

# Considerations for Implementation of Single-Use Technologies in Bioprocessing

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# Single-Use Technologies in Bioprocessing

**Adoption of single-use technologies in biopharmaceutical development and manufacturing has risen very rapidly over the last few years.**

**The advantages of implementation of single-use technologies are clearly documented.**

**However, it should be clear that single-use technologies do not fit all situations and a number of factors need to be considered prior to implementing these technologies in order to realize their full potential.**

# Factors To Be Considered

- **Facility design and layout**
- **Processing scale**
- **Product being manufactured and process flow**
- **Equipment design, mainly hardware**
- **Single use assemblies design and their manufacturability**
- **People, material and equipment workflows**
- **Regulatory requirements and constraints**
- **Post-use disposal method**

**This presentation will go over some of these critical factors so that users can make decisions that are appropriate for their specific situation and benefit the most from this technology.**

# Facility Design and Layout

In a study of a monoclonal antibody manufacturing process, disposable manufacturing drove significant reductions in:

- Labor time (21%)
- Consumption of electricity (29%)
- Consumption of water (87%)
- Use of facility space (38%)

...when compared with stainless steel-based manufacturing.

Source: Sinclair A, Leveen L, Monge M, Lim J, Cox S. The Environmental Impact of Disposable Technologies.

BioPharm Intl. Nov. 2008.

# Disposables Versus Stainless-Steel

- **Decisions** to go to single-use systems occur early in the project, typically during **conceptual engineering**.
- Single-use systems have a **large impact on the layout** of a facility and also may affect automation strategies, clean utility requirements, floor-to-floor heights, project timelines, procurement schedules, and even area classifications like heating, ventilation, and air-conditioning (HVAC) design.
- Facilities that use only single-use processing realize **substantial advantages**, but tend to be **limited in scale**.
- Most biopharmaceutical facilities **use a mixture**.

Source: Barnoon B, Bader. Lifecycle Cost Analysis for Single-Use Systems  
BioPharm Intl. Nov. 2008.

## Single-Use Technologies Benefits – Impacting Project and Plant Set-up

- Simple plant design – for green field or adaption of existing plants
  - Reduced floor space & room height
  - Reduced maintenance
  - Reduced facility engineering
  - Modular concept
- Reduce validation (no cleaning)
- Reduce of chemicals, buffer and water
- Reduced capital investment cost
- Increase of speed to market
  - Shorten production cycles
- Reduce risk of cross contamination
- Increase of flexibility
  - Easy adaption of process modifications
- Faster turnaround time



**Investment Decision Delay**



**Operational Excellence**



# Single-use Adoption Drivers

## **Rapid Facility Start up:**

Installation, Equipment design & build, Implementation

## **Flexible Operations:**

Multi-product, Quick turnaround between batch

## **Elimination of Cleaning:**

Reduce chemical waste, Better utilize labor, Reduce validation efforts

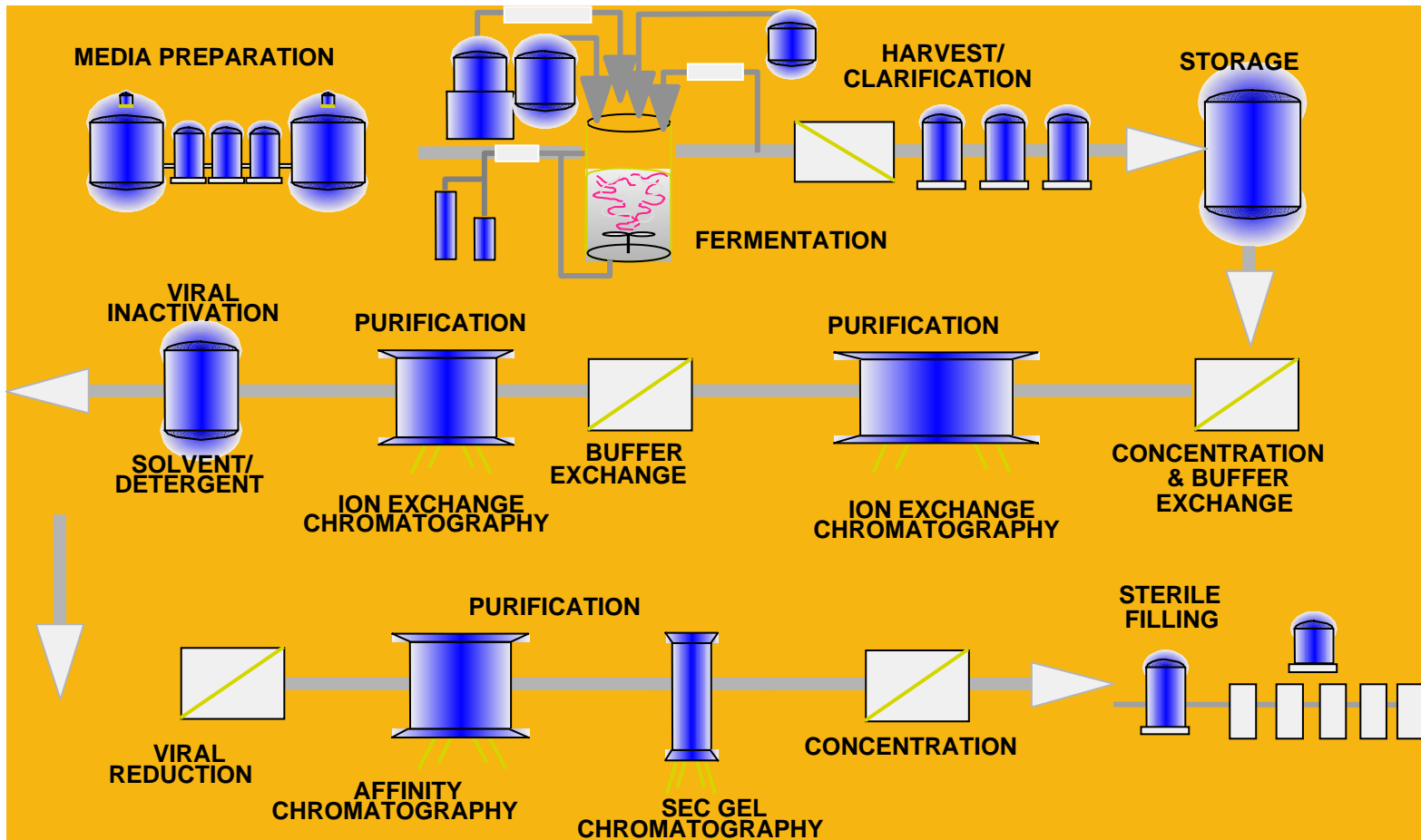
# Processing Scale

## Major Process Scale limits of Single use technology:

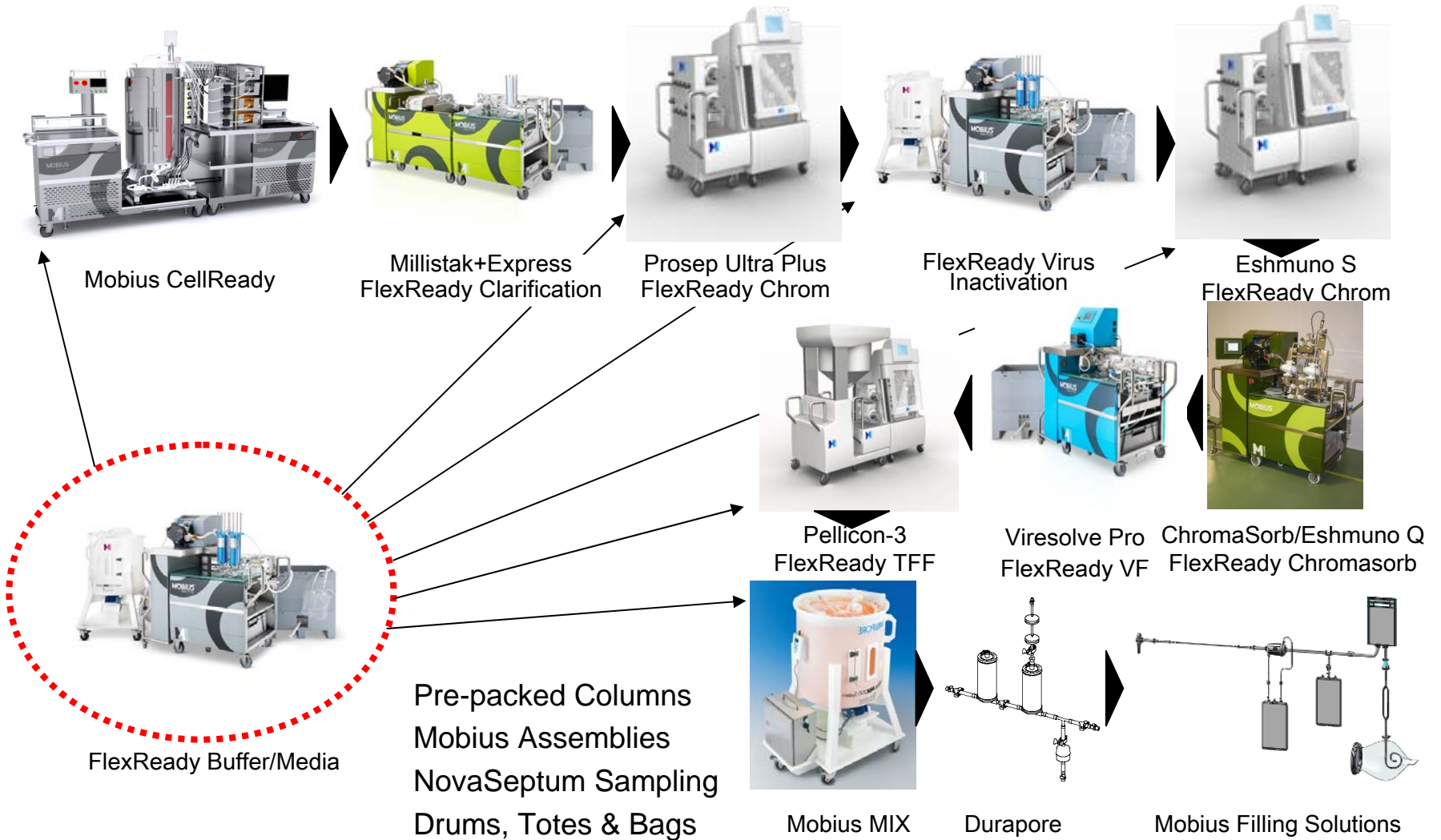
- Volume (bags, bag handling, Homogenization)
  - > 500 L mobility is limited – for handling without Forklift or other assisting Devices
  - max. volumes 3.500 L – above 1.000L containment in case of catastrophic failure (i.e. bag rupture)
- Flowrate
  - Diameter limitation for tubing
  - Size limitation in connection technology
- Components
  - Single-Use Instrumentation
  - Flowrates on Pumps and Pulsation Dampening at Higher Flowrates (Peristaltic Pumps)

For MAB production current limit in scale is in the range of 5 kg batch size.  
Classical Stainless Steel facilities for larger scale still required.

# Product being Manufactured and Process Flow

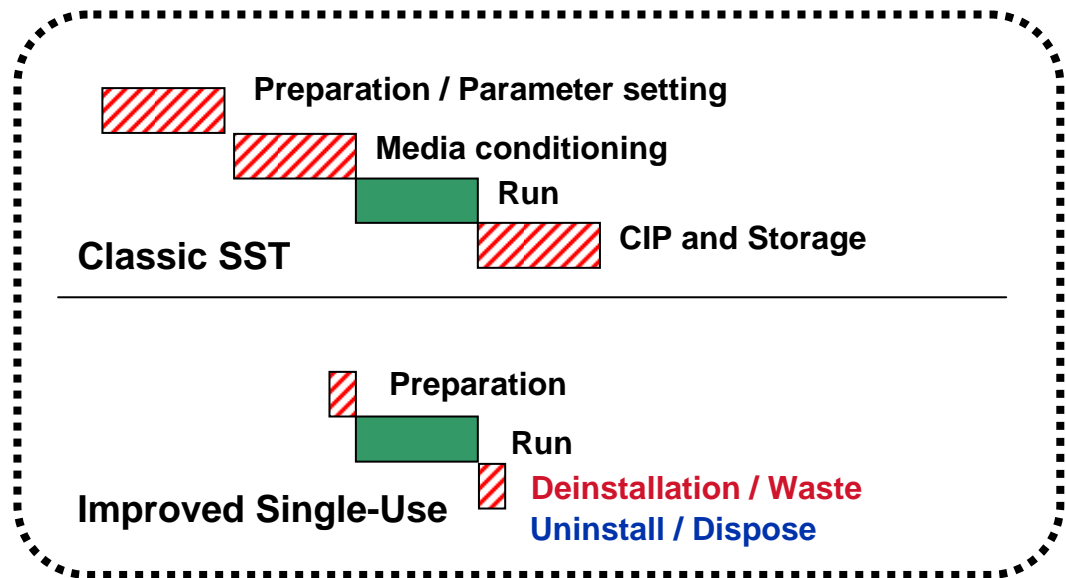
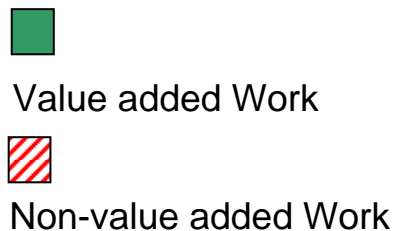


# Enabling single-use process



# Time is Money – Impact of Single-Use Technologies on Process

- Reduction of preparation
- Reduction of media conditioning
- Reduction of CIP and Storage



# Implementing a Clinical Scale Process

## - Integrating Multiple Components



**Average number of parts per unit operation    ~ 20**

**Total number for full DSP process                ~ 150**

Systems and devices form process core.

Ancillaries and transfer assemblies should be defined in a modular approach  
For maximum flexibility.

# Equipment Design Approach: Standardized systems

- **Pre-designed and qualified** - reduces design effort, and lowers risk, shortens lead times
- **Hardware and flexware designed together for compatibility** – optimized layout for process & user friendliness, simplified loading, minimized in field connections
- **Each unit ops optimized for the process** – industry leading devices for scale up and scale down, best available & novel components, process performance characterized and verified over a range of conditions
- **Standard core with configuration options**

**Development following QbD approach.**

# Hardware Design alongside SU assemblies design

Meet process needs: pumping/pressure requirements vary

Ensure ease of installation: foolproof to reduce operator error

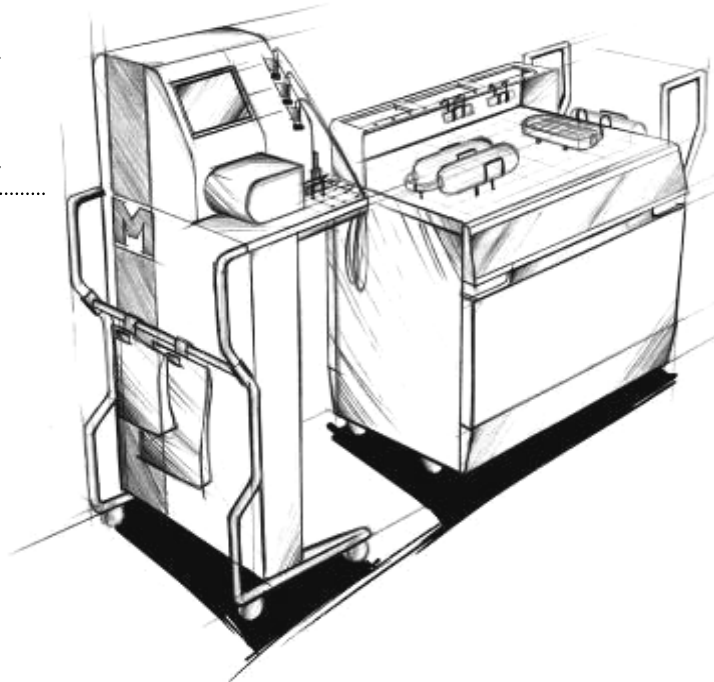
Drive Modularity: multi-functional to optimize cleanroom space use

## Pump cart

Unique pump design for buffer, virus, & clarification

Common base & electrical requirements for Buffer, virus, clarification

TFF – entire pump cart is unique to house the feed/retentate tank



## Filter cart

- Common cart for all
- Easy install of flow-path
- Removable filter supports dedicated to the application
- Shelving to support bags

*Cleanroom space optimization - cart can be used across all applications!*

# Single-use Assembly Design and Manufacturability

**Two major aspects have to be balanced in the design of Single-use assemblies:**

- To meet process needs**
- To be manufacturable from a component, assembly, quality and security of supply perspective**

# What is a Single-use Assembly ?

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

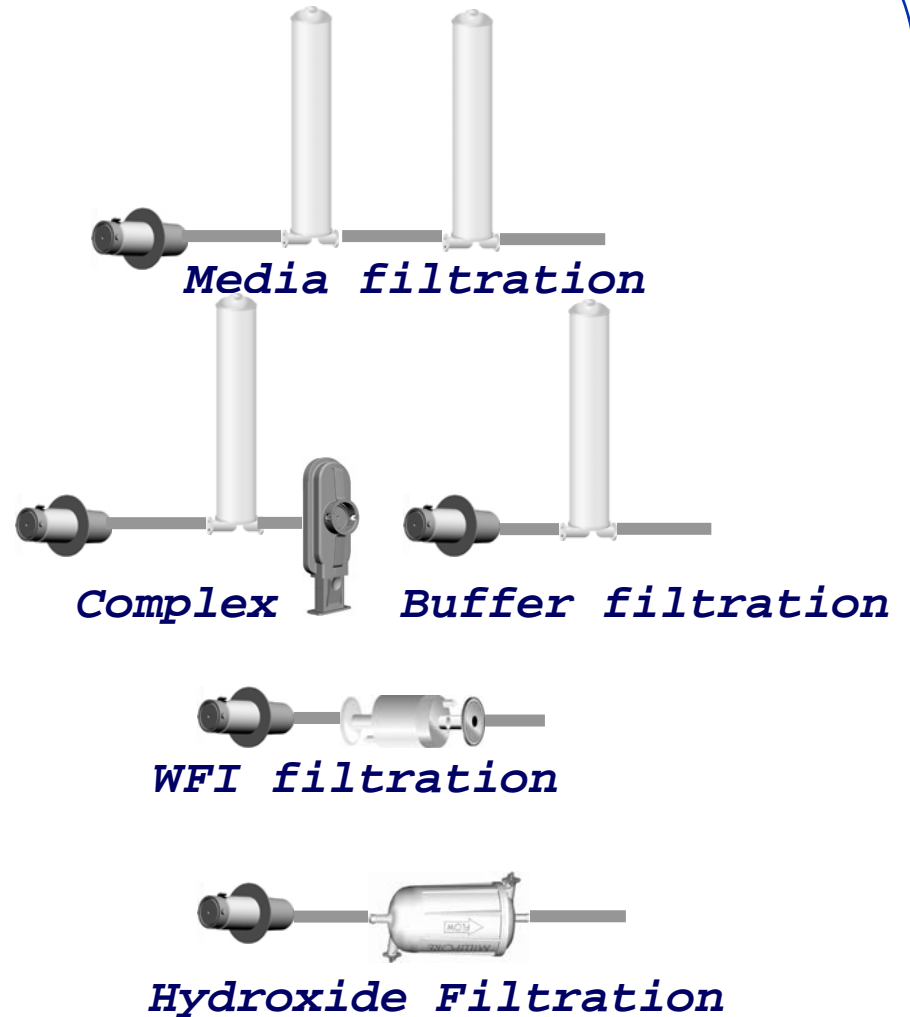
Single-use assemblies can be customized to meet defined application



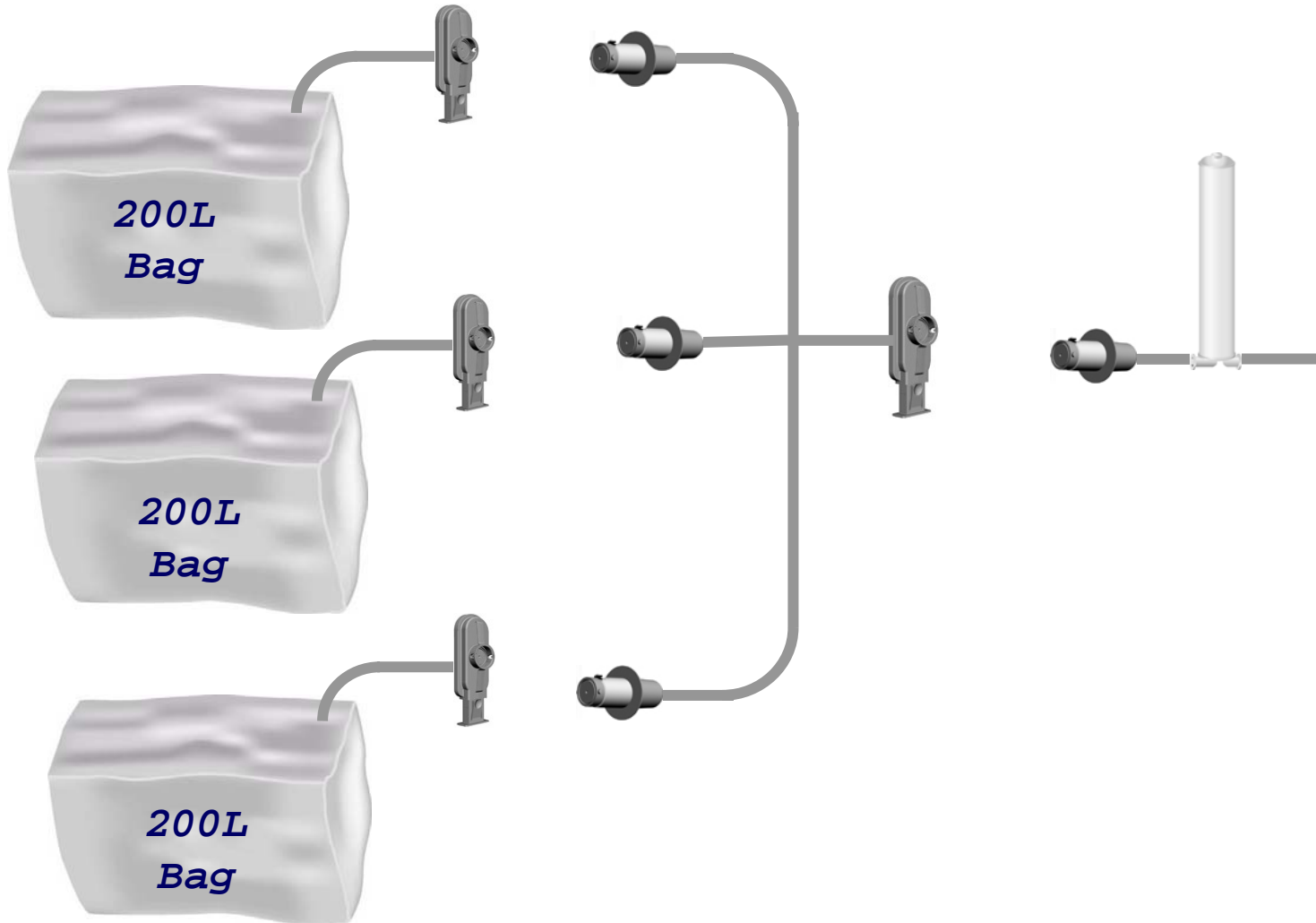
# Complexity of Single-use Applications

- **Increasing adoption of single-use systems**
  - Not all applications created equal – range from buffer preparation/storage to bulk drug substance storage/transport to final formulation/ filling
    - Storage of \$ 1000 worth of buffer to processing of >\$ 1M of drug product
- **Single-use systems range in the extent of ‘development’ effort employed**
  - Pre-engineered assemblies manufactured in 100s to 1000s per batch sold to multiple end-users
    - Ability to qualify design, manufacturing, transportation and end-use
    - Different levels of complexity – from simple filter/bag/tubing assemblies to complex TFF/Chromatography systems
  - End-user specific custom engineered assemblies manufactured 10 to 100 per batch
    - Limited ability to perform detailed qualification testing
    - Design guidelines employed and manufacturing controls in place but may not relate to the end-user process

# Assemblies: Flexible filtration



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# Assemblies: Flexible filtration

## Filters



- 0.1 Durapore PVDF
- 0.22 Durapore PVDF
- 0.5/0.1 Express PES
- 0.5/0.2 Express PES
- 0.2 Express PES

~ 20 filters of various sizes

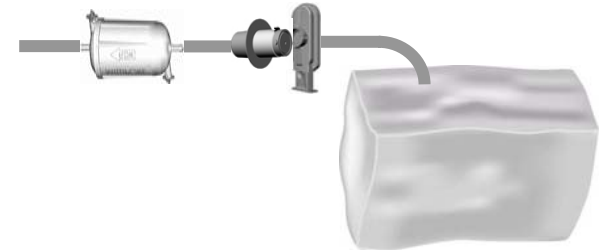
## Bags



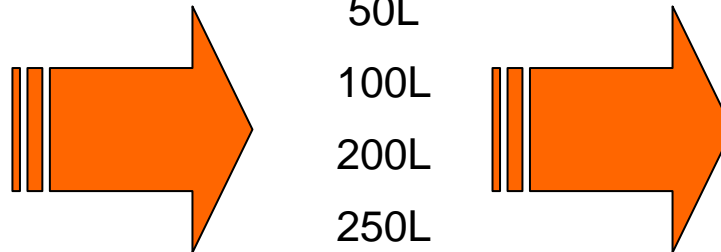
- 50L
- 100L
- 200L
- 250L
- 500L

4-6 different bags

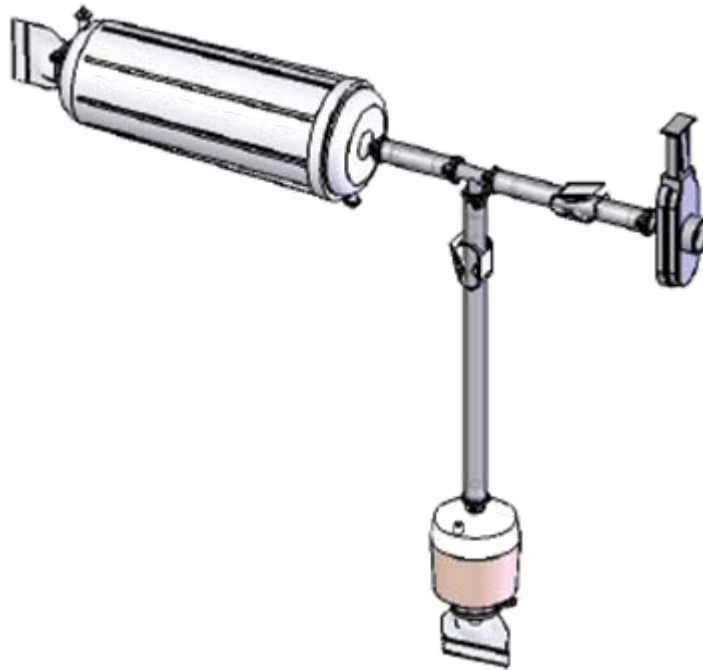
## Combinations



> 120 filtration combinations



# Assemblies: Sterile filtration



# Design for Manufacturability

Means of proactively addressing product issues early in the design cycle.  
Means for integrating specific manufacturing concerns into a product's design to obtain a product that is easier to manufacture with excellent overall quality (\*)

## DFM Guidelines – follow Good Engineering Practice

- **Reduce the number of parts** – minimize assembly error, improve chances for automation, decrease total cost
- Foolproof the assembly design – make assembly process unambiguous
- **Avoid tight tolerances** beyond the natural capability of the manufacturing processes
- **Design "robustness"** – compensate for uncertainty in manufacturing, testing and use
- Design for parts orientation and handling
- **Design for ease of assembly** by minimizing fastening steps
- **Design modular products** to facilitate the use of sub-assemblies
- Design for ease of servicing the product

(\*) [http://www.intel.com/design/quality/mq\\_dfm.htm](http://www.intel.com/design/quality/mq_dfm.htm)

# Designing for Manufacturability

## Manufacturer

### Product Design

- Understand design rules/limitations – most assembly processes are manual
  - Pay attention to: very short tubing or very long runs of silicone tubing, tolerance stack-up, same lengths of visually similar tubing, tubing ID to barb size, multi-filter (30”) assemblies, too many luer connections, packaging constraints, etc.
  - End-user needs/operator constraints
- Materials – chemical compatibility, physical compatibility (shelf life, gamma, material stress)
- Regulatory – component bioburden/ endotoxin, component cleanliness (lubricants, mold release, solvents, preservatives), E/L, particulates, Class VI compatibility (post- $\gamma$ )

## End-User

### Product Design

- Installation is mostly manual and has to be repeated over and over again
  - Pay attention to: pull force, fasteners in low pr. operations (accidental valve closure/ tubing kink), handling very long runs of silicone tubing, handling large/ complex assemblies, weight of wetted assemblies, too much packaging
  - Integrity testing of filters – pre-use?
- Materials – chemical compatibility (detergents, alcohol, NaOH), physical compatibility (shelf life)
- Regulatory – assembly bioburden/ endotoxin, E/L, USP <788>

# Designing for Manufacturability

## Manufacturer

### Process

- Apply design rules during manufacturing
- Equipment qualification, calibration, PM
- E&M Controls
- Manufacturing process window
- Qualified processes for kitting, fabrication, assembly, leak testing, packaging, sterilization

### People

- Training, testing, training...

## End-User

### Process

- Unpackaging, transport of unprotected assemblies
- Installation – surface of holders
- Assembly limitations – pressure, flow rate, temperature, etc.
- Operator limitations – weight of partially filled assemblies, height, etc.

### People

- Training, testing, training...

# Risk-based approach to design, manufacture and use: What have we done for critical applications?

- Process mapping – from design through manufacturing to end-use
  - Process FMEA – assembly, testing, packaging, shipping
  - End-use FMEA – unpackaging, handling, installation, use with end-user
- Identify high risk activities through standard RPN score and mitigate risks
- Potential risk mitigation actions:
  - Design verification through applications studies
  - Design refinement
  - 100% QC release test or improved AQL sampling plan
  - Packaging qualification
    - ISTA 2A drop & vibration tests followed by package integrity, sterility and/or functionality tests
  - Operator training for unpackaging/handling/installation
  - Assembly specific user guide
  - Pre-use leak testing

# People, Material and Equipment Flow

## People:

- Operator Manipulation for set-up and installation of assemblies
- Operator training and qualification required
- Modular assembly design for easier handling
- Fool proof design of assemblies (connections, fitting, etc.)

## Material:

- Assembly identification (labeling) for unit operations and full process
- Double bags for transfer in clean rooms

## Equipment:

- Mobile equipment set-up in clean room
- Transport of buffer holds (totes) from buffer make up area to points of use
- Zone concept – Buffer make up and hold outside production room (wall transfer)
- Room Classification – also specific to product (i.e. Pathogenic, cytotoxic, plasma derived, etc.)

# Post-use Disposal of Material

## Single-use products positive impact:

- Decreases customer energy use
- Reduces wastewater
- Avoids caustic cleaner

## Industry publications indicate that single-use in mAb processes:

- Reduce a company's carbon footprint by 25%
- Reduce water by 87% compared to traditional stainless technologies

## Disposal of Material after use:

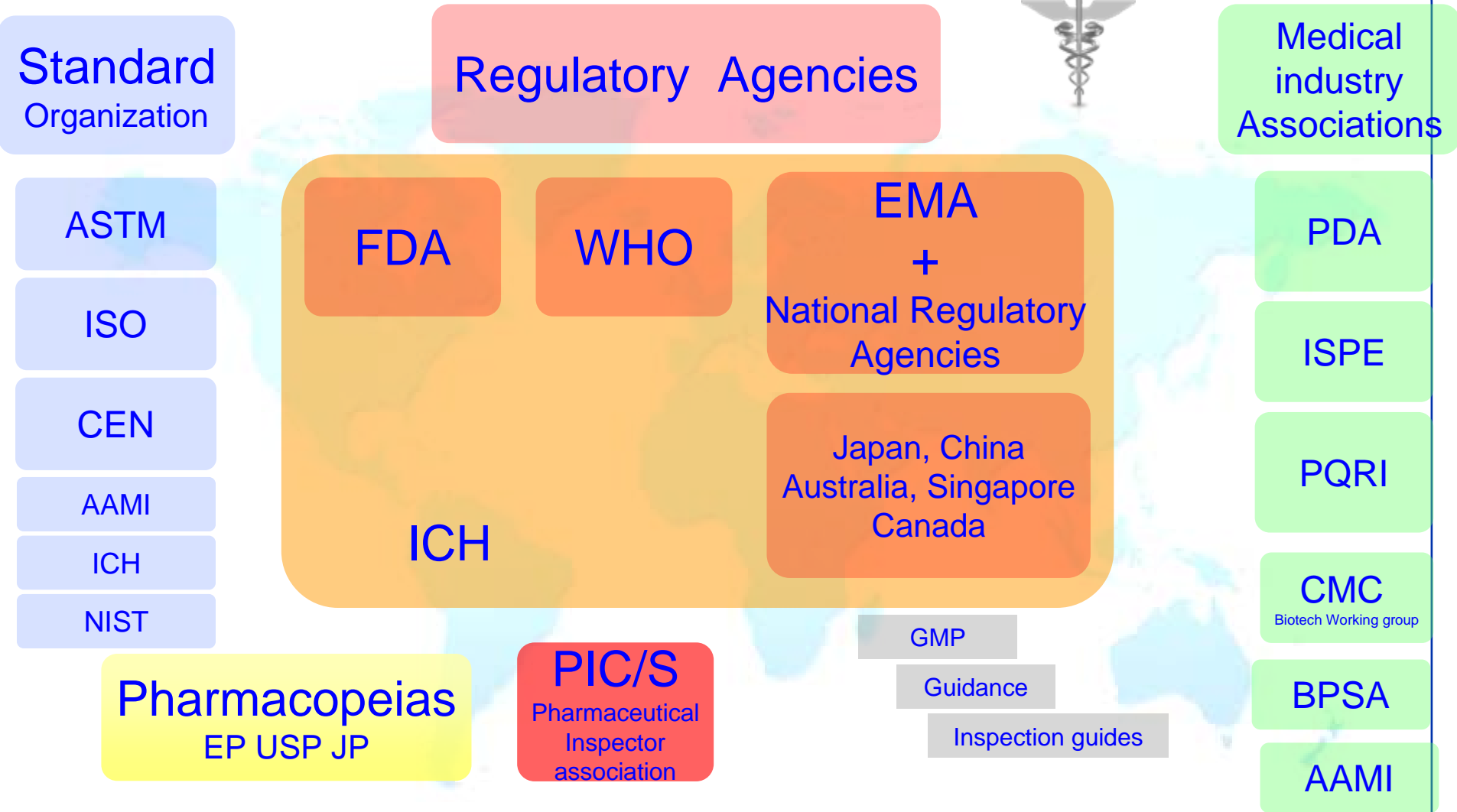
- Disposal using incineration
- Disposal as municipal solid waste/landfill

# Regulatory Requirements and Constraints

"The cGMP regulation require that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably"

(Guidance for Industry, Process Validation: General Principles and Practices. January 2011)

# Regulatory framework



# Status Quo

## **Regulatory Perspective:**

- o Highest level possible unless proven otherwise (i.e. FMEA)
- o Specific guidelines for Single-use technology in discussion
- o Requirements become more stringent

## **Suppliers Perspective & Support:**

- o Equipment qualification and validation support
- o Raw materials for components need to be compliant
- o Components need to be qualified
- o Final assemblies need to be certified
- o Qualification and certification needs to be maintained
- o Constant and repeat re-qualification of components and assemblies
- o Full assembly certification grouped according to requirements

# Assemblies: Certification Level Matrix Merck Millipore

Level	COQ	Shelf Life Claim	Sterility Claim	LAL & Particulate	Leak Testing	Class VI USP <88>
<b>Gold</b>	YES, in each box	YES, 2 years	Sterile, Qrtly Validation	Lot Release	100% of lot on full assembly & Bag	Post-gamma, component family
<b>Silver</b>	YES, in each box	YES, 2 years	Sterile, Qrtly Validation	Quarterly on representative sample	In-Process leak testing	Post-gamma, component family
<b>Bronze</b>	YES, in each box	NONE	Gamma Irradiated >25 kGy, not validated sterile	No testing performed	No Testing performed	Pre-gamma resin only

# Summary

**Single-use technology provides undeniable advantage over classical stainless steel installations within certain limits.**

**Process limits, processing scale and validation levels should be defined as early as possible.**

**Modular and standardized concepts are advantageous.**

**Classical stainless steel facilities are viable and will still be the primary choice given scale of operation. They may be partially upgraded and combined with single-use technology for certain tasks (i.e. Sampling), unit operations (i.e. Fill & Finish, terminal sterile filtration) or liquid hold and transfer (i.e. buffer, intermediate/final product hold), moving towards hybrid installations**

**Thank You !**

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