



BioPhorum

Industry Proposal For The Use Of QBD And ICH Q12 Principles To Enable Second Sourcing Of Raw Materials

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Collaborate
Accelerate™**

Agenda

- Background
- Industry Status Quo
- The BioPhorum REGULATORY Approach
- Case study: Virus-retention filters
- Concluding remarks

What is BioPhorum?



9

Phorums

>75

industry changing initiatives

120+

member companies

6000+

active participants

1

voice for the
biomanufacturing
industry

Unique **global** collaboration

Powerful vehicle for **change**

Industry leaders and experts
working in concert

Delivers results by pooling
knowledge, practices and ideas

BioPhorum REGULATORY



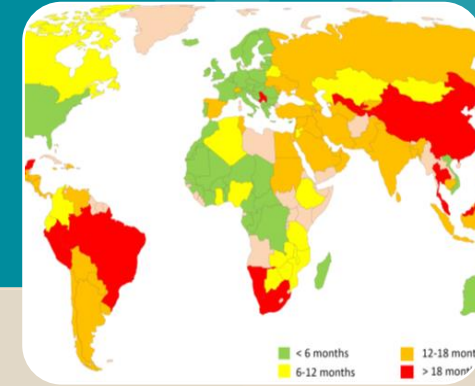
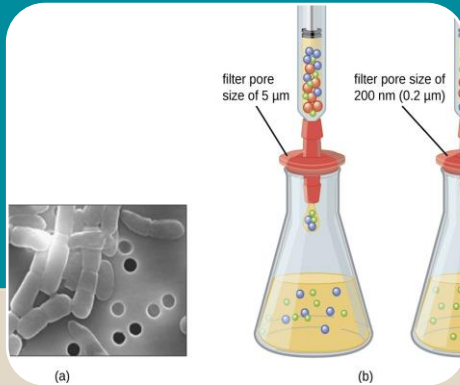
A team of **senior regulatory experts** in the field of CMC biopharma:

- **48 organizations**
- **93 team members**

Represents over 90% of the biomanufacturing industry and their suppliers

One role: *Support change and innovation in the biomanufacturing industry from a regulatory point of view*

Why Are We Discussing Registration Approaches For Raw Materials?



During pandemic product supply was constrained due to raw materials shortage

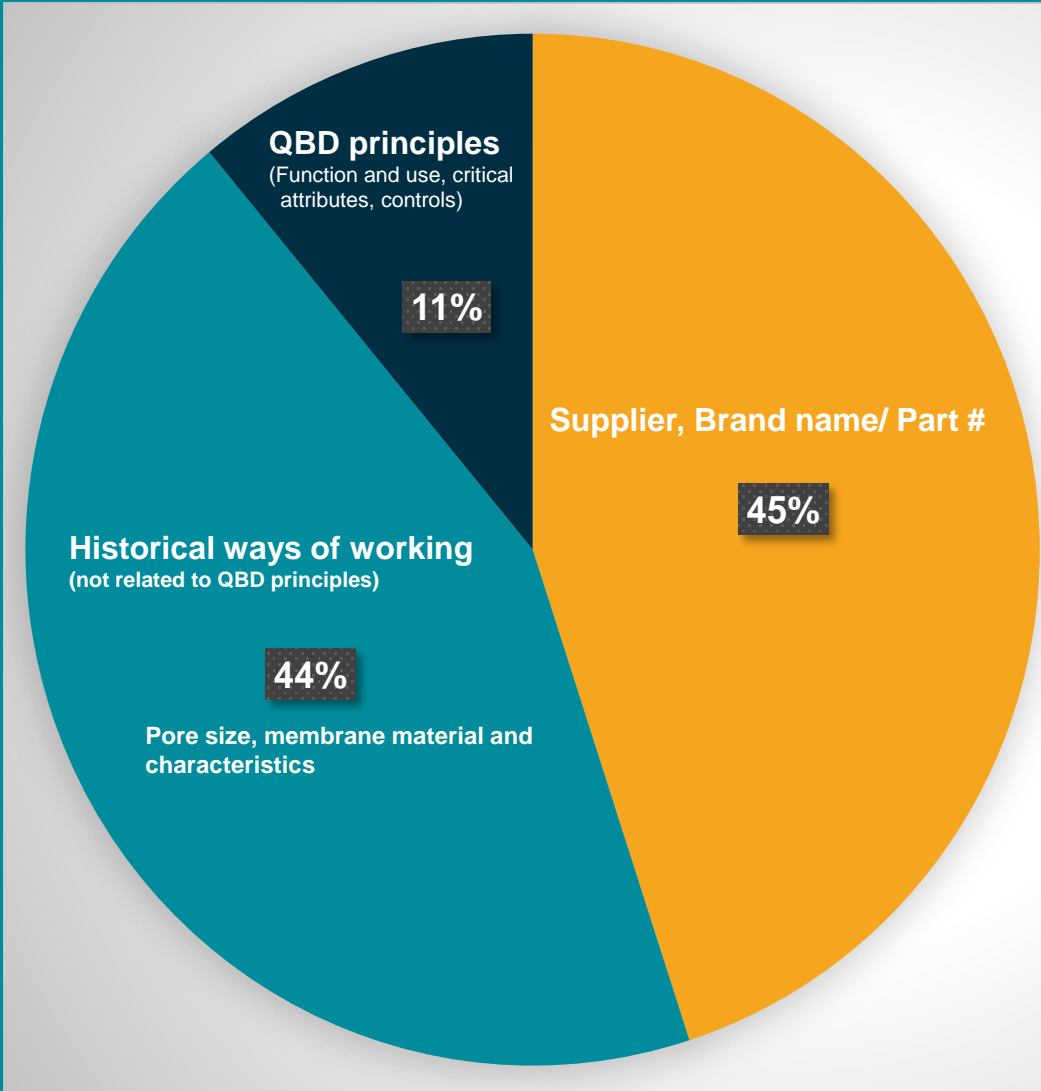
Limited flexibility in supply of process components and materials. E.g: cell culture media, purification matrixes, viral filters etc.

Variability in description of non compendial product details in regulatory documents (E.g. : brand name, supplier, model#, part#, filter characteristics etc.) and diversity in global regulatory expectations.

A change in source could impact the registered details. Might require filing of a variation which could take several years for global approval.

Industry Survey Indicates Diversity in Raw Material Registration Practices

Virus Retentive Filter



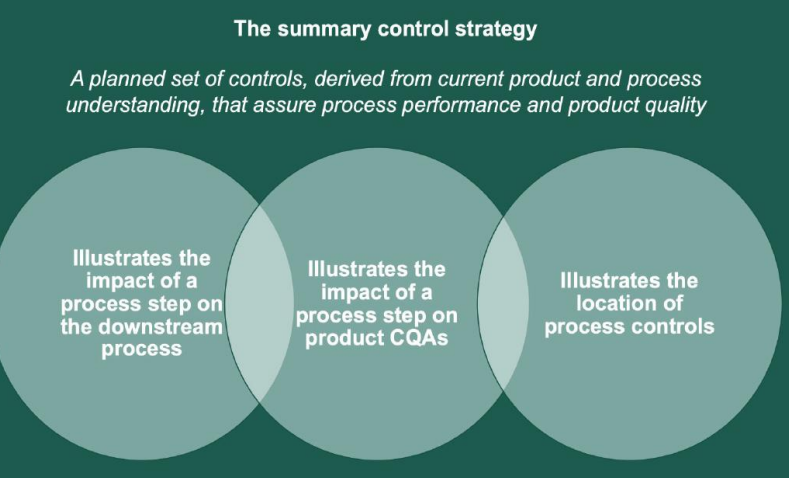
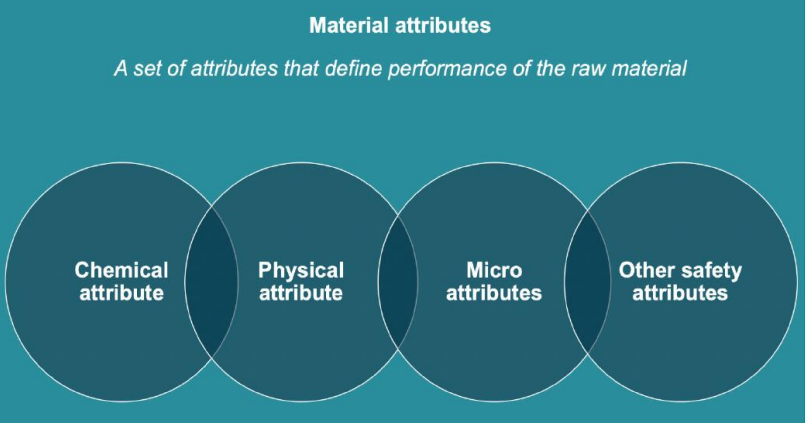
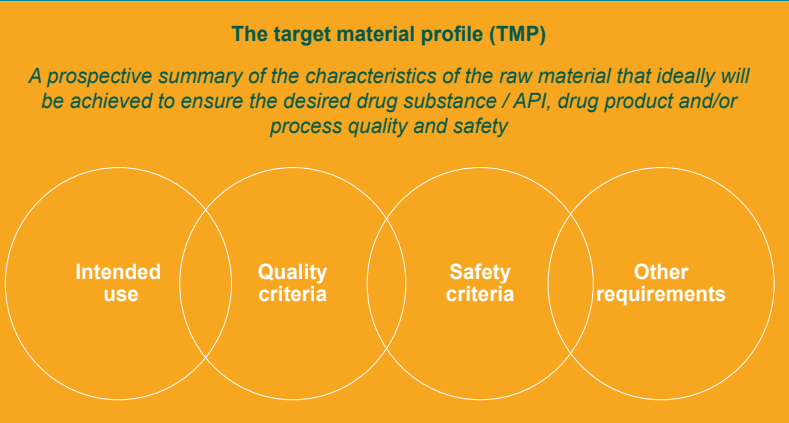
- Raw materials primarily registered using non QBD principles
- Limits the ability to introduce alternate supplier sources as,
 - *Tight controls for materials do not support demonstration of equivalency*
 - *Global regulatory approvals can be prolonged*
- Information in regulatory dossier might not be reflective of the understanding of raw material impact on product quality
- Team proposes a “Scientific Risk-Based Approach” for raw material control and registration practices leveraging Quality by Design (QBD) and/ or ICH Q12 principles

This approach offers strategy flexibility, agility and resource alternatives while enhancing understanding of impact to product quality

A Systematic And Mature Quality Approach Facilitating Alternative Raw Material Sourcing

Proposal Is Based On Fundamental Characterization Of Inputs And Output To A Manufacturing Process

A 4-Step Process To Identify Critical Material Attributes (CMA)



Definition of the CMAs and controls

Review of impact of Material Attributes on TMP and/or Control strategy helps determine impact of material on process step performance and product quality

QBD

- Registration of materials based on CMA and function
- Utilize knowledge and understanding of raw material impact on process and product quality
 - Evaluate the impact by scoring

ICH Q12

- Define CMA as established conditions
- Secure health agency concurrence on approach for management of future change and the acceptability criteria
- Allows use of PACMP

Benefits

- Increased flexibility of supply and continuity
- Improved process robustness
- Enhanced quality of regulatory submissions
- Regulatory filing relief (PQS or a reduced filing category)

I want coke...



CMA



More Options

Actually, what I want is a fizzy brown drink with a mixed taste of sugar, vanilla and caramel (these are the important attributes to me)



Proposed Raw Material Registration Strategy For Regulatory Filings

- Describe raw materials generically
- Process-specific details can be included as non-binding information (PPs like volume and flow)
- Include CMAs and controls,
 - With process controls critical to product quality (CQAs, CPPs) and manufacturability controls for consistency (PPs)
 - 3.2.S.2.2 or 3.2.P.3.3 (Description of Manufacturing Process & Process Controls)
 - 3.2.S.2.4 or 3.2.P.3.4 (Control of Critical Steps & Intermediates)
 - 3.2.S.2.3 (Control of Materials)
 - 3.2.P.7 (Container Closure System)
 - During process validation/ evaluation linking controls to batch performance and can be reported in,
 - 3.2.S.2.5 or 3.2.P.3.5 (Process Validation and/or Evaluation)
 - Development studies performed to support the risk assessment and can be reported in,
 - 3.2.S.2.6 or 3.2.P.2.3 (Manufacturing Process Development)
 - 3.2.P.2.2.1 (Pharmaceutical Development – Formulation Development)
 - 3.2.P.2.4 (Pharmaceutical Development – Container Closure System)

Making second sourcing easier: Risk-based registration of complex and innovative raw materials

Example of the virus removal filter

➤ QbD approach

- Identification of viral filter CMAs & controls via 4 Step process,
 - Definition of TMP
 - Review of product summary control strategy
 - Description of material attributes
 - Identification of the CMAs required to ensure product quality and safety

Step 1: Definition of Virus Retentive Filter TMP

➤ Intended use

- Filter must remove viruses still present in the API in a robust and consistent manner
- After polishing chromatography step and prior to UF/DF formulation step

➤ Quality criteria

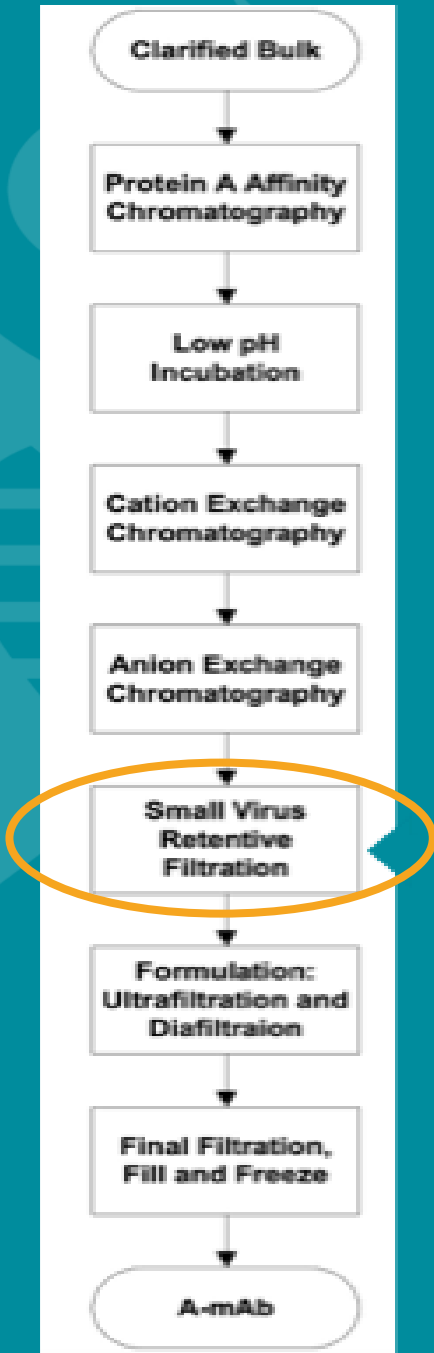
- Filter system integrity performance— pre-use (supplier check as part of release) and post use
- Allow for continuous flow and volume to be processed until defined end point is reached
- Removal of >99.99% of viruses and particle-like viruses present prior to filtration (at least with a log-factor of 4)
- Should not allow non- specific binding like protein load and availability of qualified scale down model (ICH Q5A)

➤ Safety criteria

- Extractable and leachable risk-assessment and interaction with API
- Filter compatibility with sanitization process, microbial, viral and endotoxin quality consistent with bioburden management
- Absence of biological reactivity (USP <88> Class VI / USP <87> / ISO 10993 Parts 5, 6, 10, and 11)



➤ Manufacturability criteria

- Filter must withstand process pressure
- Highly secured connections for system integrity
- Step yield



Step 2: Review Product Control Strategy for a mAB

Upstream Process	Protein A affinity chromatography	Low pH incubation	Cation exchange chromatography	Anion exchange chromatography	Small virus retentive filtration	Drug Substance CQAs
CMAs and separation steps	✓	✓	✓	✓	✓	Appearance
CMAs CPPs	✓	✓	✓	✓	✓	Identity
Protein load Elution buffer pH	✓	✓	✓	✓	✓	Protein content
Harvest time	✓	✓	Protein load Load / wash conductivity Elution pH Elution stop collect	Load pH Protein load Flow rate Load conductivity	✓	Residual host cell proteins
Buffer pH	✓	✓	✓	Load pH Protein load Flow rate Load conductivity	✓	Purity: monomers and aggregates
CPPs	✓	Buffer pH	✓	Buffer pH	✓	pH
Absence of microbial contamination	✓	✓	✓	✓	✓	Endotoxins
Absence of mycoplasma	✓	✓	✓	✓	✓	Bioburden
Low pH virus inactivation Absence of adventitious viruses	✓	✓	✓	✓	✓	Mycoplasma
Bioreactor CPPs	✓	✓	✓	✓	Operation pressure Filtration volume Post-filtration filter integrity	Absence of viruses
					✓	Glycosylation

Key
 CMA, CQA and/or CPP identified
 No critical control defined

➤ Where does the raw material fit into the process?

- Small virus retentive filtration is the final virus-removal step

➤ How does the raw material impact the overall control strategy?

- Critical contributor to viral safety of the product through control of,
 - Two CPPs, operating pressure and filtration volume
 - One CQA, post filtration filter integrity

Steps 3 and 4: Virus Retentive Filter Material Attributes and CMA Determination

Attribute	Impact	Variability	Detection
Chemical attributes			
Composition	Medium	Medium	Low
Physical attributes			
Filter dimensions	Medium	Medium	Low
Maximum load volume	Medium	Medium	Low
Maximum/ Minimum protein concentration	Medium	Medium	Low
Membrane architecture	Medium	Medium	Low
Pore size	Medium	Medium	Low
Membrane type	Low	N/A	N/A
Shedding	Low	N/A	N/A
Clearance of small viruses	High	Low	Low
Filter integrity	High	Low	Low
Microbial attributes			
Bioburden	Medium	Low	Low
Absence of viruses	Low	N/A	N/A
Absence of endotoxins	Low	N/A	N/A
Other attributes			
Dominant filtration mechanism during model virus testing	High	Medium	Low

- Systematic review of all material attributes and scoring on impact on process performance and product quality (as defined through TMP and control strategy)
 - High impact is a CMA
 - Medium impact requires control and verification
- For control strategy associated with virus retentive filters, three CMAs were identified,
 - Viral clearance achieved by filter for small viruses
 - Dominant mechanism of retention during model virus testing
 - Post filtration filter integrity
- An equivalent filter may be used that meets the acceptance criteria for the filter CMAs
 - Filter verification informed by scoring must be performed via manufacturability study, viral control strategy validation, extractable and leachable risk assessment and chemical compatibility

Traditional Versus Mature Quality Approach

Elements of the control strategy	Traditional controls	Mature quality approach – controls based on QbD principles
Virus removal	Name and part ID of the filter CPPs: filtration volume and flow/pressure	Filter CMA: log 4 reduction factor for small viruses For Name and part ID of the filter, PPs: filtration volume and flow/pressure Equivalent filters may be used and appropriate ranges of process parameters defined
Dominant mechanism	—	Filter CMA: the dominant mechanism of retention when tested for model viruses is size exclusion
Filter was able to perform its function, i.e. virus removal	CQA: filter integrity after filtration	

➤ All details in the BioPhorum paper (Free Access): <https://www.biophorum.com/download/biophorum-approach-to-the-registration-of-innovative-raw-materials-using-quality-by-design-principles/>

BioPhorum Approach Is The Start of A Transformational Journey In Registration of Raw Materials For Biologics

Registration based on knowledge and understanding of raw material impact on process performance and product quality

No cutting corners of the science

Enhanced regulatory submissions based on a Mature Approach to Quality



Aknowedgements

- The BioPhorum regulatory team
- The BioPhorum technical experts in the field of viral filtration (end users and suppliers)

For further discussions, please contact

- Kavita Aiyer: kiyer@seagen.com
- BioPhorum: isabelle@biophorum.com

The background is a dark blue field filled with numerous small, out-of-focus particles in shades of blue and red. On the right side, there are several bright, diagonal streaks of light, suggesting motion or energy. The overall effect is a dynamic, high-tech aesthetic.

BioPhorum - Collaborating Responsibly

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.

Minutes and communication of F2F meetings v1.2

Minutes

The BioPhorum facilitator(s) will capture the key discussions, proposals and decisions in an **Event Report**. This report will act as the **Minutes** of the meeting and will

- detail the objectives, attendees and agenda
- include **hyperlinks** to all the materials shared in the event and an **executive summary**. All materials shared via hyperlinks will be in pdfs to lock down the contents in their presented form.
- Contain **photos** of the presenters and the team to help participants put names to faces after the event. If you do not want to be photographed please let the facilitator know.

Our aim is to **circulate** the Event Report in draft form within six working days of the meeting, to all the participants. A final draft will then be made available to all other workstream reps and Phorum Leaders (L2s).

Circulation to guests will be at the discretion of the facilitator(s) and team.

Photos of presentations must only be taken with the express agreement of their author.

Communication

Often discussions in meetings are exploratory and involve testing ideas, solutions and approaches.

We ask that all representatives in the meeting and dialling in respect the unformed state of discussions and agree not to comment on the discussions publicly on social media or report on the discussions on open public channels, during the meeting and until the final draft of the Event Report has been circulated and any messaging and communications strategy of the team has been agreed.

This is not a bar to representatives communicating about the meeting with peers, colleagues and stakeholders in their own organisation, this is very much encouraged.

Supplier interactions policy v3.0

The BioPhorum Operations Group (BioPhorum) 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 v5.0

Introduction

BioPhorum Operations Group (BioPhorum) 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 competition/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.

When sharing third party documents on The BioPhorum Hub (or other IT systems), participants should use links to documents to avoid breaching copyright requirements.

The BioPhorum facilitators are responsible for reminding all participants of their obligations with respect to information sharing and will ensure that the relevant watermark will be included on documents.

Participants should not share outside workstream/Phorum teams unpublished material including but not limited to:

- Ask BioPhorum or survey responses including summary data
- Meeting preparation material or minutes of BioPhorum meetings
- Draft papers
- Individual opinions of representatives or their companies spoken at BioPhorum meetings
- Industry feedback captured using tools such as virtual whiteboards, polls or surveys.

Members can share BioPhorum confidential information within their own organization, but the key contact (L2) for each member 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. All participants are responsible for vetting information to be shared via their company's public disclosure review processes and that all information shared is free of any 'Confidential' label.

Participants' contact details

- Every person who participates in the BioPhorum collaboration will have access to the business contact details of other participants. These details should only be used for making contact with other participants in matters that relate directly to their work in BioPhorum.
- Use of these contact details by participants in the following circumstances is prohibited:
 - Compilation of mailing lists and advertising or marketing of any kind
 - Creating a database of contact details in any circumstances
 - Recruitment and job advertising
- Participants who are unsure as to whether their use of contact information is acceptable or not should refer to their BioPhorum representative.

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

Sharing 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.

Privacy policy

To learn more about how we collect, keep, and process your private information, please view [our privacy policy.](#)