Technology Roadmapping – Collaborating to accelerate innovation in biopharmaceutical manufacturing

Beate Muller-Tiemann

Jan 2017
Agenda

- Introduction to BPOG
- Ambition, process and structure
- Content of the Technology Roadmap
- How to get involved
BPOG is a collaboration of the World’s top biopharma manufacturers and supply partners

<table>
<thead>
<tr>
<th>Abbvie</th>
<th>Alexion</th>
<th>Amgen</th>
<th>AstraZeneca</th>
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<th>Biogen</th>
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<td>GE Healthcare</td>
<td>Genentech</td>
<td>A Member of the Roche Group</td>
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<td>UCB</td>
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</table>
BPOG has 6 Phorums covering all aspects of biopharma operations

**Drug Substance, Fill Finish, Development, Information Technology**
Accelerating the way the industry delivers near term results, making best practice development and implementation faster, cheaper and smarter

**Supply Partner Phorum**
Creating the supply chains the industry needs; defining, developing and implementing solutions for business processes, systems and culture

**Technology Roadmapping**
Revolutionising the way the industry develops longer term transformational manufacturing and technology capabilities
Focusing on strategy and 10yr time horizon, defining needs, difficult challenges and potential solutions

**Regulatory Interaction**
Ensure efforts to design and adopt advances in manufacturing are aligned through engagement with Health Agencies

**BPOG Facilitation**
Decisions are made at the right time, at the right place by the right people
Linkages are made visible to avoid redundancy
Synergies are leveraged through effective coordination
Agenda

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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 attempted after the technology is launched

- Suppliers find it difficult to innovate
  - Have to guess end user requirements
  - Risk-reward balance is poor
Audacious goal: To agree an industry technology strategy

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

to

- focus an industry community,
- provide direction, and
- resolve those critical needs for a specific timeframe by consensus
Example technology roadmap report

Selected pages from the Modular and Mobile roadmap

The degree to which each of the concepts can be applied depends on facility scale, as indicated by the relative footprint volumes in Figure 2. Modular concepts can be applied across all scales with benefit whereas BPOG concepts are not typically applicable above the 2xL scale due to Modular Clean Rooms (MCR) transport limitations. Additionally, 2xL is the largest scale of single-use biomanufacturing currently available, and single-use process equipment supports the benefits of the MCR approach, since it reduces capital expenditure and build time, transferring costs to operational expenditure that can be covered more easily against incoming revenue.

Figure 2 Applicability of Modular and Mobile Concepts

<table>
<thead>
<tr>
<th>Facility Scale</th>
<th>Modular</th>
<th>Mobile</th>
<th>Facility</th>
<th>Room</th>
<th>Equipment</th>
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<tr>
<td>2xL</td>
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There are different factors that motivate the adoption of a modular and mobile approach, and the extent to which they are used:

- Scale of the process (smaller footprint required)
- Capital needs (smaller footprint reduces capital cost)
- Need for flexibility (easy to modularize)
- Transport considerations (M CRs offer potential for reach-market support)
- Complexities associated with modular manufacturing
- Complementing (i.e., flow-through manufacturing area)
- Limitations (i.e., cleaning validation)
- Complexity (i.e., process design)
- Flexibility in process design
- Cost (M CRs have been shown to be competitive)

The scope of this document is and packaging across the full scale of possible use cases, the degree of flexibility, and the extent to which these factors motivate an modular approach.

4.3.3.2.4 The Needs/Challenges and Potential Solutions table

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Facilitate Equipment</th>
<th>Needs/Challenges</th>
<th>Solutions</th>
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<tr>
<td>APPROACH</td>
<td>Time to bring product to market</td>
<td>12 months</td>
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<td>CHALLENGE</td>
<td>Product development</td>
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<td>SOLUTION</td>
<td>Development of faster methods</td>
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<td>APPROACH</td>
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<td>SOLUTION</td>
<td>Improved cost efficiency</td>
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<td>APPROACH</td>
<td>Time to deliver product</td>
<td>15 days</td>
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<tr>
<td>CHALLENGE</td>
<td>Quality control</td>
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<tr>
<td>SOLUTION</td>
<td>Improved quality control</td>
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</table>

Contents

- Summary
- Introduction; vision, scope & benefits
- Needs, challenges & potential solutions
- Disruptive technologies
- Regulatory considerations
- Conclusions and recommendations
A strong collaboration, bringing the industry’s top people together to contribute to & benefit from the technology roadmap

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

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

- Over 170 people involved globally

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Biophorum Operations Group Ltd
Building the industry technology roadmap
A huge amount of work has gone into the creation of the 1st Edition - Over 300 pages now drafted by the teams

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<th>Face to face meetings</th>
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<td>Detail review followed by final changes to document</td>
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<td>Roadmap revision 2 Support / co-ordinate implementation</td>
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<td>Summary Vision, Map, Scope, Linkages</td>
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- Content of the Technology Roadmap
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High level Technology Roadmap structure

Industry Trends
Business Drivers

- Cost pressure
- Uncertainty
- Market Growth
- New Product Classes

- Speed
- Cost
- Flexibility
- Quality

Biomanufacturing scenarios

1. Large-scale Stainless Steel Fed Batch
2. Intermediate-scale Single-use Perfusion
4. Small-scale <500L Portable Facility
5. Small-scale <50L for Personalized Medicine

Scale

Distributed

Enabling Technologies

- Process Technology
- Inline Monitoring & Real time Release
- Modular & mobile
- Automated Facility
- Knowledge Management
- Supply Partnership Management

Drug Product

- Low volume
- High volume

Business Drivers

- Industry Trends
- Cost pressure
- Uncertainty
- Market Growth
- New Product Classes

- Speed
- Cost
- Flexibility
- Quality

Drug Product Scenarios

- High volume
- Large scale
- Stainless Steel Fed Batch
- Intermediate scale
- Multi-product Single-use Fed Batch
- Small scale
- <50L Personalized Medicine

Supply Partnership Management
Process Technologies - Process technology developments are at the heart of any efforts to increase the productivity and robustness of biopharmaceutical manufacturing.

Priority technologies & capabilities:

- **Media performance** - Richer, chemically defined medias, feeds and supplements that enable higher cell densities, higher titers, simplified media make-up, and longer media stability.

- **Robust harvesting** - Scalable harvest technologies and cell retention devices that minimize large capital investments and can handle ever increasing cell densities.

- **Viral clearance** - Standardized modular claims that provide streamlined regulatory processes and ease process development.

- **Buffer management** approaches that reduce operational constraints and space requirements for buffer preparation.

- **Single use technologies** to increase flexibility and improve closed systems, resulting in decreased capital cost, and decreased total cost of goods over the lifetime of a product.
In-line Monitoring and Real-time Release - Process technology developments are at the heart of any efforts to increase the productivity and robustness of biopharmaceutical manufacturing.

Priority technologies:

- **In-line Monitoring** - Integration of in-line proves with process control systems.
- **Innovative in-line multi-attribute sensors** - sdf
- **Predictive analytics** – Modelling. Scale-down / miniaturization
- **International regulatory acceptance of alternative approaches** - asfsdf

**Inline Monitoring and Real time Release**

**Benefits:**
- ↓ Product Release 1-2 day
- ↑ Quality, Efficiency & Supply

**Key themes:**
- Enhanced in-line monitoring unlocks potential for robust material characterisation, process control and assurance of product quality
- Hardware for advanced in-line monitoring devices including indirect and multi-attribute sensors
- Software to enable multivariate analysis, predictive models and closed feedback control loops
Modular & Mobile - Process technology developments are at the heart of any efforts to increase the productivity and robustness of biopharmaceutical manufacturing

Priority technologies & capabilities:

- **Standardisation**
  - Creation of equipment standards
  - Enable multi-supplier environment
  - Regulatory harmonisation

- **‘Facility as Equipment’**
  - Management of validation, capital & speed to install
  - Eliminate non-value add activity (manufacturers & regulators)

- **Standardisation**
  - Quick, easy scale up of processes & facilities
  - Bring production to where most needed – closer to patients
  - Speed to market

---

**Modular and Mobile**

**Benefits:**
- 70% ↓ build time
- 75% ↓ CAPEX

**Key themes**
- Manufacturing systems that are quick to configure, assemble, scale and relocate, using ‘plug and play’ standard designs and standard validation approaches
## Enabling Technologies & Capabilities – 6 teams mobilised to define detailed roadmaps

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<th>Vision</th>
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<td>Process Intensification - Intensifying production through highly concentrated reactants and products and combining unit operations into single units</td>
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<td>Continuous Processing - New separation and media technologies, coupled with advanced automation and process control</td>
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</table>
Modular & Mobile – Key Themes

**Standardization**
- Creation of equipment standards
- Enable multi-supplier environment
- Regulatory harmonisation

**‘Facility as Equipment’**
- Management of validation, capital & speed to install
- Eliminate non-value add activity (manufacturers & regulators)

**Flexibility**
- Quick, easy scale up of processes & facilities
- Bring production to where most needed – closer to patients
- Speed to market

Paradigm shift in approach to management of factory infrastructure
Process Technologies - Process technology developments are at the heart of any efforts to increase the productivity and robustness of biopharmaceutical manufacturing.

Priority technologies:
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### Six Enabling Technologies & Capabilities have been mapped in detail by the teams

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• Streamlined validation processes  
• Decreased total cost of goods |         |
| Continuous Processing - New separation and media technologies, coupled with advanced automation and process control | • Flexibility for smaller patient populations  
• Speed  
• Reduced cost and reduced facility size |         |
| **In-line Monitoring and Real-time release** |        |         |
| Enhanced in-line monitoring unlocks potential for robust material characterisation, process control and assurance of product quality  
Hardware for advanced in-line monitoring devices including indirect and multi-attribute sensors  
Software to enable multivariate analysis, predictive models and closed feedback control loops | • Enabler of Real Time Release; Product Released in 1-2 Days  
• Improved Product Quality, Operational Efficiency and Reliable Supply |         |
| **Modular and Mobile**              |        |         |
| Manufacturing systems that are quick to configure, assemble, scale and relocate, using ‘plug and play’ standard designs and standard validation approaches | • Rapid tailoring of capacity to meet demand  
• Manufacturing process available in weeks  
• Mobility of facilities through lifecycle  
• Reduction in capital expenditure |         |
| **Fully Automated Facility**        |        |         |
| Plug and play for fast response to capacity demands, with minimal staff, time to change over, and regulatory observations, that delivers products of lowest cost and highest quality, from receipt of raw materials to final drug product. | • Quicker and cheaper facility builds and lower lifecycle costs  
• Readily available and usable data  
• Reduced mfg. deviations and non-conformances  
• Streamlined real-time release  
• OPEX reduction |         |
| **Supply Partnership Management**  |        |         |
| Supply Partnership Management undertaken in a spirit of openness and trust to drive successful collaboration making best use of technology and integration of systems and processes | • Lower cost/quality ratio for raw materials, services and capex investment  
• Faster to develop, produce and make changes  
• Safe, innovative supply chains |         |
| **Knowledge Management**            |        |         |
| Integrated knowledge of product and process technology across the development, manufacturing and commercial value streams | • Accessible and applicable biomanufacturing information and knowledge, driving down development costs  
• Efficiency and quality throughout product lifecycle. |         |
Process Technologies – Key Themes

Streamlining unit operations
- Incremental efficiencies
- Culture shifts
- Future targets for performance

Linking upstream & downstream
- Continuous processing
- High value ‘hotspots’

Disruptive Technologies
- Matched to operational needs
- Integral to performance acceleration

Faster process improvement
- Regulatory impact
- Cohesive validation
## Automated Facility – Key Themes

### Key Themes

- **Full integration across all systems MES, PCS, LIMS**
  - Ability to configure a facility end to end instead of programming

- **Management of Data**

- **High Availability Automation Systems**
  - High availability depends on automation IT systems and databases. Work with supply partners is critical in this space.
  - Dependent on technology development for failure detection and swap-over

- **Reduction of manual labor through the use of robotic systems**

- **New Technologies**
  - Elimination of errors through paperless operation and guiding maintenance and support activities.
  - Reduction in cost through the use of smart scheduling techniques to maximise utilisation and the move to cloud and virtualised technologies.

- **Disruptive Concepts and Technologies**
  - Convergence of platform technologies will provide a new model for operation, with capability and intelligence distributed at much lower levels in the plant architecture (plug-and-play modules)
  - Use of large amounts of data and adaptive, machine learning to provide decision support and help eliminate delay and errors.

### Business benefits

**Reduction in OpEX**
- Reduction in complexity, manual operations, thereby improving efficiency and quality
- Rationalisation of data
- Automated use of Data (PAT & autonomous systems)

**Reduction in CapEX**
- Reduction in equipment costs, factory cost
- “Quicker to build” reducing risk by delaying the decision to build
## Supply Partnership Management – Key Themes

### Openness & Trust
- Collaboration: suppliers as an extension of the biomanufacturer
- Development: Transparency of technologies, harmonised industry standards
- Regulatory: Process characterisation & supplier controls. Provision for plug & play

### Quality Built In
- Removal of duplicated effort
- Quality requirements: Industry accepted templates & protocols
- Optimised testing: Reduced duplicate testing. Control variation at source.

### Forecasting & Demand Planning
- Transparency of capital planning
- Transparency of short & long term demand
- Industry supply chain risk analysis and shared business continuity for key supply chain constraints

### Standardisation
- Industry standard audits & auditors
- Harmonisation of RM testing requirements
- Standardised supplier validation

### Electronic Data Exchange & Supplier Integration
- Common EDE standards, common format demand information
Knowledge Management – Key Themes

Key Themes
- Clear strategy leads avoids slow starts and reduces skepticism
  - Pre-requisite for organization to assess current state and benefits
- Embed KM in business and solve real business problems to attract attention and gain momentum
  - Crucial capability to preserve & grow knowledge (any organization’s most valuable asset)
  - Minimize theoretical or abstract concepts
  - Pragmatic and easy-to-follow common sense approach
- Equal attention to People, Process, Content and Technology
  - Right technology crucial but not sufficient
  - Knowledge management not equal to information management
  - Systematic approach and cultural readiness
- Sufficient leadership commitment and sponsorship breaks through roadblocks
  - Clear ties to organization’s success measures (enable the business)
  - Dedicated measures for KM deployment and maturity
  - Right focus in the right areas first (sufficient resources)
- Implementation takes a cultural transformation
  - Change management activity requiring patience to build core competencies
  - Engage all critical stakeholders to realize maximum potential

Scope
- Integration of product and process information across the development, manufacturing and commercial (sales) value streams.
- Knowledge management platform that integrates knowledge-- from chemistry manufacture controls (CMC) development of product and process technology, through to clinical and licensed manufacturing, and selected commercial aspects (e.g., related to production triggers, patient feedback).
- “near real time” access to all types of information creating overall visibility across the value stream as well as “nearly instant” cross-product learning.

Business benefits
- Speed to market
- Cross-product learning
- Efficiency throughout product lifecycle
In-line Monitoring & Real-time Release (ILM / RTR) – Key Themes

- Unlock potential for robust process control while improving quality & operational efficiency
- End-to-end methodology, through lens of biomanufacturing scenarios
- Over past decades, key bottleneck has been batch disposition
  - Today, starts at end of production with analytical tests & requires long-lead time; mainly human operated, paper-driven system
  - Opportunity to reduce to within hours to a few days
- Enabled by integration & advancement of several elements:
  - Raw material characterization & control
  - Hardware: advanced in line monitoring, in-direct or multi-attribute sensors
  - Software for closed feedback control, multivariate analysis for predictive models
  - Rapid analytical testing for biological assays
  - Streamlined quality & business systems: review by exception
- Several technologies, methodologies & regulatory guidance required
  - Future technology critical to successfully achieving real-time release
Agenda

- Introduction to BPOG
- Ambition, process and structure
- Content of the Technology Roadmap
  - In-line Monitoring & Real-time Release
- How to get involved
Questions

• What can we do to increase the value proposition for In-line Monitoring / Real Time Release (ILM/RTR)?
• Are there other technologies not considered that could enable ILM/RTR?
• What else do you want to see in the roadmap?
• What do you see as the major technical / regulatory challenges / milestones (impediments) to successful implementation of ILM/RTR?
• Are there other ideas to accelerate timelines?
Summary

▪ Today, batch disposition starts at the end of the production batch, and requires long-lead time analytical tests with human oversight and review.

▪ This report explores inline monitoring / real-time release as process controls to improve product quality and operational efficiency.

▪ Technology roadmap tables are provided illustrating gaps in current industry and ideas of how to close those gaps over the next several years.
<table>
<thead>
<tr>
<th>Roadmap Team</th>
<th>Vision</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-line Monitoring and Real-time release</td>
<td>Process control and assurance of product quality through advanced monitoring devices, multi-attribute sensors, and PAT.</td>
<td>• Tighter product and process control</td>
</tr>
<tr>
<td></td>
<td>Complete batch disposition package contemporaneous with completion of manufacture</td>
<td>• Early issue identification</td>
</tr>
<tr>
<td></td>
<td>Global regulatory testing standards consistent with these control strategies.</td>
<td>• Reduction in waste and errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Eliminate $Bn’s of inventory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Product released 1-2 days after manufacture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduced time needed for QA review</td>
</tr>
</tbody>
</table>
## Upstream Quality Attributes or Process Parameters

<table>
<thead>
<tr>
<th>Attribute or Parameter</th>
<th>Current State</th>
<th>Technology in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>In-line pH probes</td>
<td>Robust single use sensors with feedback control</td>
</tr>
<tr>
<td>Dissolved O2, CO2</td>
<td>On-line blood gas Analyzers, off-gas analysis by MS and IR</td>
<td>In-Line CO2 probes</td>
</tr>
<tr>
<td>Glucose</td>
<td>At-line and On-line glucose analysis</td>
<td>In-line Raman, NIR with feedback control; Enzymatic chip based sensors</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>Off-line</td>
<td>On-Line UPLC</td>
</tr>
<tr>
<td>Glycan distribution</td>
<td>Off-line</td>
<td>On-line UPLC-MS</td>
</tr>
<tr>
<td>Charged isoforms</td>
<td>Off-line</td>
<td>On-line UPLC, IEC</td>
</tr>
<tr>
<td>Glycation</td>
<td>Off-line</td>
<td>On-line Intact Mass</td>
</tr>
</tbody>
</table>

In-line: sample is not removed from the process stream; can be invasive or noninvasive (“sensors”).

On-line: sample is diverted and may be returned to the process stream.
## Downstream Quality Attributes or Process Parameters

<table>
<thead>
<tr>
<th>Attribute or Parameter</th>
<th>Current State</th>
<th>Technology in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregates</td>
<td>Off-line SEC</td>
<td>On-line UPSEC, In-line MALS, MIR</td>
</tr>
<tr>
<td>Charge heterogeneity</td>
<td>Off-line CE or IEX</td>
<td>On-line UPLC</td>
</tr>
<tr>
<td>[protein]</td>
<td>In-line UV, In-line refractive index</td>
<td>Multi-wavelength diode arrays for column elution</td>
</tr>
<tr>
<td>HCP</td>
<td>On or at-line ELISA</td>
<td>At-line Mass Spectrometry</td>
</tr>
<tr>
<td>Potency (off-line testing)</td>
<td>3–5 day cell-growth assays</td>
<td>1–2 day reporter gene assays</td>
</tr>
</tbody>
</table>

On-line: sample is diverted and may be returned to the process stream  
At-line: sample is removed, isolated from and analyzed in close proximity ("tested on the factory floor")
## Opportunities for New Technologies

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Current Technologies</th>
<th>Current Turnaround time</th>
<th>Potential Technologies</th>
<th>Target Turnaround time</th>
<th>Target Sensitivity or Range</th>
<th>Target Product Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro, Viral Safety</td>
<td></td>
<td></td>
<td>Fluorescence based plate assays. Respirometry, Microflow imaging, flow cytometry</td>
<td>2 days</td>
<td>1 CFU / 10 mL</td>
<td>Multiple</td>
</tr>
<tr>
<td>Bioburden</td>
<td>Pour plate method</td>
<td>7 days</td>
<td>Fluorescence based plate assays. Respirometry, Microflow imaging, flow cytometry</td>
<td>2 days</td>
<td>1 CFU / 10 mL</td>
<td>Multiple</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Cultivation assay</td>
<td>28 days</td>
<td>qPCR (no change)</td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>In Vitro (adventitious) Virus</td>
<td>Cultivation assay</td>
<td>28 days</td>
<td>qPCR (no change)</td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>MMV</td>
<td>qPCR</td>
<td>2 days</td>
<td>qPCR (no change)</td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>LAL</td>
<td>1 day</td>
<td>Cartridge-based endotoxin testing, Mass Spectrometry</td>
<td>1 day</td>
<td>0.01 EU/mL</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
Future Needs – High Level

1. In-line monitoring and integration of in-line probes with process control systems
2. Innovative in-line multi-attribute sensors
3. Predictive analytics
4. International regulatory acceptance of alternative approaches
Future Needs – Mid Level

**In-line monitoring and sensors**
- Rapid inline product quality measurements
- Sensitive and robust measurement
- Standardized interface
- Sensors reusable / disposable

**Predictive Analytics**
- Modelling
- Scale-down / miniaturization
# International Regulatory Acceptance

<table>
<thead>
<tr>
<th>Issue/Challenge</th>
<th>Opportunity</th>
<th>Engagement Plans</th>
<th>Proposals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global acceptance of RTR</td>
<td>Provide more support for wider industry use and global regulatory acceptance</td>
<td>Work on risk assessment for release and process control.</td>
<td>Knowledge sharing with FDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk assessment consistent with ICH Q9 and compares/contrast with risk assessment for current state control strategies</td>
<td>Presentations &amp; Publications</td>
</tr>
<tr>
<td>Development of Rapid Micro Methods and Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverse Global Regulatory Requirements</td>
<td>Harmonization (ICH and WHO)</td>
<td>Systematically identify country/regional specific impediments to ILM/RTR</td>
<td>Presentations at international meetings</td>
</tr>
</tbody>
</table>

**Advantage:** reduction of errors and waste
Future Needs – More Detailed

**In-line Monitoring & Sensors**
- Multi-attribute (ideally in single port)
- Must fit standard port specifications
- Single or no calibration; at least easy
- CIP/SIP/caustic stable/pressure stable
- Sensors with capability to monitor their own performance and predict when they will fail
- Small instrument footprint
- Centralized or remote access
- Software interface with distributed control system
- Scalability (scale down)
- Moderate sample frequency (min – hours)
- Material Qualification Documents

User requirements list under development by SME’s from Supplier and Biopharmaceutical Companies
## Specific Metrics of Success for ILM/RTR example: viral safety

<table>
<thead>
<tr>
<th>METRIC</th>
<th>Description</th>
<th>Current</th>
<th>2019</th>
<th>2022</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Reduction in turnaround times for adventitious virus testing from 28 days to 2 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>NEED</td>
<td>Develop/validate methods to generate rapid results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHALLENGE</td>
<td>Obtaining world-wide acceptance from health authorities for use of new technologies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>POTENTIAL SOLUTION</td>
<td>Possible next-generation sequencing, qPCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Challenges:**
- Obtaining world-wide acceptance from health authorities for use of new technologies

**Potential solutions:**
- Possible next-generation sequencing, qPCR
## ILM/RTR Metrics of Success for Tech Roadmap

<table>
<thead>
<tr>
<th>Metric</th>
<th>5 yr Target</th>
<th>Impact</th>
<th>10 yr Target</th>
<th>Impact</th>
<th>Impact notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of non-quality</td>
<td>10% of operating cost</td>
<td>Medium</td>
<td>2% of operating cost</td>
<td>High</td>
<td>Greater control + detectability due to in-line monitoring and RTR</td>
</tr>
<tr>
<td>Time to Product availability</td>
<td>50% reduction (2 months)</td>
<td>Medium</td>
<td>90% reduction (2 weeks)</td>
<td>High</td>
<td>Ability to release in real time will allow team to react quicker to potential stockouts</td>
</tr>
</tbody>
</table>
Discussion

- What can we do to increase the value proposition for in-line monitoring and real-time release?
- Are there other technologies not considered that could enable ILM/RTR?
- What else do you want to see in the roadmap?
- What do you see as the major technical / regulatory challenges/milestones (impediments) to successful implementation of ILM/RTR?
- Other ideas to accelerate timelines?
Agenda

- Introduction to BPOG
- Ambition, process and structure
- Content of the Technology Roadmap
- How to get involved
Timing of publication and communications. How to get actively engaged

- **1st edition** will be published in May 2017, freely available to on the BPOG website.
- Complemented by broad communications mix
  - Webinars, conference presentations, articles, newsletters
- **We want your input on the roadmap’s content and scope of future editions**
  - Individual comment
  - Formal response from your organisation
  - Your organisation becoming active members of the collaboration
- **Roadmapping is all about stimulating an industry response, encouraging the required innovation to happen.**
- What solutions can you bring to overcome the difficult challenges facing the industry?
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.
Back-up slides
High level Technology Roadmap structure
- Over 300 pages now drafted by the teams

**Industry Trends Business Drivers**
- Cost pressure
- Uncertainty
- Market Growth
- New Product Classes

**Speed**
- Cost
- Flexibility
- Quality

**Biomanufacturing scenarios**
1. Large-scale Stainless Steel Fed Batch
2. Intermediate-scale Single-use Perfusion
4. Small-scale <500L Portable Facility
5. Small-scale <50L for Personalized Medicine

**Enabling Technologies**
- Process Technology
- Inline Monitoring & Real time Release
- Modular & mobile
- Automated Facility
- Knowledge Management
- Supply Partnership Management

Drug Product
- High volume
- Low volume
### Market Trends & Business Drivers – The Why

<table>
<thead>
<tr>
<th>Cost pressure</th>
<th>Uncertainty</th>
<th>Market Growth</th>
<th>New Product Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Payer pressure</td>
<td>- Regulatory approvals</td>
<td>- Emerging markets</td>
<td>- Non-mAbs, ADCs</td>
</tr>
<tr>
<td>- Biosimilars</td>
<td>- Demand variability</td>
<td>- Global reach</td>
<td>- Gene therapy</td>
</tr>
<tr>
<td>- Development</td>
<td>- Competition</td>
<td>- In region manufacture</td>
<td>- Cell therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost</th>
<th>Flexibility</th>
<th>Speed</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>-90% manufacturing cost</td>
<td>-90% changeover</td>
<td>-70% build time</td>
<td>10x robustness</td>
</tr>
<tr>
<td>-90% CAPEX</td>
<td>Demand response</td>
<td>-80% lead time</td>
<td>-90% cost of quality</td>
</tr>
</tbody>
</table>

### Biomanufacturing scenarios – The What

- **1. Large-scale Stainless Steel Fed Batch**
- **2. Intermediate-scale Single-use Perfusion**
- **4. Small-scale <500L Portable Facility**
- **5. Small-scale <50L for Personalized Medicine**

**Drug Product**
- **High volume**
- **Low volume**

**Scale**
- **Distributed**

### Enabling Technologies & Capabilities – The How

**Process Technologies**
- ↓ 90% CoGs
- ↓ 90% process investment
  - Process Intensification
  - Combination of unit operations
  - Continuous processing technologies coupled with advanced process control

**Inline Monitoring and Real time Release**
- ↓ 70% build time
- ↓ 75% CAPEX
  - Quality, Efficiency & Supply
  - Quick to configure & scale
  - Standard designs
  - Streamlined validation

**Modular and Mobile**
- 50% Facility Build Speed
- 50% ↓ OPEX costs from current
  - Agile, high quality, and robust biomanufacturing
  - Plug and Play
  - Open data standards
  - Interoperability

**Automated Facility**
- ↓ Cost of process development
- Time to introduce a change to an existing process ↓ to 1 Month
  - Cost of Non-Quality ↓ to 2% of operating costs
  - Efficient tech. transfer
  - Integrated knowledge
  - Quality throughout lifecycle

**Knowledge Management**
- Partnerships with quality built in
- Standard working, integration and real time Electronic Data Exchange
- Shared Planning

**Supply Partnership Management**
- Safe, innovative supply chains:
  - ↓ Cost of quality
  - ↓ Time

**Roadmap Vision**

- **July 17 BPOG Introduction**

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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

Total Facility Output (kg/yr)
Enabling Technologies & Capabilities – 6 teams mobilised to define detailed roadmaps

<table>
<thead>
<tr>
<th>Enabling Technologies &amp; Capabilities</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Technology</td>
<td>Process Intensification - Intensifying production through highly concentrated reactants and products and combining unit operations into single units</td>
</tr>
<tr>
<td></td>
<td>Continuous Processing - New separation and media technologies, coupled with advanced automation and process control</td>
</tr>
<tr>
<td>In-line Monitoring and Real-time release</td>
<td>Enhanced in-line monitoring unlocks potential for robust material characterisation, process control and assurance of product quality</td>
</tr>
<tr>
<td></td>
<td>Hardware for advanced in-line monitoring devices including indirect and multi-attribute sensors</td>
</tr>
<tr>
<td></td>
<td>Software to enable multivariate analysis, predictive models and closed feedback control loops</td>
</tr>
<tr>
<td>Modular and Mobile</td>
<td>Manufacturing systems that are quick to configure, assemble, scale and relocate, using ‘plug and play’ standard designs and standard validation approaches</td>
</tr>
<tr>
<td>Fully Automated Facility</td>
<td>Plug and play for fast response to capacity demands, with minimal staff, time to change over, and regulatory observations, that delivers products of lowest cost and highest quality, from receipt of raw materials to final drug product.</td>
</tr>
<tr>
<td>Supply Partnership Management</td>
<td>Supply Partnership Management undertaken in a spirit of openness and trust to drive successful collaboration making best use of technology and integration of systems and processes</td>
</tr>
<tr>
<td>Knowledge Management</td>
<td>Integrated knowledge of product and process technology across the development, manufacturing and commercial value streams</td>
</tr>
</tbody>
</table>
Strategic cycle of Technology Roadmapping
Value continues to grow through 2017

2017 provides an opportunity to exploit a strong position and accelerate change in the industry.

- **Publish roadmap edition 1 and plan / track industry response**
  - Receive feedback and challenge from across the industry to further improve the roadmap document
  - Work closely with supply partners, academia and regional hubs for rapid demonstration of innovations and development of new technologies to address fundamental challenges
  - Influence fundamental R&D that is required to deliver vision
  - Together use combined knowledge and experience to address the regulatory challenges identified

- **Roadmap edition 2**
  - Continue to build a valuable coalition for change in the industry
  - Leverage the roadmapping structure and capability into adjacent squares and deeper into critical areas
Two year cycle of roadmapping

1st Edition
- Articles
- BPI Conference Oct’16
- CASSS
- Publish May’17 BIO

TR04 Finalising the roadmap Sep’16
TR05 Plan collaborative initiatives & progress tracking May’17
TR06 2nd Edition mobilisation Oct’17
TR07 Industry Progress tracking + 2nd Edition Apr’18
TR08 2nd Edition Finalisation Oct’18

Input to planning
Feed-back
Roadmap team F2Fs - tbc

Existing Roadmap teams

2nd Edition
- Learning Review Feb ’17
- Basic roadmap
- Input to 2nd Edition
- Detailed roadmap
- Finalise roadmap

New Roadmap teams

Communications
- Engagement & feedback
- Regulatory interaction

Articles & conferences
BPI Conf Oct’17
CASSS
BIO
BPI Conference Oct’18

2016
2017
2018

Articles
Conference
Oct’16

2019

Basic roadmap
Detailed roadmap
Finalise roadmap

BPI Conference
Oct’16
BPI Conf
Oct’17
CASSS
Articles & conferences
BIO
BPI Conference Oct’18
Options for 2017 roadmapping – setting the high level context

**Process development**

- Do we step back to the development process, such is the influence this has on bio-manufacturing?

**Drug substance**

- The primary focus in roadmap edition 1 is DS – do we need to go deeper on certain technologies/topics from the roadmap?

**Drug product**

- DP is covered at a high level in the roadmap edition 1 – should we incorporate detailed DP input to edition 2?

**Other considerations:**

- 20 year time horizon and disruptive technologies
- Other product classes
- Other expression systems
External communications completed during 2016
- To prepare the industry for action

- FDA meeting
  - Office of Biotechnology Products, Silver Springs: TRM training seminar, 26 Sept 2016
    - Beth Junker, Charles Heffernan, Bert Frohlich
    - Presentation is [here](#)

- Press releases
  - March 2016 – Press release is [here](#)
  - May 2016 – Press release is [here](#)

- Conference presentations
  - Biomanufacturing Summit 2016, U Mass, 23rd May 2016
    - Rajesh Beri & Thomas Ryll – Presentation is [here](#)
    - Bert Frohlich & Thomas Ryll – Presentation is [here](#)
  - ISPE Facility of the Future, Bethesda, 14-15 Nov 2016
    - Philip McDuff – Presentation is [here](#)

- Articles published
  - BioProcess International, article 1 of 3, Dec 2016 – Article [here](#)

- Public website prepared
  - Website prepared, will further develop during 2017 – Website [here](#)
Code of Conduct – BPOG Information Sharing

Introduction
The BioPhorum Operations Group (BPOG) is a cross industry collaboration with the aim of sharing best practice in the area of Operational Excellence.
Participation in BPOG is restricted to authorized member company representatives as described in the Principles of Membership Agreement.
Whilst sharing information is central to the process of this collaboration it is important to understand what information is appropriate to share. Our companies have a great deal of confidential information and intellectual property that should not be shared within the BPOG. This document seeks to guide the reader so that the individuals and companies involved follow the correct code of conduct and problems are avoided.
It is the clear and stated intention of BPOG that the Group and its activities are conducted at all times in full compliance with relevant competition/ant-trust rules.

Responsibilities
It is the responsibility of every person who participates in a BPOG event or sharing activity to make sure they are aware of what information is appropriate to share. Furthermore, all participants are responsible for vetting any information to be shared via their company’s public disclosure review processes and that all information shared is free of any “Confidential” stamps or markings.
The key contacts (L2) for each member company should ensure confidentiality and IP issues are highlighted to their colleagues and that all applicable company policies regarding external collaboration and public disclosure are adhered to.
The BPOG facilitators are responsible for reminding all participants of their obligations with respect to information sharing.

Sharing information
The following list is representative of the types of disclosures commonly allowed by corporate policies. BPOG participants should review their company policies to ensure they are in compliance prior to any disclosures.

Information in the following areas is typically allowed;
▪ Operational excellence best practice models
▪ Management approaches and philosophies
▪ Ways of working which are about organizing and planning
▪ Generic operating procedures that are not product or process specific
▪ Information which is already in the public domain
▪ Information provided by suppliers which would ordinarily be shared with any customer
▪ Generic engineering or technical information relating to process equipment which is not product or process specific
▪ General learning and ‘context’ conclusions from QA and Regulatory activity

Information from the following areas is typically prohibited by corporate policies;
▪ Product related information
▪ Product related process data which constitutes intellectual property
▪ Specific audit or regulatory inspection findings or observations
▪ Analytical methods that are product specific
▪ Specific cost numbers where a market advantage may result or a supplier might be disadvantaged
▪ Information that is marked as confidential by the member company or a supplier
▪ Price information of any type
▪ Proprietary information including intellectual property and patented processes and equipment

BPOG event participants should direct all questions regarding information disclosure to their L2 BPOG representatives or corporate Legal departments.
Supplier Interactions Policy

- The BioPhorum Operations Group (‘BPOG’) facilitates a cross industry collaboration process for Biopharmaceutical developers and manufacturers with the aim of accelerating the rate at which the biopharma industry attains a mature and lean state benefitting patients and stakeholders alike. Collaboration modes include best practice sharing, benchmarking, joint-solution development to common challenges, definition of standards requirements and formation of collective perspectives to mutual opportunities and regulatory guidelines.

- Biopharmaceutical developers and manufacturers recognise the legally enforceable duties they have including the responsibility to control the quality of materials from their suppliers. From time to time BPOG-facilitated collaboration requires, and benefits from, supplier interaction.

- Suppliers are providers of supply chain materials such as chemicals, glass, components, excipients, and media. They are also providers of process equipment such as single use systems, engineering parts and consumables. BPOG-facilitated supplier interactions may involve: harmonising manufacturer requirements and communicating these to suppliers; seeking feedback on proposed standards; gaining opinions and ideas related to business process improvement; use of problem solving tools; and gaining support for new ways of working.

- The ultimate goal of the BPOG collaboration is to strengthen competition, assure product quality and protect patient supply.

- The purpose of this document is to set out the principles and policies that BPOG follows to ensure that BPOG-facilitated supplier interactions are conducted in the correct and appropriate way to meet all legal and business compliance requirements.

Underlying Principles and Policies

Competition Laws
- All supplier interactions will comply with anti trust and competition laws and have regard to BPOG’s anti-trust compliance statement

Member responsibilities
- Individual biopharma companies are responsible for defining their requirements of suppliers.

Innovation and commercial interests
- All supplier interactions will recognise and respect the need for suppliers to innovate and pursue their own commercial interests.

Intellectual Property
- All supplier interactions will respect suppliers’ intellectual property rights.

Confidentiality / Non Disclosure
- All supplier interactions will take into account, respect and encourage compliance with confidentiality and non-disclosure agreements.

Equal Treatment
- All suppliers will be treated equally

Communication
- These principles, policies and procedures will be communicated to BPOG members and suppliers whenever supplier interactions are planned or are taking place.

BPOG responsibilities
- It is the responsibility of BPOG Directors to ensure that these principles and policies are upheld and procedures are in place to support them.
- BPOG will educate and train its staff so they understand and follow these principles and policies and are able to communicate them when needed.
- BPOG documentation will reference or directly include relevant parts of the Supplier Interaction Policy.
- BPOG will establish and maintain records to demonstrate compliance with these principles and policies.