Advances in Disposable-Format Downstream Processing Technologies

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September 22, 2008
BPI Pre-Conference Workshop, Anaheim, CA
Presentation outline

- Driving forces for use of disposable-format downstream processing technologies
- Examples of current technologies and applications
- Implementation requirements and considerations
Driving Forces and Trends
Business and Operational Driving Forces for Disposable DSP Technologies

- **Business drivers favoring increased use of disposables:**
  - Speed to clinical proof-of-concept and commercial launch
  - Reduced capital investment and improved return on capital employed
  - Deferred expenses on early-stage programs
  - Increased facility utilization by reducing change-over time

- **Operational drivers favoring increased use of disposables:**
  - Reduced cleaning and cleaning validation costs in multi-product operations
  - Increased operational flexibility by minimizing/eliminating multi-use equipment
  - Improved process portability and fewer “facility fit” issues
  - Improved feasibility due to increasing availability of suitable disposable processing equipment throughout the biopharmaceutical flowpath
Clinical Manufacturing
Clinical Pipeline is Weighted Towards Monoclonal Antibody Products

- Biopharmaceutical pipeline is 70% mammalian cell culture
- Antibodies remain ~ 85-90% of mammalian cell culture pipeline enabling heavy use of platform processes

* As recorded in BPTC Pipeline Database

** Estimates Based on BPTC Pipeline Database Coverage
## Accelerating Speed to Clinic

<table>
<thead>
<tr>
<th>Activity</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
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<tbody>
<tr>
<td>Pre-clinical stage 1</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
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<tr>
<td>Cell line development</td>
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<td>Analytical development</td>
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<td>Process development</td>
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<td>MCB Prep/Test</td>
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<td>Reference Standard Development and Characterization</td>
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<td>Clinical formulation development</td>
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<tr>
<td>Pre-IND meeting</td>
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<tr>
<td>DS Mfg (Engineering and GMP clinical runs) and release testing</td>
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<tr>
<td>DP Mfg and release testing</td>
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<td>Stability studies (DP and DS)</td>
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<tr>
<td>IND filing</td>
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<tr>
<td>MILESTONE POINT 1 - IND Filing</td>
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</table>

- **Platform Processes**
- **Disposable Technologies**
Project Risk and Cost of Capital are Significantly Higher for Clinical Manufacturing

* - Cost of Capital estimate based on discount factors from a risk-adjusted NPV analysis
1) Technologies that
   • reduce capital investment and/or
   • increase speed to risk-reduction milestones
   are inherently more valuable in high-risk projects

2) CMC is often on the critical path in early-stage biopharmaceutical development

⇒ There is a compelling financial and risk-management argument for disposable manufacturing technologies in early-stage biopharmaceutical development
Late-Stage Development/ Commercial Manufacturing
Trend 1: Cell Culture Volumetric Capacity Continues to Expand

- [Method NOTE: Perfusion capacity adjusted to equivalent fed-batch capacity]
- Clinical supply represents approximately 5% of installed capacity
- PDCs control the majority (~80%) of total installed capacity

Mammalian Cell Culture Capacity

Distribution by Company – 2007

**Product Development Cos.**
- Amgen: 13%
- Genentech: 20%
- J&J (Centocor): 11%
- Wyeth BioPharma: 12%
- Biogen Idec: 6%
- Imclone: 8%
- Others (25): 30%

**Contract Manufacturers**
- Lonza Biologics: 28%
- Baxter BioPharma Solutions: 3%
- Wyeth BioPharma: 12%
- J&J (Centocor): 11%
- Biogen Idec: 6%
- Imclone: 8%
- Others (19): 11%
- Human Genome Sciences: 7%
- Diosynth Biotechnology: 8%
- Celltrion: 9%
- Others (30): 30%

(BioProcess Technology Consultants)
Trend 2: Increasing Titers

1978: Recombinant insulin produced

2006:
- Industry Standard: 1-2 g/L
- Industry Leaders: 3-6 g/L

Improved strains

2015-2020:
- Future Leaders: >10 g/L

Continued innovation will increase yields and drive down costs

Source: Charlebois T, “Technology and Opportunities in Mammalian Cell Culture” presented at BIOMAN 2006 Conference, Portsmouth NH (2006)
### Trend 3: Increasing Scale of Disposable Bioreactor Offerings

<table>
<thead>
<tr>
<th>Vendor</th>
<th>Scale</th>
<th>Product Name</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xcellerex</td>
<td>Up to 2,000L</td>
<td>XDR™ Bioreactor</td>
<td>Stirred-tank</td>
</tr>
<tr>
<td>Thermo Fisher (Hyclone)</td>
<td>Up to 1,000L</td>
<td>Single-use Bioreactor (S.U.B.)</td>
<td>Stirred-tank</td>
</tr>
<tr>
<td>GE Healthcare (Wave)</td>
<td>Up to 500L</td>
<td>Wave Bioreactor</td>
<td>Rocking Platform</td>
</tr>
</tbody>
</table>
Commercial Disposable-Format Manufacturing?

 Goa “The math”:
 • 2000L bioreactor operating at 15 g/L ->
   – 30 kg per batch in cell culture supernatant
 • DSP overall yield of 65-70% ->
   – 20 kg per batch bulk drug substance
 • 14-day fed-batch cycle and 90% success rate ->
   – 20+ lots per year
   – 400 kg per year per 2000L bioreactor

 Goa What does this mean for DSP requirements?
 • Capture: Affinity chromatography with binding at 30 g/L ->
   – One cycle = 1,000L column (2 m ID x 32 cm H)
   – Five cycles = 200L column (1 m ID x 25 cm H)
 • Alternative approaches needed to enable commercial disposable DSP
Current Technology Examples and Applications
Disposable Products* Now Exist Across the Entire Biopharmaceutical Manufacturing Flowpath

- Sartorius Stedim
- Thermo Fisher
- Hyclone S.U.B.
- Xcellerex XDR

Disposable Sensor Technology

- GE (Wave)
- Thermo Fisher (Hyclone S.U.B.)
- Xcellerex (XDR)

- Sartorius Stedim (Celsius)
- Flexicon (DAFPA)

- Sartorius Stedim
- Thermo Fisher
- ATMI
- TNTC

* - Suppliers profiled are not a complete list nor an endorsement of any specific company or technology
**Downstream processing unit operations**

- **Normal Flow Filtration**
  - Depth filtration for clarification
  - Nanofiltration for virus removal
  - Sterile filtration

- **Tangential Flow Filtration**
  - Ultrafiltration for concentration and buffer exchange
  - Microfiltration for clarification

- **Centrifugation**
  - Clarification
  - Inclusion body isolation

- **Cell Breakage/Homogenization**
  - For recovery of products expressed intracellularly

- **Refolding**
  - For some *E. coli* products

- **Crystallization/Precipitation**

- **Chromatography and adsorptive separations**
  - Typical downstream process includes 3 – 4 chromatography and/or membrane adsorber steps
    - Ion exchange
    - Hydrophobic interaction
    - Affinity
    - Size exclusion
    - Reverse phase
Disposable Format Depth Filtration: Improvements in Hardware Design

- Improved CIP of Hardware
  - Self-contained, disposable Pods
  - Disposable feed ports and fittings
  - No product contact with endplates or process skid

- Improved Handling
  - No messy spent filters
  - Lightweight, easy to set up and use
  - No hoist or high ceiling required

Courtesy of Millipore
Disposable format purification product examples: Chromatography and Adsorptive Separations

- Membrane adsorbers
  - Sartorius Sartobind®
  - Pall Mustang®

- Disposable chromatography columns
  - GE Ready-to-Process™
  - BioFlash™

- Other
  - Scouting columns and technologies

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Membrane Adsorber Use in Commercial DSP

...clears the DNA below detection limit


Average of eight 2,000 liter batches using 70 ml Sartobind
Average of three 12,500 liter batches using 500 ml Sartobind

DNA (pg/mg protein)

After Affinity Step
After DNA removal step

Average of eight 2,000 liter batches using 70 ml Sartobind
Average of three 12,500 liter batches using 500 ml Sartobind

Courtesy of Sartorius
Other Literature Examples of Process Use of Membrane Adsorbers

Disposable Chromatography Technology Examples: Pilot/Process Scale

Ready-to-Process Chromatography Columns (GE Healthcare)
12.6, 25.1, and 35.9 cm ID x 20 cm H

BioFlash Disposable Format Chromatography (DFC™) Columns (BioFlash Partners)
1.2, 8, and 20 cm ID x variable H
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Example of emerging TFF technology: SPF (Pall); Petrone J, RXIII Conference
Typical MAb Process Flowchart
Impact of increasing cell culture titer and scale on downstream processes

- Cell culture titers of 4 g/L are now routinely achievable for monoclonal antibodies:

- Increasing conventional and disposable bioreactor scales + increasing titers → large product amounts in DSP batches:
  - At 4 g/L, a 25,000 L bioreactor will yield 100 kg per batch
  - At 15 g/L, a 2,000 L disposable bioreactor will yield 30 kg per batch

- Increasing production scale and titers present challenges and opportunities for disposable format (and conventional) downstream process operation → New Approaches Needed
New Technology Options in Development

- **BioSMB™**
  - Tarpon Biosystems

- **Disposable-format Expanded Bed Adsorption (EBA)**
  - Upfront Chromatography

- **High capacity monolith and membrane adsorbers**
  - BIA Separations

* Suppliers profiled are not a complete list nor an endorsement of any specific company or technology.
One option: BioSMB Enables Scalable Disposable-Format Chromatography

**Study 1 – Single Column vs. BioSMB**

**Resin:** Conventional diffusive pore Protein A

**Binding capacity:** 45 g/L static, 30 g/L dynamic at 4 minute residence time

**Column diameter:** 35 cm single column, 8 cm BioSMB

**BioSMB system:** 8 – 12 columns, depending upon feed concentrations

**Feed volume:** 1000 L

**Feed concentration:** 1 – 10 g/L

**Total process step time:** 24 hours

![Graph showing comparison between BioSMB and Single Column](image)

<table>
<thead>
<tr>
<th>Feed Concentration (g/L)</th>
<th>BioSMB L resin</th>
<th>BioSMB Cycles</th>
<th>Single Column L resin</th>
<th>Single Column Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>5</td>
<td>5.8</td>
<td>6</td>
</tr>
<tr>
<td>2.5</td>
<td>6.3</td>
<td>10</td>
<td>9.6</td>
<td>9</td>
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<tr>
<td>5</td>
<td>7.5</td>
<td>17</td>
<td>15.4</td>
<td>11</td>
</tr>
<tr>
<td>7.5</td>
<td>8.8</td>
<td>22</td>
<td>21.2</td>
<td>12</td>
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<tr>
<td>10</td>
<td>11.3</td>
<td>23</td>
<td>31.3</td>
<td>11</td>
</tr>
</tbody>
</table>

Bench Scale BioSMB System

Courtesy of Tarpon Biosystems Inc.

BioSMB™ Process Development Laboratory, Leiden (NL)
Implementation Requirements and Considerations
Considerations for Implementation of Disposable DSP Technologies

- Cost
- Extractables and Leachables
- Inertia
Cost impact of disposable technologies

The use of disposable-format purification technology will generally:

• Reduce capital costs
• Reduce labor requirements for setup/cleaning/cleaning validation
• Improve facility utilization
• Increase direct materials costs

Disposable-based commercial manufacturing is increasingly a feasible option that can:

• Shift fixed to variable costs
• Improve return on capital
• Increase operating flexibility
Extractables and leachables are a potential concern with any disposable technology. The level of concern increases as product purity increases. Early work in industry (cf, Weidner) to address regulatory requests related to extractables:

- Risk-based assessment of extractables based on:
  - Process step
  - Contact time
  - Temperature
  - Solvent
  - Stage of development
  - Vendor provided information on extractables and toxicological testing
- Conduct extractable tests where warranted based on potential risk:
  - Mass transfer principles guide test design
  - Analytical methods for quantification and identification appropriate to situation
  - Results assessed against acceptance criteria or by evaluation of toxicological risk

Standards are under development for disposables equipment and materials by professional organizations such as ASME BPE (Plastics Subcommittee) and BPSA. Manufacturers are moving to address concerns related to animal-derived materials in plastic components.

Inertia: driving forces against use of novel technology and approaches

- There are significant costs and risks associated with process innovation in any highly regulated industry
  - Conservative approach to implementation of new technologies
  - Security of supply is a concern that must be addressed
- The complexity of biopharmaceutical processes provide additional challenges
- There is no good time to innovate: significant obstacles to implementation of new technologies exist at every stage of development
- Therefore, new technologies generally take longer than anticipated to implement

The relatively rapid uptake of disposables technologies is evidence of their significant value
Summary

- Business and operational drivers for use of disposable-format technologies:
  - Increasing speed to clinic and commercialization
  - Reducing capital investment
  - Improved process portability

- Current existing disposable format technology is emerging to meet many of the requirements for DSP operations
  - Membrane adsorbers
  - Pre-packed columns
  - Depth filtration

- High titer processes require consideration of alternative approaches to enable scalable disposable-format DSP
  - BioSMB
  - Expanded Bed Adsorption
  - High Capacity Monoliths/Membrane Adsorbers
Thank you!

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