BioPhorum

Mapping Future Technology Needs and Prioritization of Critical Quality Attributes for Enabling In-Line Monitoring and Real Time Release Testing

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WCBP 2019

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Disclaimer

The Information presented in this presentation was compiled by the BioPhorum member companies and represents a consensus view of its members on the current state of the technology roadmap for ILM/RTR.

The consensus view does not represent fully the internal policies of the contributing member companies.

What is BioPhorum?

Unique **global** collaboration

Powerful vehicle for **change**

Industry leaders and experts working in concert

Delivers results by pooling knowledge, practices and ideas

7 Phorums

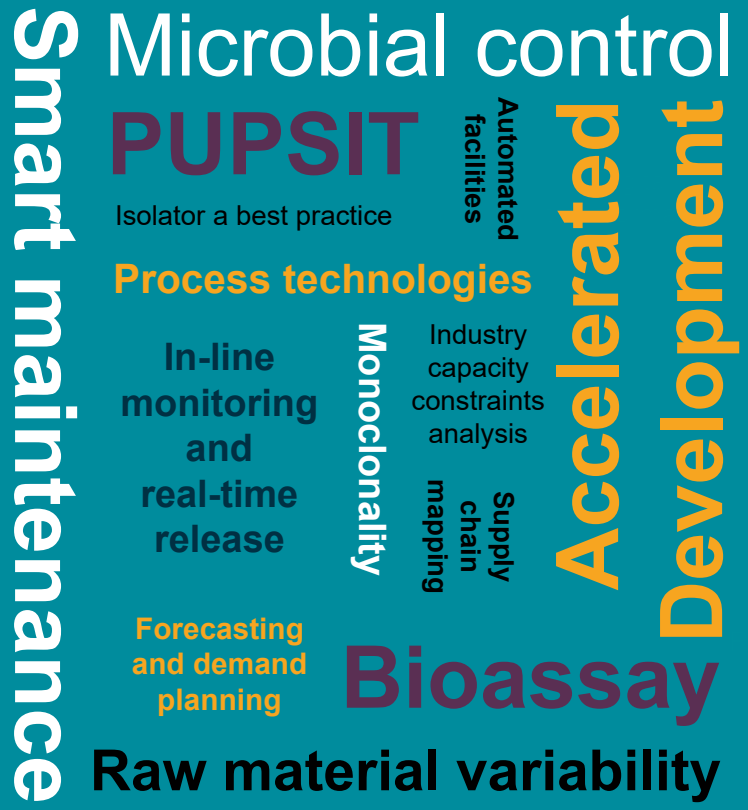
>50 industry changing initiatives

53+ member companies

2060+ active participants

7 thriving communities

1 Phorum for change



BioPhorum mission

To create an environment where the global biopharmaceutical industry can collaborate and accelerate their rate of progress, for the benefit of all

We do this by

Bringing leaders together to create future visions that focus the industry's energy on the key emerging opportunities

Mobilizing communities of the top experts around these opportunities, up and down the biopharma value chain

Creating partnerships that enable change and provide the quickest route to implementation and results

Replacing isolation with collaboration so that the industry shares, learns and builds the best solutions together

Making the journey *better, faster, cheaper*

Membership includes most of the top biopharma manufacturers

...and many of the key industry supply partners

BioPhorum First Edition Biomanufacturing Technology Roadmap

The 1st Edition Technology Roadmap (published July 2017) is freely available on the BioPhorum website http://www.biophorum.com/executive-summary/

- The result of two years effort by 31 member companies and driven by the Technology Roadmapping Phorum's Steering Committee and its six enabling technologies roadmap teams
- 8 documents covering a 10 year outlook with >400 pages of content

>5723 downloads (Dec, 2018)

Current Trends in Biopharm Development and Manufacturing

- Biopharm development and manufacturing moves towards more lean state
  - To increase current efficiency and throughput
  - To reduce waste, lead-time and compliance risk

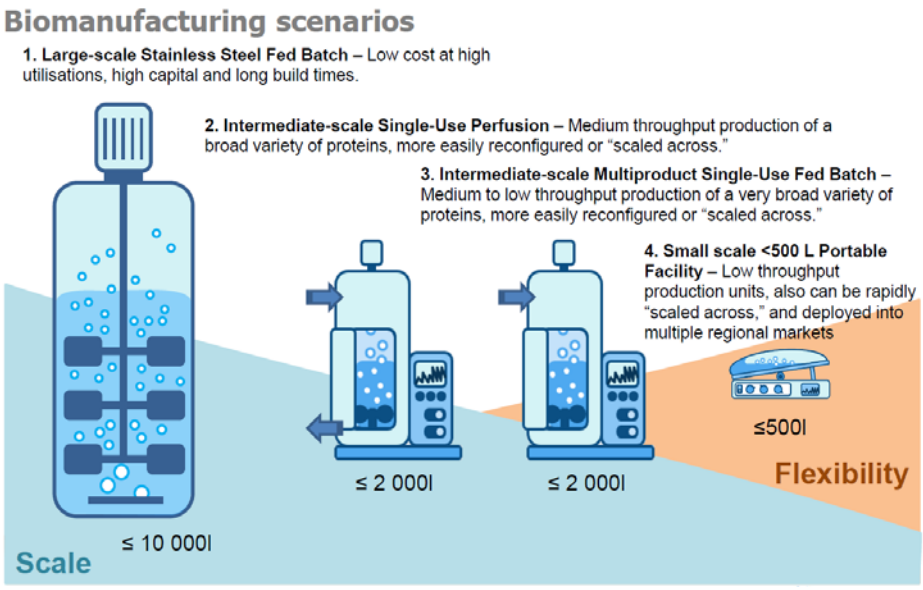
- Technology roadmaps are focused to
  - Increase product and process understanding
  - Reduce time needed to introduce process changes
  - Reduce time required to manufacture and release product
  - Reduce total cost of supply
  - Reduce cost of upfront investment in manufacturing
  - Reduce cost of development

BioPhorum First Edition Biomanufacturing Technology Roadmap

Technology Roadmap member companies work with industry stakeholders to further develop roadmap content and agree actions to finalise reports

Workstreams

- *In-line Monitoring and Real-Time Release*
- *(ILM/RTR)*
- *Automated Facility*
- *Modular and Mobile Facility*
- *Supply Partnership Management*
- *Knowledge Management*
- *Process Technologies*



Overall Metrics*

Driver	Metric	5 yr Target	10 yr Target
Cost	Total cost to supply	$50/gm (mAbs)	$10/gm (mAbs)
	Cost of upfront investment in manufacturing	$100M DS facility $50M DP facility	$50m DS facility $25M DP facility
	Cost of development	25%	75%
Speed	Time to make product (End to end speed)	2 months	1 month
	Time to release product (End to end speed)	2 weeks	1 day
	Time to produce first GMP material for the clinic	12 months	8 months
	Speed to market	5 years	3 years
	Time to introduce a change to an existing process	2 months	1 month
	Facility build speed	2 years	1 year
Quality	Cost of Non-Quality	10% of operating costs	2% of operating costs

, Not a comprehensive list

First Edition Technology Roadmap Vision

Market Trends & Business Drivers – *The Why*

Cost pressure
- Payer pressure
- Biosimilars
- Development

Uncertainty
- Regulatory approvals
- Demand variability
- Competition

Market Growth
- Emerging markets
- Global reach
- In region manufacture

New Product Classes
- Non-mAbs, ADCs
- Gene therapy
- Cell therapy

Cost	Flexibility	Speed	Quality
-90% manufacturing cost -90% CAPEX	-90% changeover Demand response	-70% build time -80% lead time	10x robustness -90% cost of quality

Biomanufacturing scenarios – *The What* (Facility types)

5. Small-scale <50L for Personalized Medicine

4. Small-scale <500L Portable Facility

3. Intermediate-scale Multi-product Single-use Fed Batch

Drug Product Low volume

2. Intermediate-scale Single-use Perfusion

Drug Product High volume

1. Large-scale Stainless Steel Fed Batch

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
- ↓ Product Release 1-2 day
+ ↑ Quality, Efficiency & Supply

- Enhanced In-Line Monitoring
- Indirect and Multivariate Sensors
- Multivariate Analysis and Predictive Modeling

Modular and Mobile
- 70%↓ build time
- 75% ↓ CAPEX

- Quick to configure & scale
- Standard designs
- Streamlined validation

Automated Facility
– 50%↓ Facility Build Speed
– 50% ↓ OPEX costs from current

- Agile, high quality, and robust biomanufacturing
- Plug and Play
- Open data standards
- Interoperability

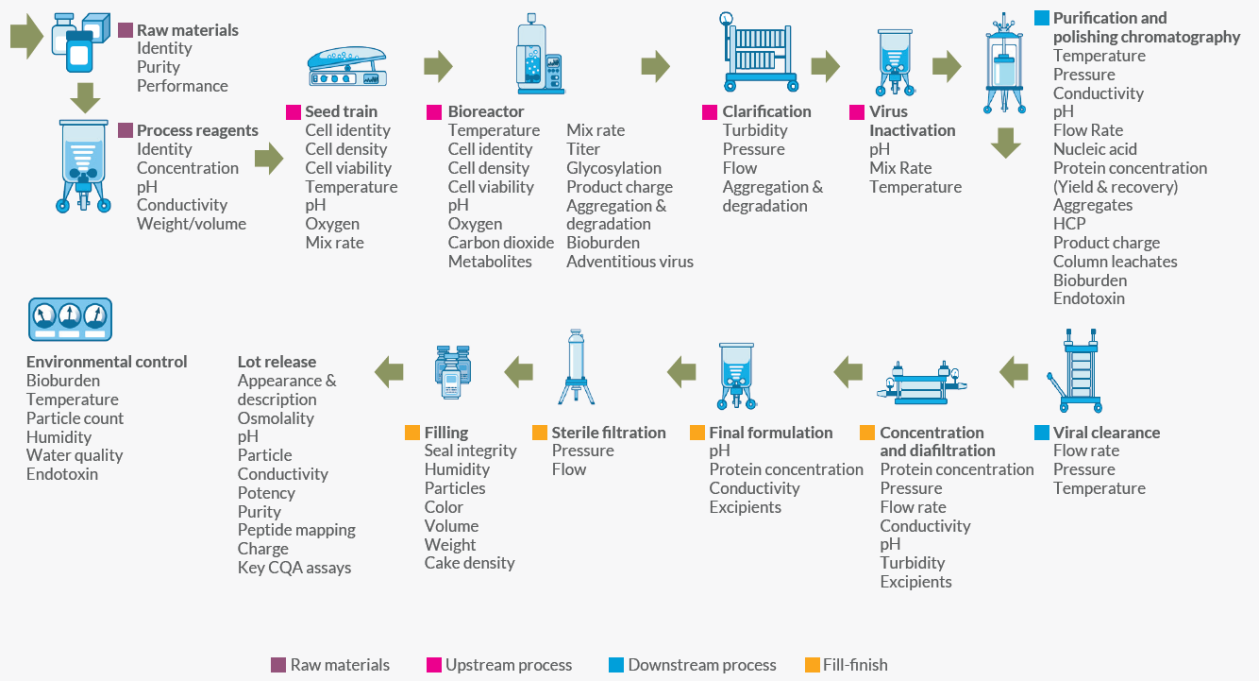
Knowledge Management
– ↓ Cost of process development
– Time to introduce a change to an existing process ↓ to 1 Month
– Cost of Non-Quality ↓ to 2% of operating costs
- Efficient tech. transfer
- Integrated knowledge
- Quality throughout lifecycle

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

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

ILM/RTR: Drivers

- Transition analytics from off-line testing to in-line testing
- Reduce complexity through use of multi-attribute and non-invasive techniques



- Future Needs, Challenges and Potential Solutions
  - Utility & Environmental Monitoring Systems
  - Raw Material Characterization
  - In-process Measurements (USP & DSP)
  - End-product Testing and Real-time Release
  - Drug Product Considerations
  - Advance Process Control & Predictive Analytics
  - Mature IT/Automation

Utility & Environmental Monitoring Systems
Opportunities for New Technologies

		Current	2019	2022	2026	Scenario(s)
(Metric 1)	Measurements performed in-line	7–28 days	7–28 days	7–28 days	1 day	
(Metric 2)	Measurements performed at-line	7 days	7 days	7 days	1 day	
Need	In-line monitoring of appearance and endotoxin in purified water and water for injection	<25%	50%	75%	90%	1, 2 and 3
Challenge	Multiple sample points. Significant resource burden in quality control laboratories	X	X			
Potential solution	Novel/innovative technologies					
Need	In-line bioburden monitoring of air	<25%	50%	75%	90%	All
Challenge	Multiple sample points. Significant resource burden in quality control laboratories	X ·	X			
Potential solution	Novel/innovative technologies (e.g. fluorescence-based)					
Need	Standardized protocols for data exchange and integration of in-line probes with control system	20%	<40%	<85%	90%	All
Challenge	Software incompatibility, non-standardized file formats and metadata associations	X	X	X		
Potential solution	Aligned framework and standardization among vendors					

Potential solutions manufacturing readiness level

Research | Development | Production

End-product Testing & Real-time Release
Opportunities for New Technologies

Attribute	Current technologies	Current turnaround time	Potential technologies	Target turnaround time	Target sensitivity or range	Target product pool	Testing potential
Microbiological, viral safety							
Bioburden	Pour-plate method	Longer	**Fluorescence-based plate assays. Respirometry, microflow imaging, flow cytometry**	2 days	1 CFU/10mL	Multiple	Off-line
Mycoplasma	Cultivation assay	Longest	**qPCR**	2 days	Negative	Cell culture fluid	Off-line
In-vitro (adventitious) virus	Cultivation assay	Longest	**qPCR**	2 days	Negative	Cell culture fluid	Off-line
MMV	qPCR	Longer	**qPCR (no change)**	2 days	Negative	Cell culture fluid	Off-line
Endotoxin	LAL	Short	**Mass spectrometry**	1 day	0.01 EU/mL	Drug substance and drug product	Off-line
General tests							
Appearance	Visual	Short	(no change)	–	–	Drug substance and drug product	Off-line
Color	Visual	Short	**Color: spectroscopic methods**	–	as in Ph. Eur.	Drug substance and drug product	In-line monitoring
Clarity	Turbidity (manual sampling)	Short	**Rapid/automated turbidity**	–	as in Ph. Eur.	Drug substance and drug product	In-line monitoring
pH	pH meter	Short	(no change)	–	–	Drug substance and drug product	In-line monitoring
Protein concentration	UV spectroscopy	Short	**In-line using slope spectroscopy, Raman**	–	0.5–250 mg/mL	Drug substance and drug product	In-line monitoring

Definitions: Time: Short <1 day, Longer 2–7 days, Longest >7 days

High priority for new technology development | **Research** | **In development** | **Available now**

End-product Testing & Real-time Release, cont.
Opportunities for New Technologies

Attribute	Current technologies	Current turnaround time	Potential technologies	Target turnaround time	Target sensitivity or range	Target product pool	Testing potential
Purity/characteristic							
Charge heterogeneity	Ion exchange chromatography, ICIEF	Short	MAM	2 hours	% acidic, % main, % basic	Drug substance	On-line
Aggregates	Size-exclusion chromatography	Short	Light scattering, Raman	2 hours	% HMW, % dimer, % main, % LMW	Drug substance and drug product	In-line monitoring
N-glycosylation heterogeneity	PNGase F release with normal phase chromatography	Longer	MAM		To be determined as in under development	First purification pool	On-line
Covalent structure, modifications	Peptide map/RP-HPLC	Longer	UHPLC, MAM	1 day	% modified	Drug substance	On-line
Size/integrity	CE	Longer	'Lab on a chip', mass spectrometry	4 hours	% reduced, % fragments, % aggregates	Drug substance	At-Line
Process-related impurities: HCPs	ELISA	Longer	Mass spectrometry for HCPs, rapid homogeneous assays	1 day	1 ng/mg	Drug substance	At-Line
Process-related impurity: DNA	ELISA	Longer	Mass spectrometry for HCPs, rapid homogeneous assays	1 day	<10 ng/dose	Drug substance	At-Line

Definitions: Time: Short <1 day, Longer 2–7 days, Longest >7 days

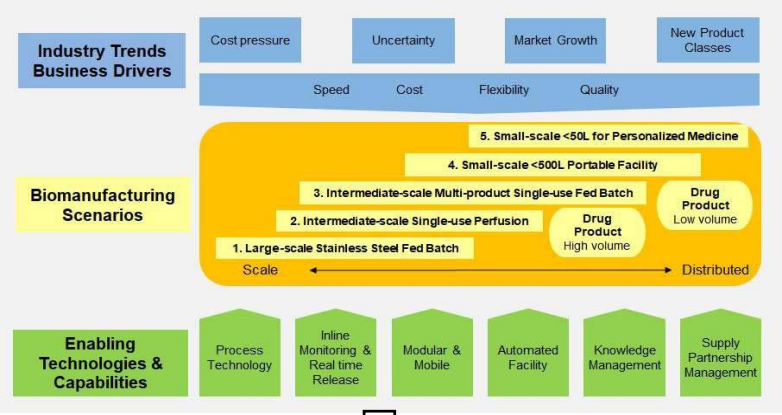
High priority for new technology development | Research | In development | Available now

Mature IT/Automation

- **Driver:** An increase in in-line monitoring and reduction of long lead-time release assays will create pressure to reduce the duration of quality review for batch release.

- Implementation of Electronic Batch Record (EBR) control system can provide continuous checks for completion of all required in-process and batch release criteria

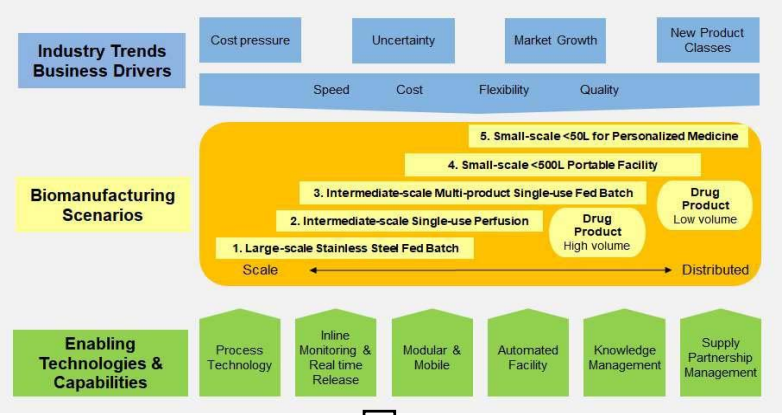
Implementation Projects



Process Technology	ILM/RTR	Modular & Mobile	Automated Facility	Knowledge Management	Supply Partnership Management
Reliable and cost effective cell removal options for higher density processes in biomanufacturing	Rapid release testing through inline monitoring	Standard Facility Design	Data analysis to evolve from big data to smart data	Managing Product and Process Knowledge across the Lifecycle	
Buffer Preparation	Rapid methods for adventitious detection & sterility assurance		Robotic technologies in biomanufacturing		
Continuous Downstream Processing			Plug & Play		

- Building upon the First Edition, 10 high value technology development projects have been mobilized to accelerate industry progress
- The 10 projects leverage pooled effort, drive standardization, provide scale for supply partners and focus regional

Implementation Projects



Process Technology

- Reliable and cost effective cell removal options for higher density processes in biomanufacturing
- Buffer Preparation
- Continuous Downstream Processing

ILM/RTR

- **Rapid release testing through inline monitoring**
- Rapid methods for adventitious detection & sterility assurance

Modular & Mobile

- Standard Facility Design

Automated Facility

- Data analysis to evolve from big data to smart data
- Robotic technologies in biomanufacturing
- Plug & Play

Knowledge Management

- Managing Product and Process Knowledge across the Lifecycle

Supply Partnership Management

In Line Monitoring and Real-time Release Project 1/7: "Rapid release testing through inline monitoring"

12 Biomanufacturers
8 Supply Partners
1 Innovation Hub

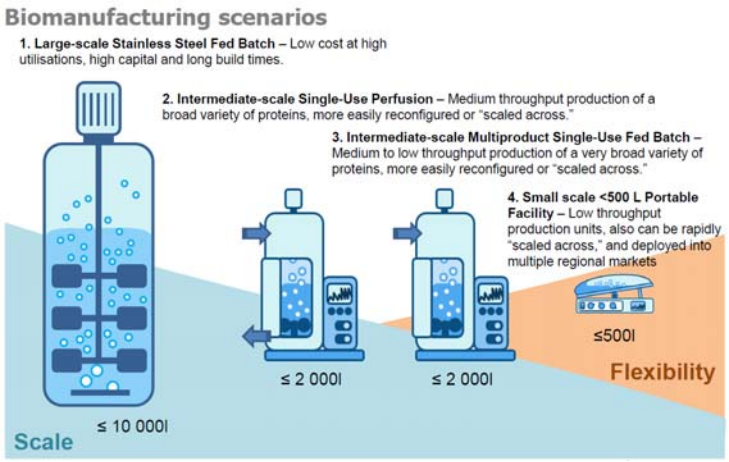
- **Project Goal & Vision:**
  - Produce a prioritized list of CQAs and in-process controls (Upstream to Drug Substance) in order to inform the industry of the CQAs that should be targeted for a transition to in-line, on-line or at-line monitoring

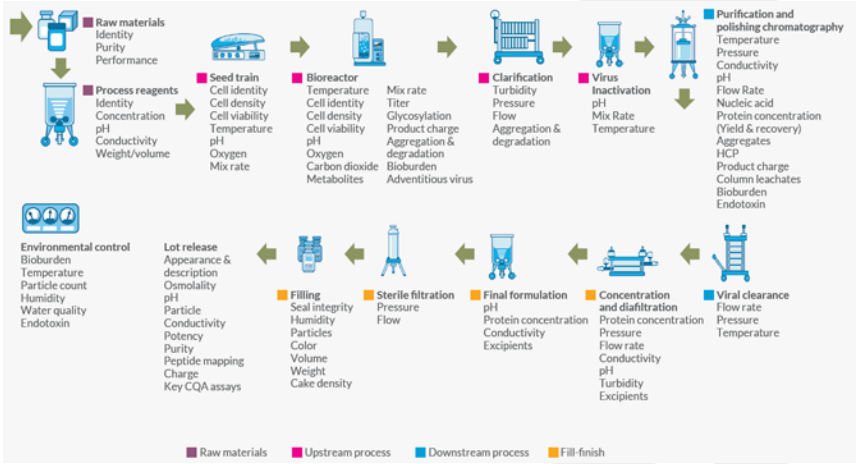
- **Deliverables:**
  - List of attributes with the highest impact on business drivers (quality, cost and speed)
  - User Requirement Specifications (URS) for the selected measurements
  - Business case tool kit
  - White paper with URS to guide the development of new in-line, at-line and on-line technologies, focused on highest impact CQAs and IPCs

Project Workflow

Scope → Step Attribute Matrix → Current & Desired state → Ranking → URS

Biomanufacturing Scenarios and mAb Process from Technology Roadmap





In scope:

- Batch mode including Fedbatch
  - Continuous to be factored in later

Out of scope:

- Specific single use aspects not included

Considerations for RTRT:

- Inline monitoring for better process control
  - Incremental vs paradigm shift
- RTRT includes both release of process intermediates and final drug substance for further processing

Step Attribute Matrix (SAM) Components

Steps

- Seed scale up
- Production bioreactor
- Harvest
- Protein A capture
- Viral inactivation
- CEX B/E polishing
- AEX FT polishing
- Virus filtration
- Formulation
- Bulk-DS Filtration / Fill

Quality attributes

- Aggregation
- Deamidation
- Oxidation
- Fragmentation
- Glycosylation profile
- Glycation
- Charge Profile
- Non-glycosylated heavy chain
- HCP Conc
- DNA Conc
- Protein A Conc

Cell culture parameters

- Antifoam Concentration
- Yeast Proteins
- B-D Glucan
- Methotrexate
- Amino Acids
- Metals (Cu, Mn etc.)
- Insulin
- MSX
- Cell Viability
- Viable Cell Density
- Glucose
- Other nutrients, metabolites, & CO2
- Glutamate
- Glutamine
- Ammonia
- Lactate
- Galactose
- IgG - also titer????
- CO2
- pH, DO (bioreactor)
- Exit Gas Composition
- BR Osmolality

Downstream control

- Turbidity
- pH Conductivity
- UV 280nm
- Pressure
- Flow

Safety and other

- Virus Safety
- Microbial Safety
- Endotoxin
- Appearance (color)
- Visible and Sub-visible Particles
- Osmolality
- Bulk-DS Concentration
- Potency/Binding: Antigen binding, Fc functional testing; FcgR, C1q and FcRn binding.
- Cell-based potency assay
- Density
- Volume / Mass / Level
- Product Concentration
- Product Mass (Volume * Conc)

Step Attribute Matrix (SAM) Components, cont.

UNIT OPERATION															
Attribute/Process Parameter Type	Current State			Desired State											
	Testing (At-, On-, In-line)	Time (test to result)	Measurement Type	Testing (At-, On-, In-line)	Time (test to result)	Measurement Type	Desired Frequency (Time interval between samples)	Quality (improves) Y/N	Critical for RTR (Y/N)	Need for Change (L, M, H)	Quality (score) "Q"	Critical for RTR (score) "R"	Need for Change (score) "C"	Weighted Score Q*R*C	

Testing Type

- Off-line
- At-line
- On-line
- In-line

Measurement Type

- In-process test
- In-process control
- Release testing
- Release and stability
- CPV monitoring
- Process Control
  - (feed-forward/backward)

Scoring

- **Improves quality? (Q: weights 1/2)**
  - Reduces variability or improves product quality
- **Critical for RTRT? (R: 1/2)**
  - Release of final drug substance and/or process intermediates for further processing
- **Need for change (C: 1/3/9)**
  - How problematic are current methods?
  - How badly do we need to change these?

Ranking principles

- Weighted ranking by step/attribute description (Q*R*C)
- SME ranking and judgements

Preliminary List of Top Ranking Attributes for RTR

1. **Glucose** – Production Bioreactor
2. **Aggregation** – CEX Bind & Elute
3. **HCP** – Anion Exchange Flow Through
4. **Cell Viability** – Seed Scale Up and Production Bioreactor
5. **Viable Cell Density** – Seed Scale Up and Production Bioreactor
6. **Charge Profile** – Production Bioreactor, CEX Bind & Elute
7. **Glycosylation Profile** – Production Bioreactor
8. **Amino Acids –** Production Bioreactor
9. **Titer/ Product Concentration** – Protein A
10. **DNA** – Anion Exchange Flow Through

- **Note:** Does not include microbial or virus safety – prioritized focus of separate workstream.

Next Steps

- Industry feedback
- Business case tool development
    - *Total Potential Annual Benefits*
    - *Materials Test Costs Off-line versus In-line*
    - *Sample Collection and Management Costs*
    - *Test Data Reporting Costs*
    - *Better Yield (Tighter control)*
    - *Reduce Investigations Related to Manual Sampling and Testing*
    - *Reduced Inventory Carrying Cost*
    - *Lab Equipment Maintenance and Calibration Costs*
    - *Decrease production material losses*
    - *Reduced Discards (average/year)*
- Develop URS for high priority cases
- Publish White Paper in Q2 2019
- Expand the scope
    - Continous manufacturing
    - Other Biologics modalities

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The following people have generously contributed their time and energy to this project

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BioPhorum Bela Green

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.

Supplier interactions policy v3.0

The BioPhorum Operations Group 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 recognize the legally enforceable duties they have including the responsibility to control the quality of materials from their suppliers. From time to time BioPhorum-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. BioPhorum-facilitated supplier interactions may involve: harmonizing 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 BioPhorum 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 BioPhorum follows to ensure that BioPhorum - 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 BioPhorum'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 BioPhorum members and suppliers whenever supplier interactions are planned or are taking place.

BioPhorum responsibilities

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

Code of Conduct – BioPhorum information sharing v2.0

Introduction

The BioPhorum Operations Group is a cross industry collaboration with the aim of sharing best practice in the area of Operational Excellence.

Participation in BioPhorum is restricted to authorized member company representatives as described in the Principles of Membership Agreement.

While 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 BioPhorum .

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 BioPhorum that the Group and its activities are conducted at all times in full compliance with relevant completion/anti-trust rules.

Responsibilities

It is the responsibility of every person who participates in a BioPhorum 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 contact (L2) for each member company should ensure confidentiality and that IP issues are highlighted to their colleagues and all applicable company policies regarding external collaboration and public disclosure are adhered to.

The BioPhorum 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. BioPhorum 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
- Organizing and planning ways of working
- Non-product or process specific generic operating procedures
- Information in the public domain
- Information provided by suppliers which would ordinarily be shared with customers
- Non-product or process specific generic engineering or technical information relating to process equipment
- 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
- Product specific analytical methods
- 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

BioPhorum event participants should direct all questions regarding information disclosure to their L2 BioPhorum representatives or corporate legal departments.