The Advantages and Challenges of Operating a GMP Facility Based on Single-Use Equipment

Bob Steininger
SVP, Manufacturing
15 November 2012
Outline of Talk

• Introduction to Acceleron
• Acceleron’s Basis for Disposable Use
• Facility Concept
• Facility and Equipment design bases
• Facility Operation
• Challenges with use of such a facility
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 ~85 individuals
• Fully integrated biotherapeutic R&D infrastructure
  – Protein engineering
  – In vivo pharmacology
• GMP protein manufacturing facility with seven fusion proteins in development in 2012, and four in the clinic
• 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, platform process, quickly make and release phase 1 and 2 material for clinical trials minimizing capital expenditure
Platform Process Schematic

- CHO Cell Culture
- Hollow Fiber Harvest
- Protein A
- Anion Exchange
- HIC
- Diafiltration
- Viral Filtration
- Concentration
Design Concepts for Disposable Facility

- **Development\production personnel on the process**, not support
- **Multiple HVACs** to provide flexibility of room uses
- **Facility has no water system.** All process solutions delivered in sterile containers
- **Facility has no steam.** All material is delivered clean and sterilely 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
Manufacturing Facility Design Basis

• 2X 1000L Disposable Reactors
• Harvest every week of one bioreactor: up to 40 batches per year @ 1 g/L
• 500g DS batch size – 20kg of protein per year
• Designed to produce a non-sterile, low bioburden, frozen Drug Substance
• Designed for multi-product production
• Provide Quality function space within facility
• Provide Warehouse function in facility
Acceleron 128 Sidney Facility

Acceleron Pharma

Created in 100 yr old building

38,000 ft²

Manufacturing was originally office area
• Approximately 12,000 ft$^2$ of GMP Area, with ~4500 ft$^2$ of production area

• Separate air handling systems for each of the four processing areas. Separate entry area to each process area off common clean corridor

• SOPs in-place to allow different products in the four manufacturing areas

• All media and buffers delivered from adjacent warehouse as portable liquid or pumped from controlled corridor through wall to controlled area.
Acceleron 128 Sidney CMF Production Area
Sidney Street Facility
GMP Areas

Small Cell Culture Area (Inoculum)

Large Cell Culture Area

Grey Corridor

Large Purification Area

Small Purification Area (post viral filter)
Process Equipment Design Criteria

- Single Use Process Equipment for all Operations – except columns and DO probes (resins dedicated to product) – **No Sterilization or cleaning validation**
- All process equipment without CIP (except columns)
- All buffers, product intermediates, and waste contained in bags within Totes
- Buffers and media delivered sterilely in limited to 20L to 500L aliquots – **No WFI, DI Water Systems**
- All liquids transferred using disposable tubing
- All disposables delivered steriley
- Sterile connections made using tube welding and CleanPak connections
## Timeline for Construction

### Concept to GMP Production 19 months

<table>
<thead>
<tr>
<th>ID</th>
<th>Task Name</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Board Approval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Initial Design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Order HVACs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Construction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pilot Validation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GMP production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **2008**
  - Board Approval: Oct-Dec
  - Initial Design: Jan-Feb
  - Order HVACs: Mar
  - Construction: Apr-Jun
  - Pilot Validation: Jul
  - GMP production: Jul

- **2009**
  - Board Approval: Aug-Oct
  - Initial Design: Nov-Dec
  - Construction: Jan-Mar

Acceloron Pharma

Page 13
Operations
and
Challenges over the Last Three Years
Challenges: Disposable Bioreactor Turnaround without Media Pre-Treatment

Schedule for Bioreactor

• Harvest 3 hr
• Clean\Replace Bag 2 hr
• Fill Bioreactor 6 hr
• Warming Media to Temperature 12 hr
• Inoculate Bioreactor 2 hr
SUB Challenges

- Simple versus complex set up
- Control of process variables
- Variability of cell growth based on configuration
Challenges: Port Cable Ties and Ports

Size Reduction

Sturdy Large Port

Less Sturdy Small Port
Implementation Challenges: Complex Assemblies

• 1000L SUB Bag
  – 100s of cable ties (manually assembled & checked)
  – Connectors
  – Tubing/filter assemblies
  – Ports for probes (DO, pH)
  – Impeller (top down)
  – Rev F
  – Partner with vendor to optimize design
• Custom
  • 24 customers/24 bag designs
<table>
<thead>
<tr>
<th>SKU Size</th>
<th>No. of SKU’s</th>
<th>No. of Customers</th>
<th>Total Purchased</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 L SUB</td>
<td>24</td>
<td>24</td>
<td>922</td>
</tr>
<tr>
<td>500 L SUB</td>
<td>19</td>
<td>9</td>
<td>434</td>
</tr>
<tr>
<td>250 L SUB</td>
<td>65</td>
<td>67</td>
<td>1,523</td>
</tr>
<tr>
<td>100 L SUB</td>
<td>15</td>
<td>17</td>
<td>370</td>
</tr>
<tr>
<td>50 L SUB</td>
<td>54</td>
<td>92</td>
<td>1,232</td>
</tr>
<tr>
<td>TOTAL</td>
<td>177</td>
<td>209</td>
<td>4,481</td>
</tr>
</tbody>
</table>
Harvest Challenges

Simple, Not Sterile, bit messier

More complex, sterile, and, sometimes, more protein loss
Simple, “Mostly” Disposable Chromatography Modules
Instrumentation Challenge: Sterility of Probes

Disposable Sensors Implementation Issues

• Pre-Calibrated, Disposable, Single-Use Pressure Sensor

• MFG needs to verify Column Pressures

• Issue
  – Vendor claims ‘can be’ but ‘does not’ gamma radiate
  – Mfg/Quality approach towards Sterility “unclear”

• Solution
  – Partnership with Vendor on Testing

• Lessons learned
  – Gather & evaluate all vendor’s documentation
  – Upfront Quality Req. & Testing Responsibility
Single Use, Disposable Diafiltration\Concentration
Peristaltic Pump: Tubing Spallaging

Spallation: Particle abrasion from the inside of the tubing

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Spallation (mg)</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 °C</td>
<td></td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- Resistance to spallation
- Reduced spallation
Biggest Challenge: Quality and Logistics
Challenges: Back-up Suppliers of Disposables – Are they interchangeable? Reliable?

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>VENDORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flasks</td>
<td>1</td>
</tr>
<tr>
<td>Bags</td>
<td>2</td>
</tr>
<tr>
<td>SUBS</td>
<td>1</td>
</tr>
<tr>
<td>Tubing</td>
<td>2</td>
</tr>
<tr>
<td>Solutions</td>
<td>2</td>
</tr>
<tr>
<td>Membranes</td>
<td>2</td>
</tr>
<tr>
<td>Filters</td>
<td>2</td>
</tr>
</tbody>
</table>
Vendor Audit/Qualification Program Essential

Vendor Controls what contacts your product!

- **Vendor Qualification Classification**
  - Accepted/Approved/Certified Vendor
  - Utility Validation Program

- **Vendor Ranking Criteria**
  - Critical Part; Sole supplier; Lead Time;
  - Cost, Quality; Vendor-History

- **Quality Agreement**
  - Change Control/Deviation Notification
  - Confidentiality Disclosure

- **Audit Program**
  - GMP Mfg, Cleanrooms, Quality Systems, Utilities
  - Med. Device QSR vs. GMP, New Vendor!
Required Ongoing Compatibility Assessment!

AT DELIVERY

AFTER 15 MONTHS

IS THE BUFFER OKAY???
Implementation Challenges: Shipping/Containment
Rely on Sterility from Vendor

• What is Effect of Gamma Irradiation?
  – Microorganisms\Viruses inactivated by damage to DNA but –
  – Effect on Plastics
  – Effects on Extractables
  – Effect on Life of Components
Storage of Drug Substance

- Solutions stored in PETG Container in Freezer at -80°C
- Risks Involved in Assessment
  - Brittleness Temperature = -40°C
  - Careful container/material selection can avoid product loss!
- PP bags are worse!

<table>
<thead>
<tr>
<th>Material</th>
<th>Brittleness Temperature °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypropylene</td>
<td>0</td>
</tr>
<tr>
<td>PETG</td>
<td>-40</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>-135</td>
</tr>
<tr>
<td>Teflon (PFA)</td>
<td>-270</td>
</tr>
<tr>
<td>Celsius Pak (EVA)</td>
<td>-80</td>
</tr>
<tr>
<td>Stainless Steel</td>
<td>N\A</td>
</tr>
<tr>
<td>COP Resin</td>
<td>-196</td>
</tr>
</tbody>
</table>
Additional Challenges: Raw Materials

- Vendor Quality Programs – Mistakes are more difficult to catch externally
- Cost of small orders
- Availability of Raw Materials - Delivery
- Shipping of Material: $0.1-0.8 /1000 Liters/mile
- EU Testing and Release of Sterile Solutions in Bags
- Stability of Solutions\Assay Test Variability
- Disposal of Waste: 50 x 200L drums\2 weeks
• Durability over Multiple Campaigns
• Durability of Facility as far as Environmental Monitoring
• Limitations of Purification Scale
• Ability to Run and Sustain 40 batches per year
• Further optimization of capital and FTE time
• User Group for such Facilities –
Acknowledgements and Questions

• Acceleron Manufacturing, Facility and Quality Staff

• Industrial Facility Design, Inc.

• J. Calnan and Associates

• ISPE Engineers in Boston Area

• Disposable Community (with special note to P. Galliher, A. Sinclair, and M. Monge)

Bob Steininger
bsteininger@acceleronpharma.com

Any Interest in Viral Removal Data Exchange and ASTM Biotechnology Standards?
Operations: Batch Cost in Plant

- 1000L bioreactor

~ $400,000-$1,000,000 batch cost in Disposable Plant Model

~ $600,000-900,000/batch at CMO with present process
Operations: Material Costs Breakdown

Fixed Cost, 1000L

- Rent: 11%
- Construction Cost: 10%
- Equipment: 9%
- Doc Systems Set up: 1%
- Personnel: 58%
- Cleaning, Facility: 2%
- Environmental Testing: 1%
- Utilities\Waste: 4%
- Maintenance: 3%
- Other: 1%

Variable Costs, 1000L

- CC Media\Sol: 14%
- CC Disposables: 9%
- CC Testing: 3%
- Pur Buffers: 15%
- Pur Resins: 8%
- Pur Disposables: 27%
- Pur Testing: 20%
- Gen Supplies: 4%

Fixed Cost is 50% of batch cost