Acceleron Pharma Company Overview

- Founded in 2003 in Cambridge, MA
- Privately held
- Partnership with Celgene for anemia-targeting programs and Alkermes for novel second generation proteins
- Currently ~155 individuals
- Fully integrated biotherapeutic R&D infrastructure
  - Protein engineering
  - In vivo pharmacology
- GMP protein manufacturing facility with seven fusion proteins in development in 2010
- Focus on novel GDF related proteins that modulate the growth of bone, muscle, fat and the vasculature
Company Pilot and GMP Manufacturing Strategy

- Bring Research Reagent, Pilot and GMP production in-house to control quality, capital outlay, and timelines for early phase products
  - Make initial research material to explore biology (rodent, dog, Human, etc.)
  - Use same technology to make non-GMP material for early toxicology studies
  - Using same process, quickly make and release phase 1 and 2 material for clinical trials minimizing capital expenditure

Design Basis for Disposable Facility

- Focused limited development/production personnel on the process, not support
- Simple facility design focused on controlled areas using one HVAC
- “One product at a time” facility
- **Facility has no water system.** All process solutions delivered in sterile containers
- **Facility has no steam.** All material is delivered clean and steriley unless cleaned as part of in-process sanitization (column cleaning)
- All process equipment is mobile, to facilitate movement at a future time
- Processes based on a platform, where equipment and number of process steps are substantially the same among different product candidates
Technology Challenges for Single Use Downstream Processing

ISPE May 2010
Parrish M. Galliher

Xcellerex
www.xcellerex.com
Presentation Outline

• Current Biopharm Industry trends and drivers
• Limitations of stainless steel mfg. technology
• Review of single use technologies
• Going beyond disposables and integrating - the FlexFactory®
• New single use technologies on the horizon
• Case studies in novel single use manufacturing
  • Microbial mAb production and purification
  • Microbial swine flu production and purification
  • Economics of mAb EB and SMB purification
• Conclusions
Challenges Facing the Biopharm Industry

Industry Challenges

• Global economic downturn
• Industry consolidation
• Fewer blockbusters
• Reimbursement pressure
• Excess capacity from higher titers, smaller pipelines, more potent drugs
• Personalized medicine = smaller markets
• Competition
  • Globalization – Asian offshore capacity coming on-line
  • Emerging follow-on / biosimilars market
<table>
<thead>
<tr>
<th>Small/new company</th>
<th>Larger established company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very tight VC funding</td>
<td>Many consolidations stalling capacity investments</td>
</tr>
<tr>
<td>6-12 months of cash</td>
<td>Excess mfg. capacity</td>
</tr>
<tr>
<td>Reaching milestones = survival</td>
<td>More technology conservative-tighter technology budgets</td>
</tr>
<tr>
<td>Less time to reach milestones</td>
<td>Concerned about biosimilars and Asian competition</td>
</tr>
<tr>
<td>No reserve cash for delays/Errors</td>
<td>Forced to evaluate more efficient manufacturing options</td>
</tr>
<tr>
<td>Much more willing to partner vs take more expensive VC money</td>
<td>Much more willing to partner-royalty/equity opportunity for CMOs</td>
</tr>
<tr>
<td>Royalty/equity opportunity for CMOs</td>
<td></td>
</tr>
</tbody>
</table>
Traditional Stainless Steel Facilities

- Prohibitive cost to build new mfg. capacity... $2,000/sq ft
- $200-$400M total installed capital cost
- 4 year timeline for new capacity
- Risk of committing capital during early high-risk stage
- Expensive to operate
- Expensive to modify
- Limited long-term asset utilization
- Low terminal value (even lower in today’s disposable environment)
- Many are obsolete before they are validated
Future Kg demand/Biologic is decreasing: *single use becomes commercial scale*

- Smaller markets
- Improved potency
- Improving yields

Xcellerex

www.xcellerex.com
FlexFactory® Single Use Biomanufacturing: Escaping the Limits of Stainless Steel

Bioreactor 1982

Bioreactor 1994

Xcellerex 2000L Bioreactor TODAY

www.xcellerex.com
Single Use Technology Review

Products and vendors listed in the following slides are provided for reference and do not constitute a complete list or an endorsement of any specific vendor or product.
Xcellerex family of single use bioreactors

All XDRs have a 5:1 turn down ratio
(Each can operate at 20% working volume)

XDR-50  XDR-200  XDR-500  XDR1000  XDR-2000

XDR-10 and XDR-5000 in development
Established Downstream Single Use Technologies

- buffer Storage bags
- buffer Mixers
- Sensors – pressure, pH, conductivity, UV, flow
- Separations – limited to filtration
  - Harvest
  - Virus removal / sterilization
  - Concentration / buffer exchange
- Purification – membranes
- Tubing welders / connectors / sealers
- Integrating stainless and disposables connectors
Advantages of Single Use Systems

Reductions in:
- Cleaning
- Sterilization
- Engineering cost
- Equipment lead time
- Utility requirements
- Validation
- Quality / Regulatory burden
- Space
- Labor
- Waste generation

Lead to

Improvements in:
- 20% reduced capital
- 15% reduced COGs
- 50% reduced facility buildout time
- 20% reduction in plant footprint
- Campaigned product flexibility
- one level increase in manufacturing quality
- 2 hr turnaround cycle time
- > 55% reduced environmental impact
### Downstream – Buffer Mixing Systems

<table>
<thead>
<tr>
<th><strong>Applications:</strong></th>
<th>Media, buffer, product processing, formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capacity:</strong></td>
<td>10 L to 10,000 L</td>
</tr>
<tr>
<td><strong>Vendors/Types:</strong></td>
<td>Hyclone MixTainer, LevTech/Sartorius levitated prop tank, Wave FlexMixer, Xcellerex XDM stirred tank</td>
</tr>
</tbody>
</table>

#### Integration

**Challenges:** powder addition, connectors

#### Scale Up

**Challenges:** powerful mixing, bags that flex to achieve mixing rely heavily on bag seam strength and durability

---

[www.xcellerex.com](http://www.xcellerex.com)
# Cell Harvest – centrifugation, filtration

<table>
<thead>
<tr>
<th><strong>Application:</strong></th>
<th>Separation of cells from growth medium during perfusion or for terminal cell harvest.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capacity:</strong></td>
<td>Up to 100-200 L/hr</td>
</tr>
<tr>
<td><strong>Vendors/Types:</strong></td>
<td>Pneumatic scale (unifuge), Spectrum and GE, WaterSep (recirc. hollow fiber), Millipore POD system, Cuno, Pall depth filtration. All product contact surfaces disposable</td>
</tr>
<tr>
<td><strong>Integration Challenges:</strong></td>
<td>recirculating systems: disposable tubing not amenable to high flow rates and pressures</td>
</tr>
</tbody>
</table>

[www.xcellerex.com](http://www.xcellerex.com)
## Dead End/Depth Filtration

<table>
<thead>
<tr>
<th><strong>Application:</strong></th>
<th>Clarification / sterilization of media, buffers and process intermediates, cell harvest, and removal of particulates.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capacity:</strong></td>
<td>Syringe filters, 30” capsules, flat membrane generally available, (larger by custom order)</td>
</tr>
<tr>
<td><strong>Vendors/Types:</strong></td>
<td>Millipore POD, Pall, Sartorius, Meissner, Cuno – larger capsules coming available, many available pre-sterilized and integrity tested.</td>
</tr>
<tr>
<td><strong>Integration Challenges:</strong></td>
<td>connector compatibility</td>
</tr>
<tr>
<td><strong>Scale Up Challenges:</strong></td>
<td>&gt;2000L capacity is lacking</td>
</tr>
</tbody>
</table>
# Tangential Flow Filtration

<table>
<thead>
<tr>
<th>Application:</th>
<th>Perfusion, cell harvest, purification, concentration, and formulation / buffer exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity:</td>
<td>Up to 13 m²</td>
</tr>
<tr>
<td>Vendors/Types:</td>
<td>Spectrum HF, GE, WaterSep hollow fiber</td>
</tr>
<tr>
<td>Integration Challenges:</td>
<td>disposable pump integration that is durable yet disposable</td>
</tr>
<tr>
<td>Scale Up Challenges:</td>
<td>recirculating systems: disposable tubing not amenable to high flows/pressures</td>
</tr>
</tbody>
</table>

[www.xcellerex.com](http://www.xcellerex.com)
# Purification – Pre-packed Chromatography

<table>
<thead>
<tr>
<th>Application:</th>
<th>binding or Flow-through removal of contaminants and/or product bind-and-elute purification of small or dilute process streams.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity:</td>
<td>variable</td>
</tr>
<tr>
<td>Vendors/Types:</td>
<td>GE Healthcare, Repligen, Applied Biosystems</td>
</tr>
<tr>
<td>Integration /scale up</td>
<td>GE supplies GE resins only with fixed bed height, largest scale</td>
</tr>
<tr>
<td>Challenges:</td>
<td>Repligen packs any resin to any height, limited to 10L columns</td>
</tr>
</tbody>
</table>
## Purification – Membranes

<table>
<thead>
<tr>
<th><strong>Application:</strong></th>
<th>Flow-through removal of contaminants, bind-and-elute purification of small or dilute process streams.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capacity:</strong></td>
<td>20 L/min., 5g DNA binding capacity</td>
</tr>
<tr>
<td><strong>Vendors/Types:</strong></td>
<td>Pall, Millipore and Sartorius functionalized filter membranes.</td>
</tr>
</tbody>
</table>

**Integration Challenges:** connectors, area

**Scale Up Challenges:** less binding capacity compared to chromatography resins in general
## Virus Reduction

<table>
<thead>
<tr>
<th><strong>Application:</strong></th>
<th>Mechanical reduction of viral load by nanofiltration.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capacity:</strong></td>
<td>15 - 200 L/hr. (depending on pore size, filter medium &amp; process stream)</td>
</tr>
<tr>
<td><strong>Vendors/Types:</strong></td>
<td>Millipore dead end, Pall dead end, Asahi-Kasei</td>
</tr>
<tr>
<td><strong>Integration Challenges:</strong></td>
<td>connectors</td>
</tr>
<tr>
<td><strong>Scale Up Challenges:</strong></td>
<td>larger scale requires more area</td>
</tr>
</tbody>
</table>

www.xcellerex.com
# Vial Filling

<table>
<thead>
<tr>
<th>Applications</th>
<th>Aseptic filling into vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity</td>
<td>Clinical to commercial {??}</td>
</tr>
<tr>
<td>Vendors/Types:</td>
<td>Millipore Acerta bag based filling system, MedInstill injection filling/laser sealing, Bosch</td>
</tr>
<tr>
<td>Integration Challenges</td>
<td>connectors</td>
</tr>
<tr>
<td>Scale Up Challenges</td>
<td>not clear yet</td>
</tr>
</tbody>
</table>
### Sensors

<table>
<thead>
<tr>
<th>Applications:</th>
<th>Process wide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity:</td>
<td>N/A</td>
</tr>
<tr>
<td>Vendors/Types:</td>
<td>Wave Biotech, (pH, DO2), Fluorometeric, Finesse and PreSens optical sensors, microprobes</td>
</tr>
</tbody>
</table>

Cytoxicity, irradiatability, fit up into bags, tubing, dead zone elimination, signal

<table>
<thead>
<tr>
<th>Integration Challenges:</th>
<th>response time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale Up Challenges:</td>
<td>stability, non-fouling, validatable</td>
</tr>
</tbody>
</table>
Economics of Disposables vs Stainless courtesy Foulon et al, Roche June 2008

Figure 3: Start-up phase, highest savings (summary cost breakdown)

- Capital charge
- Materials
- Consumables
- Labor

Figure 4: Regular production, highest savings (summary cost breakdown)

- Capital charge
- Materials
- Consumables
- Labor

www.xcellerex.com
# Environmental Advantages of Disposables: Water Consumption & Waste Generation

<table>
<thead>
<tr>
<th>Water Usage - Traditional (L per batch)</th>
<th>Waste - Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFI</td>
<td>PW</td>
</tr>
<tr>
<td>36,201</td>
<td>41,358</td>
</tr>
<tr>
<td>Waste - Traditional</td>
<td>Aqueous</td>
</tr>
<tr>
<td>79,155</td>
<td>67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Water Usage - Xcellerex (L per batch)</th>
<th>Waste - Xcellerex</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFI</td>
<td>PW</td>
</tr>
<tr>
<td>9,957</td>
<td>-</td>
</tr>
<tr>
<td>Waste - Xcellerex</td>
<td>Aqueous</td>
</tr>
<tr>
<td>11,554</td>
<td>189</td>
</tr>
</tbody>
</table>

- ~85% reduction in water usage & waste
- 3x increase in lbs of plastic usage & waste
### Environmental Advantages of Disposables: Carbon Footprint

<table>
<thead>
<tr>
<th>POUNDS CARBON / BATCH</th>
<th>Single Use</th>
<th>%</th>
<th>Stainless</th>
<th>%</th>
<th>Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIP</td>
<td>0.0</td>
<td>0.0%</td>
<td>388.5</td>
<td>1.0%</td>
<td>388.5</td>
</tr>
<tr>
<td>CIP</td>
<td>30.5</td>
<td>0.2%</td>
<td>1,988.0</td>
<td>4.9%</td>
<td>1,957.5</td>
</tr>
<tr>
<td>Transporting Plastic</td>
<td>148.5</td>
<td>0.8%</td>
<td>0.0</td>
<td>0.0%</td>
<td>-148.5</td>
</tr>
<tr>
<td>Pumping Water &amp; Wastewater</td>
<td>3.7</td>
<td>0.0%</td>
<td>28.7</td>
<td>0.1%</td>
<td>25.0</td>
</tr>
<tr>
<td>Steel Fab. Amortized per Batch</td>
<td>2,970.7</td>
<td>16.6%</td>
<td>7,723.8</td>
<td>19.2%</td>
<td>4,753.1</td>
</tr>
<tr>
<td>Polymerizing Plastic per Batch</td>
<td>799.3</td>
<td>4.5%</td>
<td>0.0</td>
<td>0.0%</td>
<td>-799.3</td>
</tr>
<tr>
<td>Extruding Plastic</td>
<td>499.6</td>
<td>2.8%</td>
<td>0.0</td>
<td>0.0%</td>
<td>-499.6</td>
</tr>
<tr>
<td>WFI Still</td>
<td>7,308.7</td>
<td>40.8%</td>
<td>29,828.8</td>
<td>74.3%</td>
<td>22,520.1</td>
</tr>
<tr>
<td>Cleanroom Energy</td>
<td>132.1</td>
<td>0.7%</td>
<td>204.1</td>
<td>0.5%</td>
<td>72.0</td>
</tr>
<tr>
<td>Incinerating Plastic</td>
<td>6,029.3</td>
<td>33.6%</td>
<td>0.0</td>
<td>0.0%</td>
<td>-6,029.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17,922.4</td>
<td></td>
<td>40,161.9</td>
<td></td>
<td>22,239.5</td>
</tr>
</tbody>
</table>

55% reduction in carbon footprint

Courtesy Leveen & Monge, ISPE Tampa Conference, 02 March, 2009

www.xcellerex.com
Going beyond just disposables
Introducing the FlexFactory®

• FlexFactory™
  • Portable mini-clean rooms
  • Disposable mfg. equipment
  • Automation - eFactory™
    • Process control
    • e-process control/doc. software
    • On-Line quality assurance
    • On-line environmental monitoring

www.xcellerex.com
The Fully Integrated Disposable FlexFactory®

Hundreds of disposable processing components

Fully integrated GMP FlexFactory

Xcellerex

www.xcellerex.com
Going beyond just Single Use: Advantages of the FlexFactory®

Reductions in:
- Cleaning
- Sterilization
- Engineering cost
- Equipment lead time
- Utility requirements
- Validation
- Quality / Regulatory burden
- Space
- Labor
- Waste generation

Lead to

Improvements in:
- 20% 50% reduced capital
- 15% 30% reduced COGs
- 50% 70% reduced facility buildout time
- 20% 40% reduction in plant footprint
- Campaigned simultaneous product flexibility
- one three level increase in manufacturing quality
- 2 hr turnaround cycle time
- > 55% reduced environmental impact

www.xcellerex.com
Economic comparisons – biopharm facilities
stainless steel vs just disposables vs FlexFactory

- COGs
- Plant footprint
- Capital
- Time to GMP (months)

www.xcellerex.com
New technologies in Downstream Single Use Manufacturing

Single use tubular bowl centrifuge – Pneumatic scale

Single pass ultrafiltration - Pall

Pre-packed chromatography: GE, Repligen, Natrix

Simulated moving bed chromatography – Tarpon, Novasep

Expanded bed chromatography – Upfront

Genderless, re-useable sterile connectors
Case studies:
Microbial single use manufacturing:

1) Purification of mAb using:
   - single use expanded bed
   - single use prepacked simulated moving bed

2) Purification of Swine flu HA:
   - single use prepacked chromatography

3) EB and SMB economics
Traditional microbial mAb production

- Inoc prep → fermentation → centrifugation
- homogenization ← fermentation
- centrifugation ← homogenization
- Protein A capture → HIC → UF/DF
- ion exchange ← Protein A capture
- HIC ← ion exchange
- UF/DF ← HIC
- Bulk fill ← UF/DF
Single use microbial mAb production

- Inoc prep → XDR fermentation → Chemical lysis
- homogenization → centrifugation → filtration
- Expanded Bed Protein A → Pre-pack PA → SU UF/DF
- Pre-pack ion exchange → SU UF/DF → Bulk fill

Xcellerex

www.xcellerex.com
Microbial XDR-50L Single-Use Bioreactor

Microbial turbo XDR-50
- 6 blade rushton turbine
- 6 blade upper pitched blade
- baffled
- 400 rpm
- 1000 hr⁻¹ kLa
- Glycol jacket cooled
- Electronic exit gas condenser
- 370 OD
- 125 g/L DCW
Pseudomonas bacterial fermentations
XDR-50 – HA subunit vaccine and anti-fluorescein mAb

OD raised to 370 via media development

7331 XDR-50 Bioreactor Runs
Pseudomonas DC606 (4.4.20 Mab)

www.xcellerex.com
confidential

www.xcellerex.com
XDR-50 Pseudomonas (Pfenex, Inc.) bacterial fermentations – mAb titer (fully folded)

XDR-50 Bioreactor Runs
Mab 4.4.20 Production (via LabChip)
DC606 (4.4.20 Mab) vs. DC907 (Secretion 4.4.20 Mab)

<table>
<thead>
<tr>
<th>Time (Hour of Culture)</th>
<th>DC606 (4.4.20 Mab)</th>
<th>DC907 (Secretion 4.4.20 Mab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>12:00</td>
<td>9.0</td>
<td>9.0</td>
</tr>
<tr>
<td>24:00</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>36:00</td>
<td>13.0</td>
<td>13.0</td>
</tr>
<tr>
<td>48:00</td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>60:00</td>
<td>17.0</td>
<td>17.0</td>
</tr>
<tr>
<td>72:00</td>
<td>19.0</td>
<td>19.0</td>
</tr>
</tbody>
</table>

www.xcellerex.com
Expanded Bed Protein A capture System now available in single use
Figure F-3. The 10cm Rhobust system during wash step following load of unclarified harvest lysate on Protein A resin.
Expanded Bed System – PA mAb elution

**Figure F-4.** The 10cm Rhobust system during the elution step of product from unclarified harvest lysate.
Purification of XDR50 DC606 08-009, 4-4-20 mAb using Upfront Protein A EBA in Batch Mode
Bind and Packed Bed Wash and Elution
4-12% NuPage BIS Tris MOPS Non-reduced Gel (50min, 200V, 120mA, 25W)
Release Method – Thawed harvest, 5X Lysis Buffer
Clarification Method – None

1. SeeBlue MW Std
2. IgG Standard
3. Load (diluted 1:10)
4. Flowthrough
5. pH 5.0 Wash
6. pH 3.5 Elution (pH adjusted to 8.3)
7. 0.1M HCl Strip (pH adjusted to 7.8)
8. 0.1M NaOH Strip (pH adj. to 8.2)
9. Peroxide/DTT treated Anti-Shiga sample
10. IgG Standard

20uL loaded for each
Single use simulated moving bed chromatography – beta system courtesy Tarpon Biosystems
SMB Impact vs Batch Protein A Chromatography scale up example:
- 3.5 g/L mAb titer
- 2000L batch

<table>
<thead>
<tr>
<th></th>
<th>Batch</th>
<th>SMB</th>
</tr>
</thead>
<tbody>
<tr>
<td># columns:</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>productivity g/L-day:</td>
<td>360</td>
<td>2630</td>
</tr>
<tr>
<td>processing time:</td>
<td>5 hrs</td>
<td>8 hrs</td>
</tr>
<tr>
<td>liters PA resin:</td>
<td>88L</td>
<td>8L</td>
</tr>
<tr>
<td>cycles/batch</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>$ protein A resin:</td>
<td>$880,000</td>
<td>$80,000</td>
</tr>
</tbody>
</table>

courtesy Tarpon Biosystems

www.xcellerex.com
Swine Flu HA Downstream His-tag-SUMO Purification Platform

1. Harvest Broth w/ His-Tagged HA
2. Lysis w/ Lysis buffer (2 Hr, Room Temp)
3. Expanded Bed IMAC Chromatography
4. HIC Chromatography
5. Cleavage of His-Tag (2 Hr, Room Temp)
6. Subtractive IMAC Chromatography

Purified HA SUV

~12 Hour Process
XDR-50 Pseudomonas (Pfenex, Inc) bacterial fermentations - swine flu HA

7331 XDR LiveFire 2009 Bioreactor Runs
*Pseudomonas* Strain MID5059

Cell Specific Production via Chemical Lysis Sample Prep Up to Hour 40

<table>
<thead>
<tr>
<th>Titer/O.D.</th>
<th>Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
</tr>
<tr>
<td>0.4</td>
<td>20</td>
</tr>
<tr>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>0.6</td>
<td>40</td>
</tr>
<tr>
<td>0.7</td>
<td>50</td>
</tr>
</tbody>
</table>

www.xcellerex.com
Pre-Packed Chromatography
HA subunit vaccine purification

Figure F-104. The AKTA Ready chromatography system with a BioFlash 8cm IMAC disposable column in line.

AKTA Ready with 8 cm BioFlash IMAC column
Pre-Packed Chromatography
HA subunit vaccine purification
### Economics: baseline vs SMB/EB

#### Courtesy Biopharm Services

<table>
<thead>
<tr>
<th>Cost Type</th>
<th>Baseline</th>
<th>SMCC</th>
<th>EBA</th>
<th>SMCEBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital</td>
<td>0.60</td>
<td>0.35</td>
<td>0.38</td>
<td>0.32</td>
</tr>
<tr>
<td>Materials</td>
<td>1.96</td>
<td>1.36</td>
<td>1.44</td>
<td>1.16</td>
</tr>
<tr>
<td>Consumables</td>
<td>3.87</td>
<td>1.61</td>
<td>1.43</td>
<td>1.16</td>
</tr>
<tr>
<td>Labour</td>
<td>1.10</td>
<td>0.56</td>
<td>0.50</td>
<td>0.41</td>
</tr>
<tr>
<td>Other</td>
<td>0.14</td>
<td>0.08</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>7.66</td>
<td>3.95</td>
<td>3.83</td>
<td>3.13</td>
</tr>
<tr>
<td>Relative Cost</td>
<td>-</td>
<td>-49%</td>
<td>-50%</td>
<td>-59%</td>
</tr>
</tbody>
</table>

**COGS Savings:**
- SMB: -49%
- EB: -50%
- SMB/EB: -59%

**MAb Overall Cost/Dose Comparison**

- 2000L perfusion
- 5 g/L titer
- 49% yield
dose = 400mg

**www.xcellerex.com**
Conclusions

• Single use technologies for downstream are improving:
  • Expanded bed simplifies primary capture
  • Prepacked chromatography facilitates plug and play
  • SMB - major breakthroughs in COGS, high titer capable
• FlexFactory: integrating downstream disposables with USP
  • Open platform, simultaneous multi-product manufacturing
  • 70% reduction on time to build/validate to GMP ready (9 mo.)
  • Reductions: capital: 60%, footprint: 40%, COGS: 30%; time 70%
• Eco impact: -85% water use, -55% carbon footprint, 3 x increase in waste plastic

www.xcellerex.com
THANK YOU!

Xcellerex

170 Locke Drive, Marlborough, Massachusetts 01752

www.xcellerex.com

1.866.Xcellerex

www.xcellerex.com
Successful Implementation of Single Use Systems for Commercial Scale Biomanufacturing: The Industry/Supplier Partnership

Paul Slaman
Shire HGT

James Dean Vogel, P.E.
Process Facility Services

Our purpose
We enable people with life-altering conditions to lead better lives

Summary

- ISPE Single Use Technology: Approaches in Unique Facility Design, Successful Implementation & Exploring Future Growth Opportunities
  Date: 11 May 2010
  This presentation will be held at the Acceleron Pharma facility in Cambridge, which has embarked on a manufacturing strategy using single use technology. We will explore facility design considerations through a tour of the Acceleron Pharma facility, learn of the successful implementation strategy for commercial scale biomanufacturing at Shire HGT, and learn from Xcellerex's founder about novel applications in downstream processing.

- PLEASE NOTE: The Acceleron Pharma Facility Tour SOLD OUT. The networking reception and following presentations are still available and are OPEN to Members and non-members.

- Location:
  Acceleron Pharma, Inc.
  128 Sidney Street, Cambridge, MA 02139

- Speakers:
  Bob Steininger, Senior Vice President, Manufacturing, Acceleron Pharma
  Paul Slaman, Manufacturing Technical Services, Shire HGT
  James D. Vogel, Consultant, Process Facilities Services, Inc.
  Parrish M. Galliher, Founder and Chief Technology Officer, Xcellerex, Inc.
Summary-

- Successful Implementation of Single Use Systems for Commercial Scale Biomanufacturing: The Industry/Supplier Partnership
  - Paul Slaman, Manufacturing Technical Services, Shire HGT
  - James D. Vogel, Consultant, Process Facilities Services, Inc.
- The basis of design for the Shire HGT ATLAS plant incorporates single use/disposable components at all unit operations with key bioprocess unit operations performed in these systems. The use of these components will permit the organization to achieve speed to market and benefit from the overall simplification of tasks associated with plant design, construction, ICV, and routine operations. The use of these systems does present some unique challenges for a validated, commercial facility that will need to be addressed to be successful.
- Of critical importance is interpretation and adherence with CFR 211.65 and other applicable regulatory requirements. Understanding and characterizing the risks associated with single use components requires an assessment of the impact and a decision on choosing the right component for the application. This decision making process does not occur unilaterally; strong supplier partnerships are required for success.

Shire Human Genetic Therapies (HGT)

- Shire HGT is a global business unit dedicated to discovering, making and supplying treatments for rare genetic diseases to patients around the world.
- We have a robust pipeline of products in development, and target genetic diseases caused by single-gene mutations such as Hunter Syndrome, Fabry and Gaucher diseases. Our commercial products include:
  - VPRIV®
  - Elaprase®
  - Replagal®
- Because of the small patient and healthcare provider population associated with these diseases, we are committed to building outstanding relationships with these groups and providing the best therapies possible.
Shire HGT LTP-400 “ATLAS”

Project Atlas

Shire HGT Lexington Commercial Manufacturing Facility

Level 1 Layout

To be as brave as the people we help
Why ATLAS?

- Shire HGT’s growing demand for licensed commercial products
- Robust Pipeline/Clinical products
- Next Generation products
- Our basis of design (BOD)

Why Single Use?

- Multi-Product Facility Challenges
- Maintaining Flexibility
- Operational Considerations
- Speed
Unique Challenges associated with Single Use Systems

• Technical Challenges

• Business Challenges

• Regulatory Challenges

Shire HGT Single-Use Risk Assessment Program

• The Goal is to apply the industry’s best practices to improve Shire’s level of control of their Components, Assemblies and Materials

• Key is that we ensure that the Shire Staff are proficient and understand the process!

• Help Vendors understand the process!
Shire HGT Single-Use Risk Assessment Program

- Considerations:
  - Regulatory
  - Industry Understandings
  - Process Requirements
  - Material and Equipment Science

- Today - State of the Industry
- Future - Ensure the program evolves with:
  - Changes in the Regulations and Industry
  - Successful vendor partnerships

State of the Industry

- Single Use components are used in the Biopharmaceutical Industry
  - Long standing items used for years.
    - Transfer operations (filters and tubing)
    - Short exposure times
  - Recent Trends
    - Gamma Irradiation
    - Large Scale
    - Less Stainless Steel
State of the Industry

- Recent Trends at Shire HGT
  - Bag assemblies
    - Product
    - Solutions
    - Sampling
    - Large Scale up to 200 liters.
    - Mixing
    - Sensors
    - Filtration
  - Integrated Manifolds
    - Sampling
    - Product and solution transfer
    - Filtration

Regulatory Requirements

- FDA
  - cGMP-211.65
  - GMPs of the 21st century
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  - Q8-Pharmaceutical Development
  - Q9-Risk Management
  - Q10-Quality Systems
CFR 211.65
Equipment Construction

- (a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

- (b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Industry Activities

- The industry is evolving.
  - Bio-Process Systems Alliance (BPSA)-Industry consortium which has published many guidance articles.
  - PDA-Technical Reports
  - ASME BioProcessing Equipment (BPE) Standard-Published first requirements in 2009.
  - ISPE
    - Product Quality Lifecycle Implementation (PQLI)
    - Baseline Guides
    - Disposables Community of Practice
PM-7 Single-Use Components and Assemblies

An Internationally recognized Conscientious Standard coordinated with the BPSA and ISPE.

- Identification
- Labeling
- Certificate of Compliance
- Inspection and Packaging
- Joining Methods
- Biocompatibility
- Sterilization

Evolution vs. Revolution

- Single Use Risk Assessment is an Evolution
  - Within Shire!
  - Within the Industry!
  - Especially with the Vendors!
- The Goal is to apply the industry’s best practices to improve Shire’s level of control of their Components, Assemblies and Materials
- This is a gradual process…An Evolution
- Key is that we ensure that the Shire Staff are proficient and understand the process!
- Help Vendors understand the process!
Vendors are key to Shire HGT’s Success!

- Strong Vendor partnerships are required:
  - To meet today’s needs and
  - To ensure success in the future
    - Technical
    - Business
    - Regulatory

SHIRE HGT SINGLE-USE BUSINESS PROCESS
Overview

• This procedure is used to define and evaluate the risk associated with the application of components, assemblies (including single-use) and their materials in Shire HGT manufacturing processes. …
• Will result in an assessment of the potential impact that a component, assembly and its materials may have on a manufacturing process…. 
• Result in the best possible decision in choosing components/assemblies and their materials for use in the manufacturing process.

Shire Article and Material Risk Assessment Procedure
MATERIALS REVIEW

Article/Material Capability

The capability of the Article/Material to meet the process demands. This will be demonstrated by:

- Vendor and or Shire testing and documentation to support the Article/material's application to the process.

The goal is to substantiate the Article/material's:

- Robust Manufacturing Practices
- Robust Supply Chain Practices
- General BioProcess Performance.

Process Comparison-

- Was the Article/Material used before?
- Previous Process Comparison?

First Time Evaluation?
Single Use Component Information Received

**Article/Component Information**
- Drawings
- Certificates of Compliance
- Animal Free Statements
- Extractable Studies
- Leachable Studies
- Validation Studies
- Product Communication

**Vendor Information**
- Client Forms and Responses
- Audits
- Vendor Communication

**Lot Information**
- Sterilization
- Certificates of Analysis

**Commercial Information**
- Supply Chain Information

Article/Material Assessment

- Certificate of Analysis
- Test Results
  - USP Class VI
  - Leaks.
  - Material properties testing.
  - Pretreatment
  - Assembly assurance.
  - Extractables.
Materials Review Continued

- The following categories are assigned:
  - Acceptable of Green
  - Conditionally Acceptable or Yellow
  - Unacceptable or Red

Materials Review

- Balance - Need to assess all probable risks. Theoretical risks should be considered, but only formally addressed through risk assessment if they carry extraordinary patient safety or regulatory compliance significance.
Extractables vs. Leachables (BPE)

- **Extractables**: Chemicals that can be removed from articles using appropriate solvents (e.g. polar and non-polar) for the purpose of identification and quantification of potential leachables.
- **Leachables**: Chemicals that migrate from the article into the process fluid of interest (e.g. water, buffered solutions, drug product, etc.) under normal and/or accelerated conditions (typically exposure time and/or temperature). Leachables are typically a subset of extractables, but can also be created as a result of chemical reactions with other leachables and/or components.

Types of Extractables/Leachables Studies

- **Exhaustive Solvent Extractables**
  - Organic solvent
  - Water (Purified and WFI)
- **Extractables per known protocol**
- **Extractables/Leachables (Lextractables)**
  - Water conditions
  - Common solutions
    - PBS
    - NaOH
    - Phosphoric Acid
- **Leachables**
  - Product
  - Drug Substance
  - Intermediate Solutions
    - Buffers
    - Media
Material Review - Vendor role

- Yesterday - Shire HGT received what was available.
- Today - Shire HGT is stating what is minimum.
- Future - Shire HGT requests the proper information is available to ensure Risks are addressed!
  - Vendor Technical Information
  - Vendor Quality Systems
  - Vendor Supply Chain Management
  - Shire HGT/Vendor Partnership
  - Component Change Management!

PROCESS REVIEW
Process Design Space

- The Design Space for each aspect considered are evaluated.
- The potential of the process to interact with the article/material is essential for this evaluation.

Process Assessment

- Product/Process Contact
- Process Step
- Process Conditions
- Volume/Surface Area
- Time of Exposure
- Pretreatment
Cell Banking

Cell Growth

Harvest of Cells

Cell-free post-harvest
100

Post-viral inactivation/filtration
puriﬁcation
500

Final bulk drug substance

Final ﬁlled drug substance
1000

ASSESSMENT
PROCESS DESIGN SPACE
RISK VS.
ARTICLE/MATERIAL
CAPABILITIES
Assessment

• The Process Design Space Risk will be evaluated against the ability of the Article/Material Capability to meet the Risk.
• The assessments will be classified as:
  • Acceptable
  • Conditionally Acceptable
  • Unacceptable

Shire Article and Material Risk Assessment Procedure

Process Assessment

Process/Article Comparison

Acceptable

Conditionally Acceptable

Article/Material Assessment

Unacceptable
Shire HGT Single-Use Risk Assessment Program

- The Goal is to apply the industry’s best practices to improve Shire’s level of control of their Components, Assemblies and Materials
- Considerations:
  - Regulatory
  - Industry Understandings
  - Process Requirements
  - Material and Equipment Science
- Future-Ensure the program evolves with:
  - Successful Vendor Partnerships!