FACILITY DESIGN FOR EFFICIENCY AND NEXT-GEN PROCESSING

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Agenda

- Upstream and Downstream Technologies
  - Facility Design
  - Next Generation Processing
  - Single Use Technology
  - Process Economics
Bristol Myers Squibb – Devens, MA Building 210

Goal of new suite: Increase throughput, while decreasing manufacturing footprint and shortening processing durations

SINGLE USE MANUFACTURING

MANUFACTURING
- 3x 2,000L Mammalian Process
- Next Generation Manufacturing utilizing Single use Technology
- Hybrid Ballroom Design

Building 210 Facility Classification - Upstream

Grade/Iso Classification | Class
---|---
5 | 100
6 | 1,000
7 | 10,000
8 | 100,000
Controlled Non-classified (CNC) | Not applicable
Upstream Process Flow
Current state: Inoculum Seed Expansion and Fed-Batch Process

Future state: Perfusion Seed and High Density Fed-batch

Vial Thaw – Inoculum Prep (Grade 8 Space)
Shake Flask Expansion (CNC Space)

Traditional

- Requires BSC (grade 5) and a grade 7 background - Requires EM during all open operations
- Multiple flasks at each stage to ensure redundancy in case of contamination

Novel Approach – Closed Shake Flask Design

- Closed flasks have tubing that allows for closed sampling and closed transfers to the subsequent flask.
- Combination of closed flasks and isolator gives ability to operate in CNC
- Incubators are located in CNC area - Less Gowning, EM Efficiencies

Cell Bag Bioreactor N-2 Setup

Weight Control

\[ W_s = \text{Rocker Scale Weight (kg)} \]

- Control pump speed based on rocker scale weight, \( W_s \)
- Drives perfusion rate based on vessel volumes per day
- Connected to 0.2 μm floating filter outlet port

MEDIA INLET PUMP

FRESH MEDIA

MEDIA

PERFUSATE / HARVEST MEDIA

Rocker scale

Flowsensor

PERFUSION PUMP
### Dynamic Control of Perfusion Rates

**Challenge:** Perfusion process can consume large volumes of media, driving up cost

- Dynamic control of perfusion rates lowers perfusion media utilization rates without impact to cell growth
- ~30% reduction in perfusion media

**Evaluation of titers in Day 10 (High Density Fed-Batch) to Day 14 (Fed-Batch) across five cell lines / process**

- **High Density:** $10 \times 10^6$ cells/ml
- **Fed-Batch:** $1 - 4 \times 10^6$ cells/ml
### Building 210 Facility Classification - Downstream

<table>
<thead>
<tr>
<th>Grade/Iso Classification</th>
<th>Class</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
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<td>6</td>
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</tr>
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<td>Controlled Non-classified (CNC)</td>
<td>Not applicable</td>
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</table>

### Downstream Process Intensification

#### Current-Gen Batch Purification

1. Protein-A
2. VI
3. Polish 1
4. Polish 2
5. VF
6. UF/DF

#### Next-Gen Intensified Purification

1. Protein-A
2. VI
3. Polish 1 & 2
4. VF
5. UF/DF
Chromatography Skid

- Capable of running:
  - Single-Column Batch
  - Multicolumn Continuous Capture
  - Pool-less Integrated Batch Polishing
- Capable of in-line dilution
- CIP Header to “functionally” close the chromatography operation
- Compatibility with legacy processes

Multicolumn Continuous Capture

Schematic Representation of Batch vs. MCC

- In MCC capture, the first column is loaded beyond its 1% DBC and the flowthrough is captured onto the second column in the loading zone
- The sequential loading allows for better capacity utilization and productivity without sacrificing yield or impurity clearance
  - 2-3X increase in productivity
  - 50% decrease in buffer consumption
**Batch vs Multicolumn Continuous Capture (MCC) Performance**

- **Yield**
  - Did not sacrifice yield

- **Productivity**
  - 2-3X increase in productivity

- **Buffer Consumption**
  - 50% decrease in buffer consumption

**Multicolumn Continuous Capture – Protein A Cost Model Example**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Column Volume (L)</th>
<th>Total Resin Cost ($12,500/L)</th>
<th>Capacity Utilization %</th>
<th>Total Time (hr)</th>
<th># of Cycles Needed</th>
<th>Material Processed per Cycle (kg)</th>
<th>Productivity (g/L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Gen</td>
<td>70.7</td>
<td>$883,750</td>
<td>55%</td>
<td>11</td>
<td>3</td>
<td>3.2</td>
<td>12</td>
</tr>
<tr>
<td>Next Gen Scenario #1</td>
<td>31.8</td>
<td>$397,500</td>
<td>92%</td>
<td>13</td>
<td>4</td>
<td>2.8</td>
<td>23</td>
</tr>
</tbody>
</table>

- 67% capacity utilization increase
- Total resin savings: $486,000 (per campaign)
- 55% cost decrease per batch
Pool-less Integrated Batch Polishing (IBP)

Eliminate intermediate product pool hold tanks between chromatography steps

Example IBP FT/FT HIC/CEX operation

- Three formats evaluated:
  - FT → FT
  - FT → B&E
  - B&E → FT
- Eliminates need for in-process hold vessel
- 2x increase in productivity over traditional batch
- Automated column valve switching based on UV trigger criteria enables robust and consistent operation
- Less sampling for bioburden mapping
- Increase stability of in-process pool due to decrease in hold times
- Reduced footprint

Parallel operation

Series (HIC → CEX)

Parallel operation

Batch vs Pool-less Integrated Batch Polishing (IBP) Performance

Did not sacrifice yield or impurity clearance

2X increase in productivity
**Chromatography Skid – CIP Header (Closing Open Connections)**

**CHALLENGE**
- Chromatography skids have standard open TC connectors.

**OUR SOLUTION**
- Skid designed with a single sanitization inlet used to clean all flow paths.
- Lynx connector combined with standard aseptic connectors are installed on inlets and outlets prior to sanitization.
- All open connections are made prior to sanitization.
- After sanitization, Lynx connector is activated by quick twist to create open flow path through the skid.

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**Automated Viral Inactivation**

- Standardizes dispense rate, dose volume, and maximum and minimum wait times for viral inactivation and neutralization
- Reduces operator error and overshooting

![pH vs Percent Volume Added](chart.png)

**ACID – 0.1N HCl**
**BASE – 2M Tris**
# Summary of Next Generation Manufacturing Benefits

<table>
<thead>
<tr>
<th>Facility</th>
<th>Area of facility</th>
<th>Process Metrics Assumptions</th>
<th>~ Annual Output (metric tons/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current State (SUF 1) 3 x 2000L Bioreactors</td>
<td>36,400 sq. ft.</td>
<td>Lots = 66 (5 day cadence)  Titer = 6 g/L  DSP yield = 70%</td>
<td>0.56</td>
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<tr>
<td>Next Generation Manufacturing (SUF 2) 3 x 2000L Bioreactors</td>
<td>20,120 sq. ft.</td>
<td>Lots = 90 (3-4 day cadence)  Titer = ~10 g/L  DSP yield = 70-80%</td>
<td>1.24</td>
</tr>
</tbody>
</table>

**Goal of new suite:** Increase throughput, while decreasing manufacturing footprint and shortening processing durations

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# Acknowledgements and Questions

**PROCESS DEVELOPMENT**
- Sanchayita Ghose
- Michael Borys
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