Facility Design and Resource Optimisation for Multi-Product Vaccine Manufacturing

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May, 2015
Overview

• Understanding manufacturing costs
• Case study - Facility design and operation
  • Impact of single-use systems
  • Impact of segregated processing areas
  • Impact of changeover scheduling strategies
• Summary
Understanding manufacturing costs
Classic biomanufacturing costs

Classic scenario for biomanufacturing

- Single product: low flexibility
- Capital intensive
- Long construction lead time
- Fixed costs dominate
- Major gamble prior to launch
Facility utilization is key to minimizing production costs

Scenario in flexible facilities

- High degree of utilization due to process flexibility
- Output scale and demand match
- Multi-product production possible to drive further utilization improvements

The negative effect of under-utilization can hardly be compensated elsewhere, unless one builds small and (partly) disposable to reduce fixed cost by any feasible means.
Observations on cost drivers form a basis for facility design strategies

**Observations**

- Fixed costs dominate costs in conventional facilities
- Facility utilization is the dominating cost driver

**Strategies for improved facility utilization**

- Implementation of single-use systems
- Facility design to improve utilization
- Changeover scheduling

Single-use
## Single-use technologies

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Single-use option available</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell culture</td>
<td>Yes</td>
<td>Options exist from multiple vendors, but limited in size.</td>
</tr>
<tr>
<td>Microbial fermentation</td>
<td>Yes</td>
<td>A few options exist, limited in size.</td>
</tr>
<tr>
<td>High pressure homogenizer</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mixing</td>
<td>Yes</td>
<td>Mature application. Many options from different vendors, limited in size.</td>
</tr>
<tr>
<td>Liquid handling</td>
<td>Yes</td>
<td>Mature application. Many options from different vendors, limited in size.</td>
</tr>
<tr>
<td>Clarification</td>
<td>Yes</td>
<td>Depth filtration - Mature application. Many options from different vendors. Centrifugation – Options exist</td>
</tr>
<tr>
<td>Chromatography</td>
<td>Yes</td>
<td>Options exist, both for skids and columns (columns are typically used several times), but limited size range.</td>
</tr>
<tr>
<td>TFF</td>
<td>Yes</td>
<td>Options exist, both for skids and filters but limited size range.</td>
</tr>
<tr>
<td>Ultracentrifugation</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Claims made related to single-use systems

On costs

- Reduce capital investments (20-50% from comparable stainless facility)
- Delay investments
- Reduce validation cost (e.g. CIP methods)
- Reduce cleaning costs – personnel, water, steam and chemicals
- Increase some consumables costs (for disposables)
- Add and take away as needed - avoid cost of a rebuild
- Standardize and modularize – cheap to change, cheap to operate

On revenue

- Shorten time to readiness of facility
- More product, especially for multi-product facility
- Flexible. Be alert for the next challenge.
Case study: Facility design and operation in stick-build facility
Case study design: Cell-based vaccine facility

- 500L scale cell-based vaccine
- Vial-to-reactor upstream process
- Filtration and chromatography downstream
- Single- or multi-purpose
Evaluating the impact of single-use systems
Two possible process designs

**Stainless Steel**
Conventional process equipment, but single-use buffer hold bags

**Single-Use**
Single-use equipment where possible
Basic facility design requirements

- Production Building - production and clean utilities
- Warehouse – raw material, consumables, product
- Central Utilities Building – Non GMP utilities
- Administration Building - Offices, QC Laboratory, Canteen
Facility and utility design differences when implementing single-use

<table>
<thead>
<tr>
<th>Facility</th>
<th>Floor area (m²)</th>
<th>SST</th>
<th>SU</th>
<th>SST-SU difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production building</td>
<td>2580</td>
<td>1968</td>
<td>-24%</td>
<td></td>
</tr>
<tr>
<td>Admin &amp; lab building</td>
<td>1111</td>
<td>1111</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Warehouse</td>
<td>337</td>
<td>611</td>
<td>+81%</td>
<td></td>
</tr>
<tr>
<td>Central Utilities Building</td>
<td>325</td>
<td>325</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4353</td>
<td>4015</td>
<td>-8%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Utilities</th>
<th>Generator capacity</th>
<th>SST</th>
<th>SU</th>
<th>SST-SU difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified Water generator (L/day)</td>
<td>18000</td>
<td>2200</td>
<td>-88%</td>
<td></td>
</tr>
<tr>
<td>WFI generator (L/day)</td>
<td>14000</td>
<td>1300</td>
<td>-91%</td>
<td></td>
</tr>
<tr>
<td>Clean Steam Generator (kg/h)</td>
<td>87</td>
<td>17</td>
<td>-80%</td>
<td></td>
</tr>
</tbody>
</table>

SST = Stainless Steel
SU = Single-use
### Capital investment distribution when implementing single-use

<table>
<thead>
<tr>
<th>Component</th>
<th>Stainless Steel (SST)</th>
<th>Single use (SU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excavation</td>
<td>~ 40%</td>
<td>~ 50%</td>
</tr>
<tr>
<td>Installation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buildings</td>
<td>~ 30%</td>
<td>~ 20%</td>
</tr>
<tr>
<td>Construction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancillary facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>~ 15%</td>
<td>~ 15%</td>
</tr>
<tr>
<td>Piping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrumentation</td>
<td>~ 15%</td>
<td></td>
</tr>
<tr>
<td>Contractors fee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start-up Contingency</td>
<td>~ 15%</td>
<td></td>
</tr>
<tr>
<td>Working capital</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total capital investment</strong></td>
<td><strong>30% lower</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total capital investment for SU is 30% lower than for SST
Project execution comparison when implementing single-use systems

**Stainless Steel**
- Basic: 6 months
- Detailed Design: 14.5 months
- Procurement: 17 months
- Construction: 22.5 months
- Verification: 10.5 months
- Validation: 12 months

Duration: 43 months

**Single-use**
- Basic: 6 months
- Detailed Design: 14.5 months
- Procurement: 16 months
- Construction: 21.5 months
- Verification: 9.5 months
- Validation: 9 months

Duration: 37 months
Drivers for project timeline reductions

A Single-Use strategy means

- More standard, off-the-shelf equipment units
- Few long lead equipment items
- Less complexity in facility
- Less installation work

The Effects

- Facility construction will set the time frame
- Time saving in cleaning validation
- Less risk of delays

Shorter project adds value if on critical time-line
Time saved frees up resources for other activities
A single-use strategy provides a strong throughput benefit in multi-product facilities

- **3 products:**
  - Stainless Steel: 16% more batches with SU
  - Single-use: 29% more batches with SU

- **1 product:**
  - Stainless Steel: 16% more batches with SU
  - Single-use: 29% more batches with SU
Summary of Findings: Single-use system implementation

- Facility size is similar, but distribution of clean room and warehouse space is different
- Capital investment and project timelines are reduced
- Higher impact on output in a multi-product facility compared to a single-product facility
Thank you

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