An Introduction to Single-Use Systems

PDA Israel
Single Use Equipment
Tel Aviv, 7th May 2018
1. What are Single-Use Systems?
2. Single-Use Components
3. Single-Use Systems
4. Associated Services
5. Limitations and benefits of SUS
6. Biopharmaceutical Manufacture
7. Production costs: Single-Use vs Multiple-Use Technology
8. Biopharmaceutical Industry adoption of SUT
What are Single-Use Systems?
1. What are Single-Use Systems?

- Systems based on Single-Use components
- Components typically manufactured from plastics (Thermoplastic/Thermoset)
- Mainly used in the research and manufacturing of biopharmaceuticals
- Intended for one-time use (1 batch)
- Alternative to traditional systems mainly in Stainless Steel
- Also known as “Disposables”
Single-Use Components
Material = f (PC, CR)

Process Characteristics (PC): type of fluid, temperature, pressure, manufacturing layout, etc.

Customer Requirements (CR): gamma radiation, specific brands already validated, specific brands preferred, etc.

Contact VS Non-Contact components

Contact components → ADCF, USP Class VI
Purpose: Transfer of fluids in all biopharmaceutical process steps

- Platinum Cured Silicone is the most commonly used
- Specific formulations for specific applications and requirements:
  - Peristaltic pump applications (TPV) → Low spallation
  - Applications with aggressive chemicals → PFA, PTFE, FEP, etc.
  - Sterile Welding/sealing requirements (TPE) → Weldable/Sealable
2. Single-Use Components. Fittings & Connectors

**Purpose:** Union of other components with each other

- Tube-to-tube barbed fittings
- Ear clamp
- Molded Tri-clamp
- Sanitary fitting cap
- Quick connectors
- Luer
- Sanitary fittings
- Cable tie
Purpose: Continuous control of process parameters: P, T, pH, Cond., Q, etc.

- **Invasive sensors**: in contact with process fluids
  - Pressure sensor
  - Temperature sensor
  - Flow rate sensor

- **Non-invasive sensors**: NOT in contact with process fluids
  - Air bubble sensor
  - Flow rate sensor
  - Level detection at drip chambers
Purpose: Filtering of process fluids

- Depth filters
- Membrane filters
- TFF
- Death end

Clarification and prefiltration

Bioburden reduction, sterile filtration, virus filtration, air/gas vent filtration
Purpose: Storage, transport and product hold; Mixing; Cell cultivation and fermentation; Sampling

- Multilayer films (bags)
- For liquids and also for powders
- 2D (pillow) bag. End-ported and/or face-ported
- 3D bag. Top-ported, bottom-ported and/or face-ported
2. Single-Use Components. Other components

Thousands of different components!

- Plastic sanitary flange clamp
- Ratchet tubing Clamp
- Needle free valve
- Gaskets
- Dosing (filling) needle
- Dust bag
- Valve
Single-Use Systems
## 3. Single-Use Systems

<table>
<thead>
<tr>
<th></th>
<th>TUBING</th>
<th>FITTING/CONNECTOR</th>
<th>SENSOR</th>
<th>BAG/BOTTLE</th>
<th>FILTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUBING SYSTEM</td>
<td>YES</td>
<td>YES</td>
<td>OPT</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>FILTERING SYSTEM</td>
<td>YES</td>
<td>YES</td>
<td>OPT</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>(optional: small bags/bottle usually for sampling)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAG/BOTTLE SYSTEM</td>
<td>YES</td>
<td>YES</td>
<td>OPT</td>
<td>YES</td>
<td>OPT</td>
</tr>
</tbody>
</table>

*Parenteral Drug Association*
Associated Services
4. Associated Services

• Radiation
  - Most used: *gamma radiation* (25kGy-40kGy)
  - Systems ready-to-use

• Integrity test
  - Most used: *pressure decay testing*
  - Lower the risk of lost time, loss of product and improve operator safety
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

Limitations and benefits of SUS
5. Limitations and benefits of SUS

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Process/Product Flexibility</td>
<td>Technical limitations</td>
</tr>
<tr>
<td>- Turnaround times</td>
<td>+ Running Cost</td>
</tr>
<tr>
<td>+ Speed of implementation</td>
<td></td>
</tr>
<tr>
<td>- Investment Cost</td>
<td></td>
</tr>
<tr>
<td>+ Product Safety</td>
<td></td>
</tr>
</tbody>
</table>
Biopharmaceutical manufacture

BIOPHARMACEUTICALS

• Drugs (proteins) produced using microorganisms (i.e.: bacteria, yeast, mammalian cells and insect cells)
• Very sensitive → high control of process parameters
• More complex proteins → more effective and safer
• Expensive treatments: 10.000€/patient-100.000€/patient per year
• >10 years to develop a biopharmaceutical

MAIN TREATMENTS

• Diabetes, cancer, hepatitis, growth disturbances, skin diseases, rheumatoid arthritis and blood disorders.
MEDIA/BUFFER PREPARATION

UPSTREAM

API Production and Cell Cultivation
- Inoculum Production
- Cell Cultivation

API Fermentation
- BAX
- API

API Isolation and Concentration
- HAB
- POB
- POB

DOWNSTREAM

API Polishing
- BDS Formulation and Filling
- BDS Freezing and Storing and Thawing
- BDS Labeling and Packaging

FORMULATION AND FILLING

Connecting People, Science and Regulation®
6. Biopharmaceutical Manufacture. PFD
6. Biopharmaceutical Manufacture. PFD

Inoculum Production and Cell Cultivation

API Fermentation

API Isolation and Concentration

Connecting People, Science and Regulation®
Production costs

Single-Use vs Multiple-Use Equipment
• **Cost** is one of the main factors to evaluate SU implementation

• **Costs considered:**

  - **Investment costs:** Capital used to build a facility ready for production including the equipment, piping, instrumentation, automation, and building. Included indirect costs as contractors and engineering
  
  - **Running costs:** Cost to maintain the facility in operation. Included raw materials, consumables, utilities, and personnel
**7. Production costs: Single-Use vs Multiple-Use Technology**

2x1000L BR; Cult. time: 14d; 48 batches/year; Product titer: 3g/L after cultivation

**Comparison of investment costs**

<table>
<thead>
<tr>
<th>Investment</th>
<th>MU facility T€</th>
<th>SU facility T€</th>
<th>difference T€</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process and clean utilities</td>
<td>9555</td>
<td>6018</td>
<td>-3537</td>
<td>-37</td>
</tr>
<tr>
<td>Automation and instrumentation</td>
<td>4778</td>
<td>3034</td>
<td>-1744</td>
<td>-37</td>
</tr>
<tr>
<td>Process piping and isolation</td>
<td>4778</td>
<td>825</td>
<td>-3953</td>
<td>-83</td>
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<tr>
<td>Building, HVAC, electrical and black utilities</td>
<td>5706</td>
<td>6090</td>
<td>384</td>
<td>7</td>
</tr>
<tr>
<td>Engineering cost</td>
<td>7445</td>
<td>4790</td>
<td>-2655</td>
<td>-36</td>
</tr>
<tr>
<td>Offices and laboratories</td>
<td>3500</td>
<td>3500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Start-up cost</td>
<td>6832</td>
<td>6941</td>
<td>109</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total investment cost</strong></td>
<td><strong>42594</strong></td>
<td><strong>31198</strong></td>
<td><strong>-11396</strong></td>
<td><strong>-27</strong></td>
</tr>
</tbody>
</table>

**Comparison of running costs per year**

<table>
<thead>
<tr>
<th>Investment</th>
<th>MU facility T€/year</th>
<th>SU facility T€/year</th>
<th>difference T€/year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total investment cost (T€)</td>
<td>42594</td>
<td>31198</td>
<td>-11396</td>
<td>-27</td>
</tr>
<tr>
<td>Running costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total labor</td>
<td>2993</td>
<td>3150</td>
<td>157</td>
<td>5</td>
</tr>
<tr>
<td>Raw material</td>
<td>756</td>
<td>756</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Consumables</td>
<td>2640</td>
<td>3984</td>
<td>1344</td>
<td>51</td>
</tr>
<tr>
<td>Utilities</td>
<td>434</td>
<td>423</td>
<td>-11</td>
<td>-3</td>
</tr>
<tr>
<td>Waste</td>
<td>10</td>
<td>16</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Maintenance and insurance</td>
<td>1316</td>
<td>852</td>
<td>-464</td>
<td>-35</td>
</tr>
<tr>
<td><strong>Total running cost</strong></td>
<td><strong>8149</strong></td>
<td><strong>9181</strong></td>
<td><strong>1032</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>

Connect the Dots, Science and Regulation®
7. Production costs: Single-Use vs Multiple-Use Equipment

Costs vs Time

- 48 batches/year
- 96 batches/year

Conclusions

- SU supposes:
  - Reduction of investment costs
  - Increase of running costs
- A comprehensive economic study is necessary before deciding whether or not to implement single-use technologies
- Most economical option → **Hybrid systems**
Biopharmaceutical Industry adoption of SUT
Growing but overall adoption remains small
- Conservative attitudes tend to dominate the biopharmaceutical industry → slow adoption of newer manufacturing technologies
- Attractive for smaller lesser-funded companies and multiproduct facilities
- Attractive for low-volume manufacturing → Preclinical and Clinical stages

- Portion of SUT within the total industry capacity → ≈ 10%
- Portion of SUT in new installations → ≈ 25%-50%
- Market growth 2015-2018 → ≈ 20%
Thank you for your attention

ANY QUESTION?

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