A Global Technology Roadmap for Biopharmaceutical Manufacturing: An Update from BPOG

Presentation to
Bioprocess International (BPI)
Boston, MA  2016

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5th October 2016
Agenda

- **Who** is BPOG
- **What** is a Technology Road Map:
  Introduction to the Biopharmaceutical Industry Collaboration
- **Why** a Road Map is needed. Why now...
- **How** is the Map Created: The Methodology
- **Now!**: Overview of key roadmap content to date
  - Market trends & business drivers
  - Biomanufacturing scenarios
  - Initial process modelling results
- **When**: Next Steps
Who is BioPhorum Operations Group (BPOG) 
Industry collaboration that brings together 33 bio-manufacturers, collaborating in six phorums to accelerate the industry

<table>
<thead>
<tr>
<th>Abbvie</th>
<th>Alexion</th>
<th>Amgen</th>
<th>AstraZeneca</th>
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<td>Eisai</td>
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<td>Fujifilm Diosynth Biotechnologies</td>
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<td>Genentech, A Member of the Roche Group</td>
<td>Genzyme, A Sanofi Company</td>
<td>GlaxoSmithKline</td>
<td>Immunogen, Inc</td>
<td>Ipsen Innovation for patient care</td>
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<td>Roche</td>
<td>Samsung</td>
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<tr>
<td>Shire</td>
<td>Takeda</td>
<td>UCB</td>
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</table>
6 Phorums covering all aspects of operations and accelerating biopharma industry’s journey to maturity

http://www.biophorum.com/
http://www.biophorum.com/accelerate
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What is a Technology Road Map?!

An industry technology roadmap is –

a dynamic and evolving collaborative technology management process

For:

- determining precompetitive critical needs and drivers,
- identifying technology and/or manufacturing targets, and
- assessing/modeling potential solutions
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Why is a Technology Roadmap needed for the Biopharm Industry?

**Complex industry has traditionally held back innovation…**

- Complex global regulatory environment
  - Multiple jurisdictions
  - Varying requirements

- Biomanufacturers are risk averse
  - The penalties are severe for delays and setbacks in drug commercialization
  - Uncertainty around product comparability between scales and process changes
  - New technology may not be adapted because of perceived risks to program
  - Everyone wants to be a Fast Second!

- Biomanufacturers and Suppliers develop technologies in isolation

- Technology standardisation usually only occurs after the technology is launched

- Suppliers find it difficult to innovate
  - Have to guess end user requirements
  - Risk-reward balance is poor
Audacious goal:

**Revolutionise the way the industry develops longer term transformational manufacturing and technology capabilities**

To agree an industry technology strategy

- Focus the industry on longer term strategy & 10+yr time horizon,
- provide direction, and
- defining needs, difficult challenges and potential solutions
- resolve those critical needs
Why is this approach different this time?

- More collaborative cross-company/institution approach
- To include all stakeholders...

- Longer-term view (we’re all better off in the long run if we work together...)
- Addressing barriers to implementation:
  - Cultural and Behavioral
  - Regulations and compliance
  - Commercialization timeline risks
  - Product comparability risk
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Following the Lead from other Industries.....
Using method from University of Cambridge’s Institute of Manufacturing

**Semiconductor Industry**

**NASA**
Technology Roadmapping Steering Committee

- Developed a strong Steering Committee
  - Required decision making
  - Driving roadmap
  - Subject matter experts access

- Diverse participants
  - 17 biomanufacturers
  - 6 supply partners recently joined (and growing)
  - Academics & regional centres, e.g. MIT, AMBIC, CPI, SEDB, NIIMBL

- Over 130 people involved globally
Overview of Methodology for Technology Roadmap Construction

1. Evaluate Biopharmaceutical Market Trends
2. Identify Main Business Drivers & Metrics
3. Develop Representative Scenarios
4. Define Scenario/Options Matrix and Objectives
5. Model Facility Types
   - Fix: Process/Facility Type
   - Vary: Throughput, utilization, product mix
6. Identify/prioritize Opportunities for Improvement
7. Identify Potential Solutions and Alternatives
8. Define Development Timelines and Pathways

Business Scenarios (Key Drivers) vs. Biomanufacturing Facility Type Scenarios (Options)

Model Business Scenarios
- Fix: Throughput, Product mix
- Vary: Process/facility design

Identify/prioritize Advantages / disadvantages
Identify Potential Solutions and Alternatives
Define Development Timelines and Pathways
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Evaluating Biopharmaceutical Market Trends (Step 1)

- Robust Pipelines
- Strength of Sales (Biologics)
- New Treatment Modalities
- Personalised medicine
- Advances in Systems Biology
- Payer pressure on cost of drugs
- Rising Costs of Drug Development
- Biosimilars Competition
- Clinical Failures
- New product classes
- Market growth
  - Volume / year / drug
  - Number of drugs supplied
  - Global reach and emerging markets
- Cost
  - Payer pressure
  - Biosimilars
  - Cost of clinical failure
- Uncertainty of approvals and sales
- Emerging Markets
- In-region manufacturing requirements
- Complex Global regulatory environment
- Demand Forecasts
- Social / Political Perceptions
- Market Share
- Dose Requirements
Collective Brainstorming by Industry Experts
Defining Main Business Drivers and High Level Roadmap Structure (Step 2)

**Industry Trends**
- Payer pressure on cost
- Diversification of product groups
- In region manufacturing
- Personalised medicine

**Business Drivers**
- Speed
- Cost
- Flexibility
- Quality
  - Process intensification
  - Continuous processing
  - Automation
  - Inline monitoring
  - Modular and mobile
  - Knowledge management

**Technology Areas**
- Technology standards
- Real time Release
- Vendor interaction
- Supplier Management
- Regulatory Harmonisation
- Keep workforce capable
- Multi-use and flexible facilities

**Enablers**
- Knowledge management
Developing Representative Scenarios (Step 3)

**Purpose of Business Scenarios**
- To help evaluate biomanufacturing strategies and technologies that will have greatest impact for a particular set of business drivers
- Not all companies have the same set of ‘Key’ business drivers or metrics

**Purpose of Biomanufacturing / Facility Type Scenarios and Options**
- Represent today’s typical facilities (current state-of-art)
- Many companies have existing assets that need to be utilized and even potentially expanded
- Serve as starting point for technology road map
Defining Objectives and Options for Modeling (Step 4)

- **Purpose of Modeling**
  - Identify areas of opportunity for improvement within a given scenario / facility type.
  - Compare performance between options within a scenario or between scenarios relative to a given metric
    - e.g. compare estimated Cost of Goods using different process formats
  - Process parameter sensitivity analysis
  - Identify bottlenecks in throughput and breakpoints in technology strategy/selection.
  - To evaluate the technology improvements proposed by the roadmap teams

- **Limitations of Current Models**
  - Performance estimates are not absolute. Models are not calibrated to any specific circumstance such as location or specific organizational context
  - For relative comparisons only; Default values for base line comparison (e.g. price of raw material costs, equipment and labor, installation factors

- **Excluded**
  - Site purchase, staffing cost and raw materials & consumables up to production
  - Central development labs and site offices
  - Site warehousing
  - Black utilities
Processing Options (and Symbols)

**Upstream Process** (Bioreactors)

- **Batch** (*Fed-batch*)
- **Continuous** (*Perfusion*)

**Downstream Process** (Purification Train)

- **Batch**
- **Continuous**

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**Stainless Steel** *(SS)* *(Conventional)*

- **Batch**
- **Continuous**

**Single-use** *(SU)* *(Disposable)*

- **Batch**
- **Continuous**

**Hybrid** *(SS+SU)* *(Volume dependent)*

- **Batch**
- **Continuous**
Modeling Cases

High-demand Product (High Volume)

- SS-B / B
- SS-B / C

Low-demand Product (Low Volume)

- SU-B / B
- SU-B / C
- SU-C / B
- SU-C / C

Design

10,000 kg/yr 1,000 100 10 1 0.1
Process Modeling – Biopharm Services using BioSolve Software

- Initial modelling done using a platform mAb process
  - Targeting 1,000 or 100 kg per year output
  - Using 12.5kL SS or 2kL SUB reactor and combinations of B/B, B/C, C/B and C/C processing
  - Capital Investment and COG
  - Parameter sensitivity analysis

### Batch Downstream example

<table>
<thead>
<tr>
<th></th>
<th>Centrifugation/1° Depth Filtration</th>
<th>2° Depth Filtration</th>
<th>Protein A</th>
<th>Virus Inactivation</th>
<th>CEX</th>
<th>AEX F/T</th>
<th>Viral Filtration</th>
<th>UF/DF</th>
<th>Final Filtration</th>
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<tbody>
<tr>
<td>Yield</td>
<td>87%</td>
<td>96%</td>
<td>97%</td>
<td>98%</td>
<td>97%</td>
<td>97%</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
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<tr>
<td>Flow</td>
<td><img src="image" alt="Flow Diagram" /></td>
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<td><img src="image" alt="Flow Diagram" /></td>
</tr>
<tr>
<td>Comments</td>
<td>Removed when using Perfusion USP</td>
<td>200LMH 400 L/m²</td>
<td>Batch – 35g/L</td>
<td>PCC – 55 g/L</td>
<td>200 g/L</td>
<td>250 LMH 600 L/m²</td>
<td>40 LMH</td>
<td>300 LMH 250 L/m²</td>
<td></td>
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</table>
Overview of modeling 1,000 kg and 100 kg output per year

- Next round of modeling will float output assuming more realistic facility designs ("6-pack" facilities)
- Initial exercise already useful in pointing to opportunity areas
Continuous downstream processing reduces COG
Continuous upstream processing has no cost benefit over batch

- Continuous Processing reduces capital impact
- Perfusion systems have high media cost impact
- Processes c-d, higher consumable component due to single-use systems
Net Present Cost: Scaling up vs. Scaling Out....

Conventional
“Six-pack” Facility
6 x 15,000L Stainless Steel Bioreactors

Expanded or Multi-Facility
6 x 2,000L Single-use Bioreactors
Batch versus Continuous, 1,000 kg using 2,000L scale

Scenario 1c – Batch USP/ Batch DSP

- WFI: 2808 m³/year
- Batch Cycle: 0.26 Weeks

Scenario 1f – Cont. USP/Cont. DSP

- WFI: 14089 m³/year
- Batch Cycle: Weeks

CoGs Table

<table>
<thead>
<tr>
<th>CoGs</th>
<th>USD</th>
<th>Batch</th>
<th>Gram</th>
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</thead>
<tbody>
<tr>
<td>Capital</td>
<td>91,805.61</td>
<td>13.06</td>
<td>7%</td>
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<tr>
<td>Materials</td>
<td>43,114.52</td>
<td>6.13</td>
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<tr>
<td>Consumables</td>
<td>124,768.51</td>
<td>17.75</td>
<td>28%</td>
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<tr>
<td>Labour</td>
<td>64,073.21</td>
<td>9.11</td>
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<tr>
<td>Other</td>
<td>24,267.30</td>
<td>3.45</td>
<td>1%</td>
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<tr>
<td>TOTAL</td>
<td>348,029.15</td>
<td>49.50</td>
<td>36%</td>
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</tbody>
</table>

- No Pool

A few Results of the Initial Process Parameter Sensitivity Analysis

- Upstream and Downstream Yields are major cost drivers

**Cell Culture Yield**

- 12.5k B/B
- 12.5k B/C
- 2k B/B
- 2k B/C

**Downstream Recovery**

- ProA Yield
- Polishing Yield
- ProA Yield 100kg
- Polishing Yield 100 kg

- 100 kg/year
- 1,000 kg/year

**Graphs**

- Titer (g/L) vs. COG ($/g)
- % Yield vs. COG ($/g)
Interaction between Perfusion Rate and Cell Concentration and Productivity

**Perfusion Parameters**

- Cell specific perfusion rate and perfusion media costs are major cost driver

- If cell specific perfusion rate is increased, higher cell mass and higher specific productivity is required to maintain cost
Initial Flags for Technology Opportunities

- **Upstream batch titer**
  - Perfusion applications to batch culture
  - Culture duration

- **High downstream step yields**
  - Purity and impurity profiles (simple and robust product modalities)
  - Resin features (capacity and impurity clearance)

- **Perfusion media costs and specific perfusion rate**
  - Media design and waste product formation
  - Highly concentrated and balanced media of low cost

- **Consumables cost**
  - Improved filter capacity and production processes

- **Buffer production strategy**
  - Buffer concentrates and in-line dilution

- **Production cell lines**
  - Cell specific productivity
  - Impurities and product quality features (glycans)
  - Harmonized expression system
Conclusions and Next steps

- Significant progress has been made in bringing the industry together for this precompetitive collaboration

- A work in progress, More work to be done

- Will take some time and a few iterations. First time this is being done with wide industry participation

- Vendor and academic partner participation

- Technology innovation opportunities are beginning to be identified

- More modeling to be done to help assess value and prioritize

- Plan to publish completed road map before mid of 2017
Acknowledgements

- Andrew Sinclair
- Alan Calleja
- Paul Ilott
Thank You!

Disclaimer

- This presentation was prepared by the BPOG Consortium. The opinions and views expressed are from the BPOG Consortium and do not reflect the views of individual member companies.
Anti-Trust Compliance Statement v4.0

- It is the clear policy of BioPhorum that BioPhorum and its members will comply with all relevant anti-trust laws in all relevant jurisdictions.

- All BioPhorum meetings and activities shall be conducted to strictly abide by all applicable antitrust laws. Meetings attended by BioPhorum members are not to be used to discuss prices, promotions, refusals to deal, boycotts, terms and conditions of sale, market assignments, confidential business plans or other subjects that could restrain competition.

- Anti-trust violations may be alleged on the basis of the mere appearance of unlawful activity. For example, discussion of a sensitive topic, such as price, followed by parallel action by those involved or present at the discussion, may be sufficient to infer price-fixing activity and thus lead to investigations by the relevant authorities.

- Criminal prosecution by federal or state authorities is a very real possibility for violations of the antitrust laws. Imprisonment, fines or treble damages may ensue. BioPhorum, its members and guests must conduct themselves in a manner that avoids even the perception or slightest suspicion that antitrust laws are being violated. Whenever uncertainty exists as to the legality of conduct, obtain legal advice. If, during any meeting, you are uncomfortable with or questions arise regarding the direction of a discussion, stop the discussion, excuse yourself and then promptly consult with counsel.

- The antitrust laws do not prohibit all meetings and discussions between competitors, especially when the purpose is to strengthen competition and improve the working and efficiency of the marketplace. It is in this spirit that the BioPhorum conducts its meetings and conferences.