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.

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
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
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

- **MEDIA PREPARATION**
- **FERMENTATION**
- **HARVEST/CLARIFICATION**
- **CONCENTRATION & BUFFER EXCHANGE**
- **ION EXCHANGE CHROMATOGRAPHY**
- **VIRAL REDUCTION**
- **SOLVENT/DETERGENT**
- **PURIFICATION**
- **BUFFER EXCHANGE**
- **PURIFICATION**
- **CONCENTRATION**
- **STERILE FILLING**
- **AFFINITY CHROMATOGRAPHY**
- **SEC GEL CHROMATOGRAPHY**
Enabling single-use process

- Mobius CellReady
- Millistak+Express
- FlexReady Clarification
- Prosep Ultra Plus
- FlexReady Chrom
- FlexReady Virus
- Inactivation
- Eshmuno S
- FlexReady Chrom
- Pellicon-3
- FlexReady TFF
- Viresolve Pro
- FlexReady VF
- ChromaSorb/Eshmuno Q
- FlexReady Chromasorb
- Pre-packed Columns
- Mobius Assemblies
- NovaSeptum Sampling
- Drums, Totes & Bags
- Mobius MIX
- Durapore
- Mobius Filling Solutions
Time is Money – Impact of Single-Use Technologies on Process

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

Value added Work
Non-value added Work
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

- **Predesigned 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

- 200L Bag
- 100L Bag
- Media filtration
- Complex
- Buffer filtration
- WFI filtration
- Hydroxide Filtration
Assemblies: Flexible filtration
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-γ)

**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”

Regulatory framework

Standard Organization
- ASTM
- ISO
- CEN
- AAMI
- ICH
- NIST

Pharmacopeias
- EP
- USP
- JP

Regulatory Agencies
- FDA
- WHO
- EMA
- National Regulatory Agencies
  - Japan
  - China
  - Australia
  - Singapore
  - Canada

Pharmaceutical Inspector Association
- PIC/S

Guidance
- GMP
- Inspection guides

Medical Industry Associations
- PDA
- ISPE
- PQRI
- CMC
- Biotech Working group
- BPSA
- AAMI

ICH
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

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