Disposables impact upon large scale mammalian facility design

Dave Wolton
VP manufacturing
Overview

• CMC
• Design assumptions for a new facility
• Conventional facilities vs Lean
• Think global
• 2000L suite at CMC Copenhagen
• Summary
Contract Manufacturer of Biological Therapeutics utilizing MAMMALIAN & MICROBIAL CELL CULTURE TECHNOLOGIES

- Cell-line Development – CHEF1™ technology
- Upstream/Downstream – process development and manufacture
- Analysis, Characterization, Formulation, Quality and Regulatory
Design assumptions
Design assumptions

<table>
<thead>
<tr>
<th>g/L</th>
<th>No. Of reactors</th>
<th>Prot. A Size</th>
<th>Kg per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g/L</td>
<td>12 * 2000L</td>
<td>80cm*15cm bed height</td>
<td>1,200kg</td>
</tr>
<tr>
<td>5g/L</td>
<td>12*1000L</td>
<td>80cm*20cm bed height</td>
<td>1,125kg</td>
</tr>
</tbody>
</table>

- Plant runs for 300 days per year
- Protein A Cycles per batch approx. 4
- Harvest two reactors every 2 days
- Assumed product campaigns are the norm
- Cell culture only work days

= 2 x 10,000L stainless plant
Footprint comparison

6 x 12,000L Stainless Conventional design

12 x 2,000L Disposable Lean design

12 x 2,000L Disposable Lean design
Footprint comparison

Media Preparation
Footprint comparison

Cell Culture
Footprint comparison
Footprint comparison

Purification
Footprint comparison

Buffer
Conventional vs Lean facilities
Footprint comparison

• Downsides of 6 x 12,000L stainless facility
  • Time taken to move people round the facility
  • Multiple change areas
  • Large air volume to keep warm/cool and filtered
  • Multiple large lifts needed
  • Difficult communication between teams
  • Complicated materials and people flow
  • High gowning costs
Footprint comparison

- Downsides of a conventional 12 x 2,000L disposables facility
  - Separate buffer and media teams
  - Large areas reserved for moving 1000L totes
  - Hi grade seed area needed
  - More change areas
Lean facility
Mezanine cut away to show media mixing system
Mezanine
How?
(What new equipment is needed)
Contained media mixing – Hyclone

Hyclone Powdertainer
Contained media mixing - Lormac
Contained powder addition

- Risk assessment to the environment for making media in the suite.
- Industry examples
  - Microbial facilities often add powdered media directly to the bioreactor and sterilise in-situ.
No seed lab required

Cryo-storage of the working cell bank in Bags

Tubing weld directly onto a controlled bioreactor
No seed lab required

- Risk assessment for contained thaw
- Industry examples
  - A number of facilities already use contained thaw.
  - The work can be carried out in a Vertical laminar flow cabinet for added safety
  - Bioburden testing is routine in upstream mammalian facilities
Buffer systems

How do you make and store up to 6,000L of buffer and not use large numbers of buffer bags?
Buffer towers

Answer

• Position 2,000L buffer towers next to the column
• Top up’ from 1,000L single use mixers.
### Waste comparison example

#### 2,000L Buffer Towers

<table>
<thead>
<tr>
<th></th>
<th>1000L mix</th>
<th>buffer (a+b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

#### Per Run

- **Equipment**
  - 2 bags of 1000L mix
  - 5 bags of buffer

#### Per Month

- **No. Bags**
  - 10 runs of 1000L mix: 10x2
  - 5 runs of buffer: 5x1
Use of buffer towers

- Risk assessment for topping up buffer towers
- Industry examples
  - A number of facilities top up systems
    - Perfusion media tanks
    - Oxygen/Nitrogen/ tanks
    - Bulk supplies of ethanol and Sodium Hydroxide
  - Filter in and filter out
  - Splitting of seed cultures in Waves/rollers and shakers
Upsides of the design

- Upsides of a Lean 12 x 2,000L disposables facility
  - Amalgamated teams (smaller headcount)
  - Less movement of buffers and media
  - Smaller footprint
  - Simpler flows of people, product and materials
Staffing requirements

- 300-500
- 70-120
# Staffing requirements

<table>
<thead>
<tr>
<th>Department</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>12 technicians, 9:00 to 5:30, 7 days a week</td>
</tr>
<tr>
<td>Purification</td>
<td>24–36 technicians, 24 hour, 7 days a week</td>
</tr>
<tr>
<td>Buffer–Media</td>
<td>0 technicians</td>
</tr>
<tr>
<td>HR</td>
<td>1 manager, 1 admin.</td>
</tr>
<tr>
<td>QC</td>
<td>No change from current factories</td>
</tr>
<tr>
<td>Maintenance</td>
<td>1 HVAC, 1 Utilities, 2 Equipment/Cal Plant</td>
</tr>
<tr>
<td>Automation</td>
<td>0 IT, 3–4, Electronic batch records preferable</td>
</tr>
<tr>
<td>Stores</td>
<td>Same as current factories</td>
</tr>
</tbody>
</table>

Stores
Same as current factories
HVAC

AHU 1
ISO 7 in operation

AHU 2

AHU 3
ISO 7 in operation

AHU 4
ISO 5 in operation

Reduced Carbon emissions
Think global
### Powdered media

<table>
<thead>
<tr>
<th>Step</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powders delivered to media suppliers facility</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>Powders stored at media suppliers facility</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Powders dispensed at media suppliers facility</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Media preparation</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Goods out at media suppliers facility</td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td>QC at media suppliers facility</td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Goods in at Biotech facility</td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
<tr>
<td>QC at Biotech facility</td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>On plant cold storage</td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
<td>Bioreactor hall</td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
</tbody>
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### Liquid media

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<tr>
<td>Powders delivered to media suppliers facility</td>
<td><img src="image11.png" alt="Image" /></td>
</tr>
<tr>
<td>Powders stored at media suppliers facility</td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>Powders dispensed at media suppliers facility</td>
<td><img src="image13.png" alt="Image" /></td>
</tr>
<tr>
<td>Goods out at media suppliers facility</td>
<td><img src="image14.png" alt="Image" /></td>
</tr>
<tr>
<td>Goods in at Biotech facility</td>
<td><img src="image15.png" alt="Image" /></td>
</tr>
<tr>
<td>QC at Biotech facility</td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
<tr>
<td>On plant cold storage</td>
<td><img src="image17.png" alt="Image" /></td>
</tr>
<tr>
<td>Bioreactor hall</td>
<td><img src="image18.png" alt="Image" /></td>
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</tbody>
</table>
Central dispensary supplying multiple small factories with identical amounts
New 2000L facility in Copenhagen
New 2000L facility in Copenhagen
Integrated 500L depth filter system
Integrated 500L depth filter system
Integrated 2000L depth filter system
Summary

• Slide from Johannes R. Roebers, PhD
Thanks to

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• Nick Bevan - Wyeth