Biomanufacturing Capacity
The Bottleneck Moves Downstream

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Steady growth in the number of biopharmaceutical products…

- Number of approved products in the US has steadily increased from approximately 20 in 1995 to 115 today
  - Graph includes products approved but later withdrawn from market and produced via both mammalian cell culture and microbial fermentation
  - Data includes 92 products approved by EMEA
  - Data does not include all products approved by EU member states before centralized procedures were adopted
Coupled with continued growth of product sales…

- 2009 WW sales for 130 biologic products exceeded $95 billion
  - 11% of total pharmaceutical market
  - 16% annual growth rate
- In 2009, 27 biopharmaceutical products with worldwide sales in excess of $1 Billion
  - 1 fewer “blockbuster” product than in 2008
  - 10 manufactured by microbial fermentation
  - 17 manufactured by mammalian cell culture
  - 9 antibody-based products, including full length antibodies, antibody fragments, and Fc-fusion proteins
Has led to growing demand for biopharmaceutical manufacturing

- Approximately 13 metric tons of product manufactured by microbial fermentation
  - 63% of total annual protein production
  - Insulin accounts for >>90% of this production
  - 6 kg of monoclonal antibody-based products (e.g., Fabs)
- Approximately 7.5 metric tons produced in mammalian cell culture
  - 7,599 kg monoclonal antibody and Fc-fusion protein products
  - 111 kg recombinant proteins
But as demand has grown…

- Industry responded by:
  - Investing in capacity expansion and
  - Dramatically improving process productivity
The result...

• **Sufficient mammalian cell culture capacity worldwide** to meet current annual production needs with a high probability of sufficient capacity for the foreseeable future (through middle of decade)

Geographic distribution of cell culture capacity

- Data from 101 companies in 28 countries worldwide indicates an increase in capacity from approximately 2.5 million liters in 2009 to approximately 4 million liters in 2015.
- Capacity growth will be greater in Asia than in EU or North America.
- Recent economic downturn resulted in slowing of projected capacity expansion plans.

Ref: Adapted from E. Reynolds, PhD Dissertation, MIT (2010)
10 companies control 80% of worldwide capacity

Top 10 companies control of mammalian cell culture capacity forecast to decrease slightly to 73% by 2015
  - Genzyme forecast to be replaced by Celltrion by 2015 in Top 10
Balance of worldwide cell culture capacity between product companies and CMOs

- Product companies currently control approximately 70% of total capacity, decreasing slightly by 2015, as CMOs (or Hybrid companies) gradually increase share of cell culture capacity
Continued innovation has increased expression levels and yields, but...

- Commercial products have expression levels in the range of 0.2 – 3.0 g/L with the highest titers seen for monoclonal antibody products.

- New technologies to improve cell line development and expression levels coupled with improved and optimized media, supplements, and bioreactor conditions have increased titers of products in development.

Refs:  
T. Charlebois, BIOMAN 2006 Conference, (2006);  
M. Smith, BPI Europe Conference (2005);  
Most facilities were built for lower titer (<3 g/L) processes

- Current facilities struggle to match downstream capacity with bioreactor output due to large process volumes and high titers
  - Technologies that enable higher bioreactor titers will exaggerate the DSP bottleneck
  - Limitations not only in DSP equipment throughput but also in buffer and product hold tankage

Photos courtesy of Lonza Biologics
Most facilities were built for lower titer (<3 g/L) processes (cont.)

- Optimization of existing purification technologies efforts largely successful at meeting requirements to date, but
- Use of novel technologies is likely to be increasingly necessary as
  - upstream productivity continues to increase
  - disposable technologies come on-line

Photo courtesy of Lonza Biologics
The biopharmaceutical manufacturing facility of the future will...

- Incorporate high titer (>10 g/L) processes
- Use disposable technologies to reduce capital investment and operating costs
  - Anticipated reduction of over 50% (J. Roebers, BPI [2009])
- Require greater DSP space and capabilities to better handle the high titer bioreactor output
  - Ratio of bioreactor space to DSP space will decrease
- Use smaller bioreactors to produce similar quantities to today’s larger bioreactors
  - Reduced capital requirements may enable smaller companies to construct their own facilities rather than outsource
Single use and disposable technology will change the “look and feel” of future facilities

- Reducing capital investment and improving return on capital
- Increasing facility utilization by reducing change-over time
- Reducing fixed piping
- Reducing cleaning and validation costs in multi-product operations
- Increasing operational flexibility by minimizing or eliminating multi-use equipment
- Improving process portability and the ability to manage and implement process changes

Photo courtesy of Acceleron Pharma
Approaches to debottlenecking downstream processing

• Use of “negative chromatography” as an alternative to a dedicated capture step
  • High product titers enables capture of impurities while product flows through column

• Process bioreactor harvest in multiple batches
  • Clarify and freeze bioreactor harvest for purification in smaller batches

• Use of “disruptive” technologies such as precipitation, expanded bed, and simulated moving bed (SMB) chromatography

Ref: A. DePlama GEN (2010 May 1)
Multi-column chromatography is extremely scalable and reduces costs, and...

- Fully disposable processing train for a BioSMB™ system can be paired with disposable bioreactors resulting in smaller process footprint
- Higher throughput per square foot of manufacturing space enables high titer processes to fit in existing facilities or new disposables-based plants

Figures courtesy of Tarpon Biosystems
Applicable to all chromatographic modes – even size exclusion chromatography

Continuous gel filtration chromatography of a vaccine VLP using a 12 column process set-up

Figures courtesy of Tarpon Biosystems
Protein A process intensification example using multi-column chromatography

- Process uses same fundamental phenomena as batch processes
  - No change in media and buffer composition
  - Same steps for binding, washing, and elution as in the corresponding batch process
- System volume depends on mass transfer kinetics, not binding capacity or titer

<table>
<thead>
<tr>
<th></th>
<th>Batch</th>
<th>BioSMB</th>
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<tbody>
<tr>
<td><strong>Titer</strong></td>
<td>3.5 gm/L</td>
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<td><strong>Batch size</strong></td>
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<tr>
<td><strong>Productivity [g/L/day]</strong></td>
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<td><strong>Processing time</strong></td>
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<td><strong>Protein A media [L]</strong></td>
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<td><strong>Buffer [L]</strong></td>
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<tr>
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<tr>
<td><strong>Cycles per batch</strong></td>
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<td>19</td>
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<tr>
<td><strong>Protein A Media Costs</strong></td>
<td>$ 880k</td>
<td>$ 80k</td>
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</table>

Data courtesy of Tarpon Biosystems
The biomanufacturing facility of the future?

- Plant has 6 x 2,000 L bioreactors (possibly disposable reactors)
- 12 day fed-batch CHO culture
  - 2,000 volume, 15 g/L = 30 kg in harvest
  - 80% purification yield = 24 kg per batch
- Harvest every 2 days
  - 167 harvests (334 days) = 4 tons/year
- 1 Purification train serving single bioreactor

- Estimated facility cost < $100M
- Estimated COGS $70 per gram

• Photo courtesy of Xcellerex
Future biomanufacturing facilities will need to balance multiple factors

- Biopharmaceutical manufacturers will increasingly need to develop flexible supply networks to deal with an increasing variety of product types with differing manufacturing processes
  - Antibodies
  - Antibody-drug conjugates
  - Vaccines
  - Cellular therapies
  - Novel engineered proteins

- No one facility will fit all products or processes
- Effectively managing change will increasingly become a core competency
Conclusions

• Sufficient capacity worldwide to meet annual production needs for the foreseeable future
  • Uneven distribution of capacity may present difficulties to some companies trying to access capacity
  • Increasing downstream productivity will become increasingly important to match upstream productivities

• Product and process innovations, including wider adoption of disposable technologies, will increasingly be driven by:
  • Reducing development times
  • Improving return on capital
  • Improving product quality and process knowledge
Thank You!

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