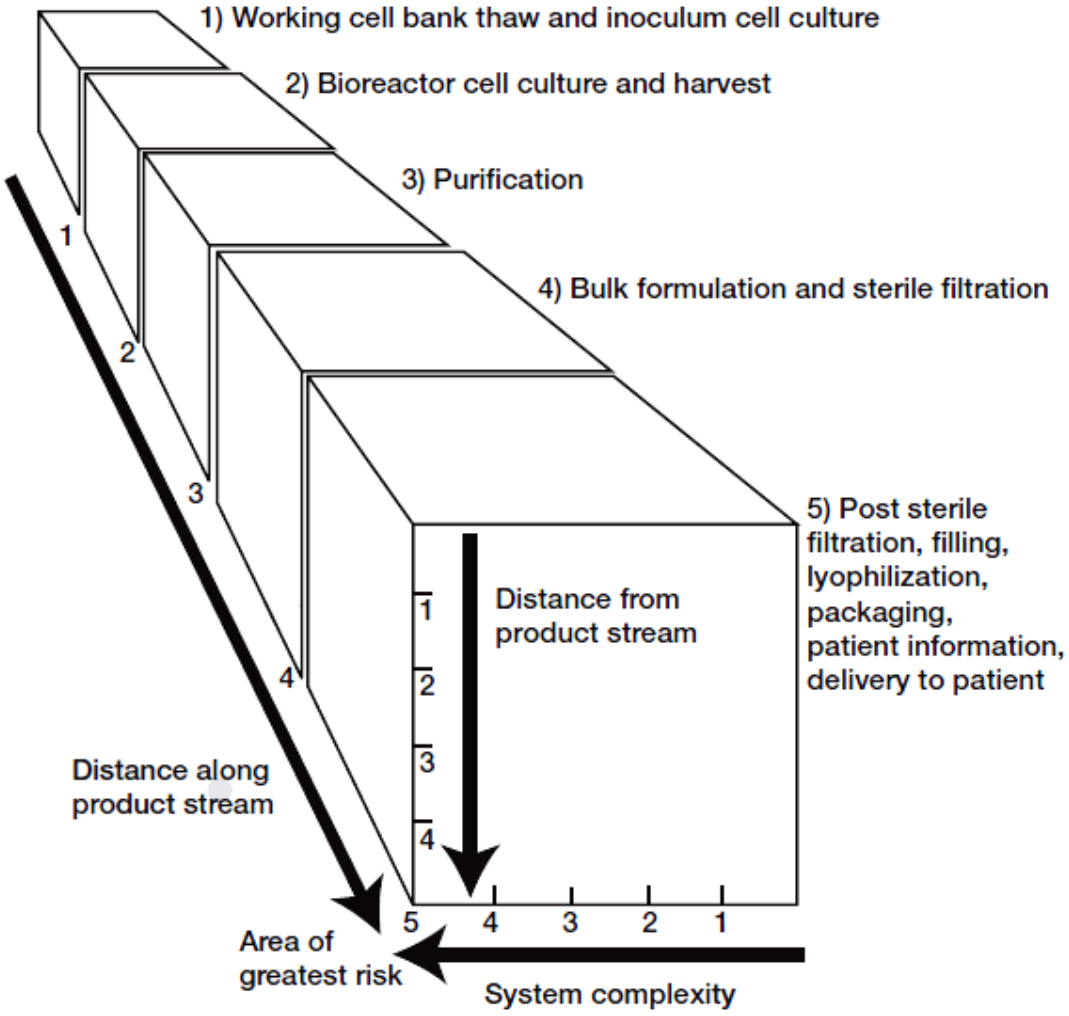
Risk assessment and qualification

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

Risk level vs Process Steps



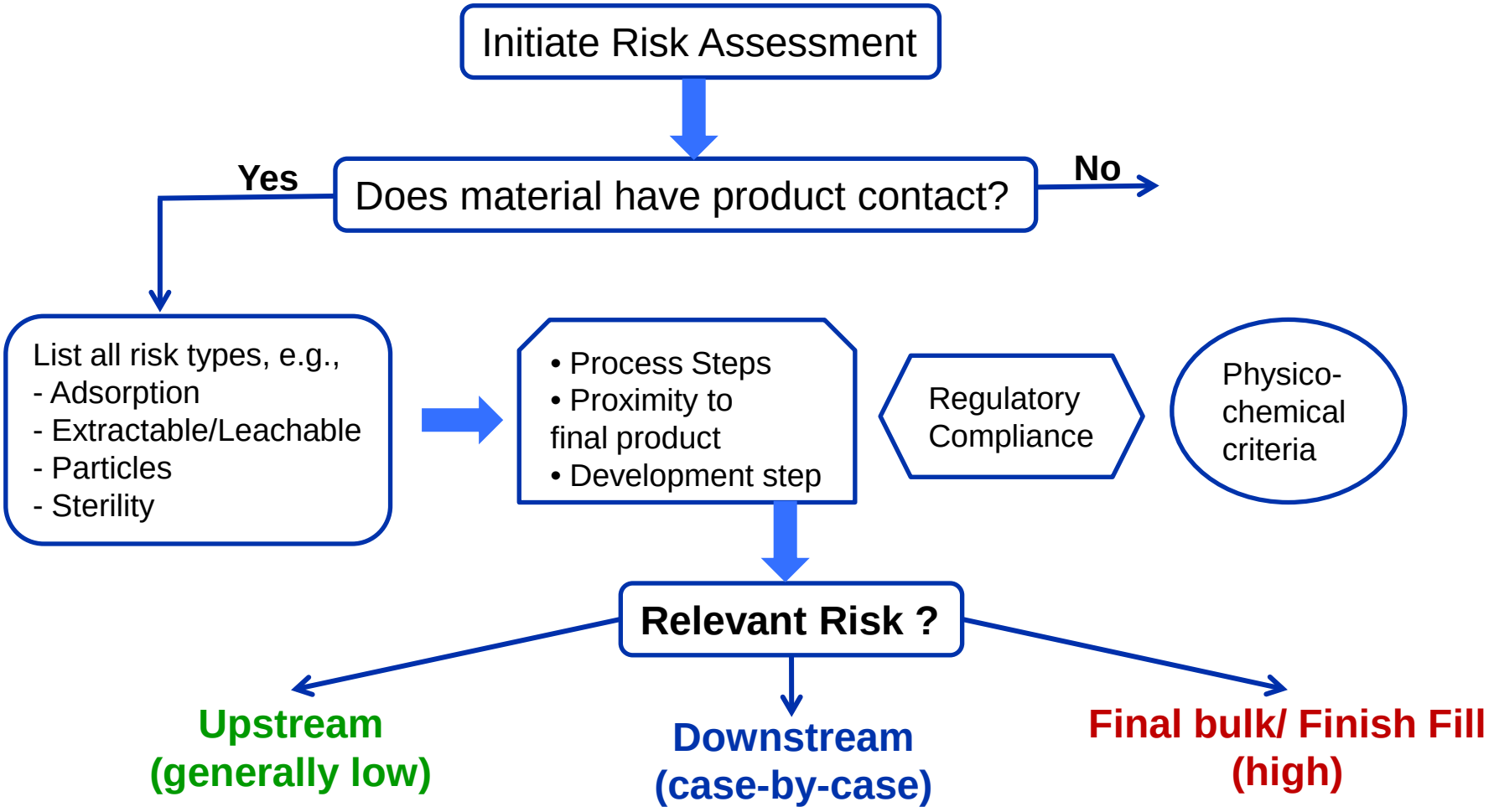
Vaccine Finish & Fill – A high risk operation

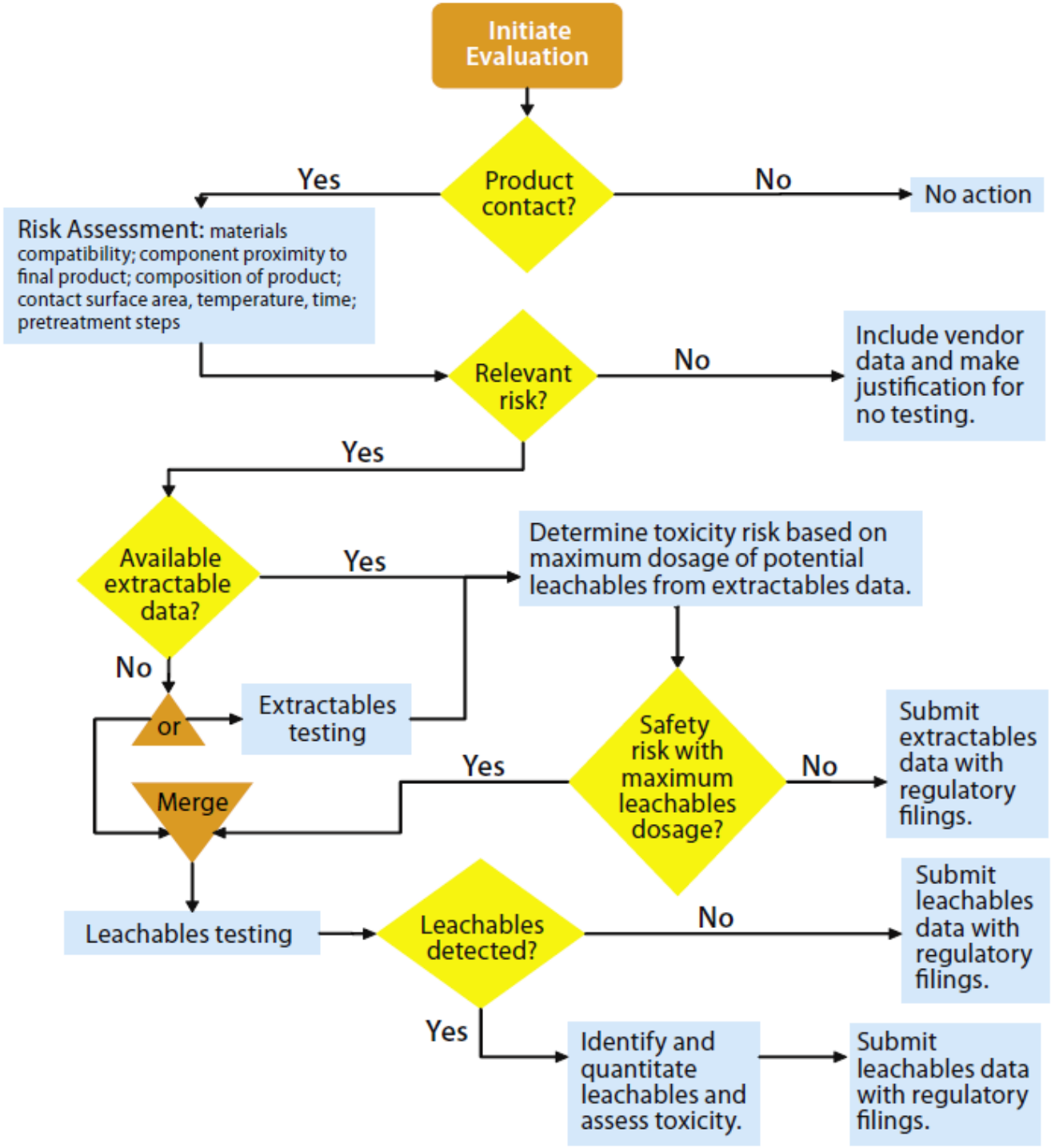


Source: James Oliver, 3D risk assesment model, *JVT,* Autumn 2008, page 70-76.

Guideline for Risk Assessment

Generally applicable for vaccine processes

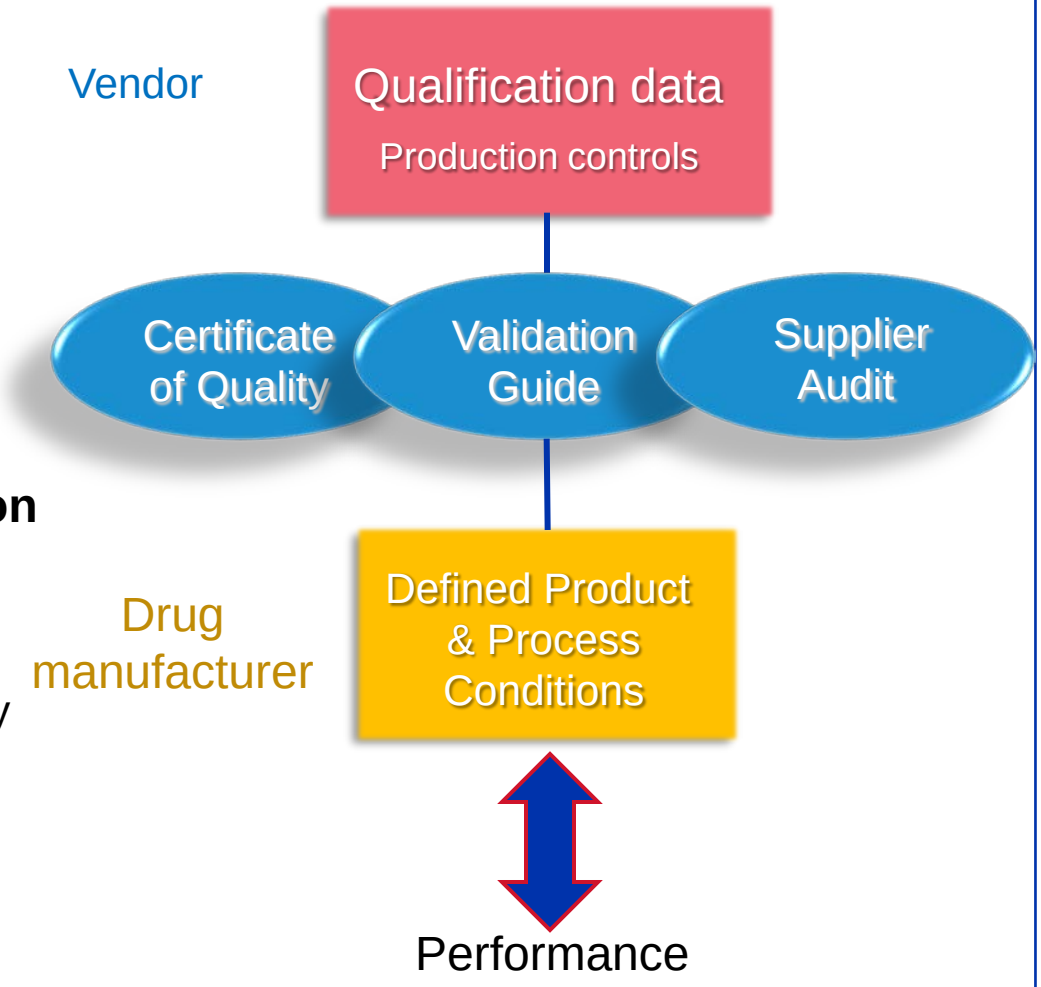



Initiate Evaluation
Product contact?
Yes
No
No action
Risk Assessment: materials compatibility; component proximity to final product; composition of product; contact surface area, temperature, time; pretreatment steps
Relevant risk?
No
Include vendor data and make justification for no testing.
Yes
Available extractable data?
Yes
Determine toxicity risk based on maximum dosage of potential leachables from extractables data.
No
or
Extractables testing
Merge
Safety risk with maximum leachables dosage?
Yes
No
Submit extractables data with regulatory filings.
Leachables testing
Leachables detected?
No
Submit leachables data with regulatory filings.
Yes
Identify and quantitate leachables and assess toxicity.
Submit leachables data with regulatory filings.

Validation considerations

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

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



Risk assessment and qualification

- Chemical compatibility
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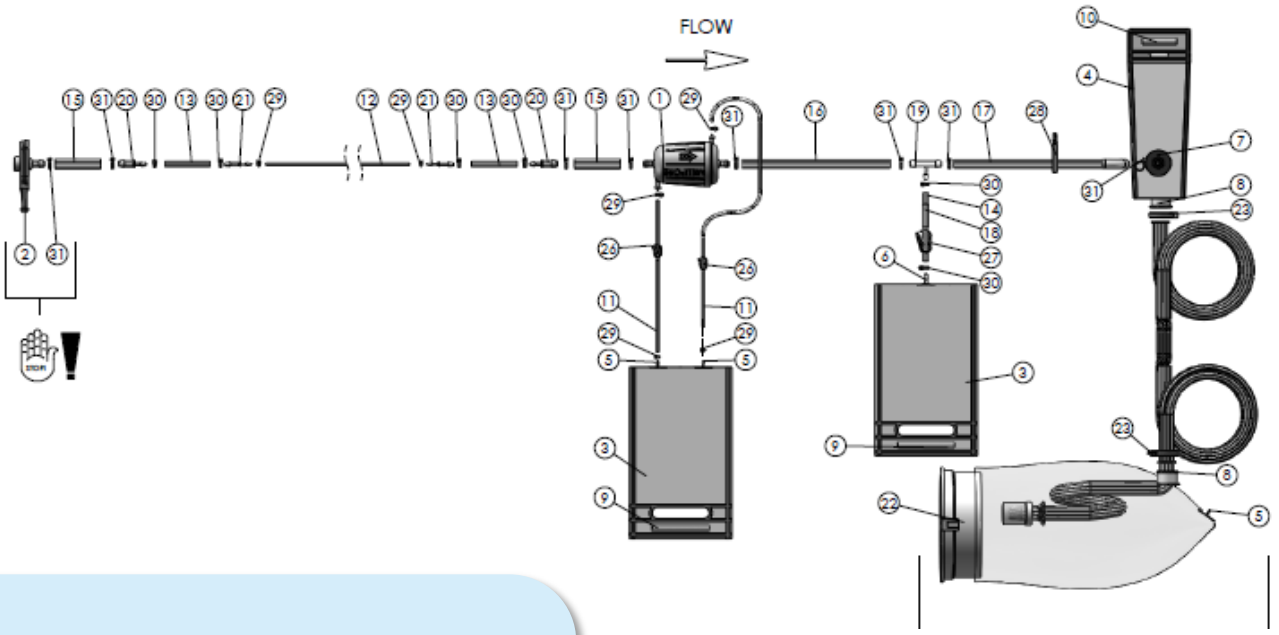
Example: Final Formulation & Fill Finish Assembly

100L MIX Bag

+



Batch size: 100 L
Max. contact: 24 hours (worst case)
Process temperature: RT
Product: Influenza vaccine
Dosage: 0.5 mL/vial

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 = µg/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

- Single use adaptation in vaccine manufacturing is growing exponentially
- Single use can be easily tailored and customized to a specific application need
- Good design practice is critical for success of single use implementation
- Appropriate use vendor/public domain information regarding validation is essential
- Risk assessment focused on application/ need is the base of single use implementation in vaccine manufacturing
- Implementation of single use technologies is a multi-stage collaborative process between vendor and end-user

Thank You