PATIENT-CENTRIC REQUIREMENTS FOR THE SUPPLY OF RAW MATERIALS INTO BIOPHARMACEUTICAL MANUFACTURING
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INTRODUCTION

Raw material variability and control of the supply chain are important issues for the biopharmaceutical industry. The industry is still at an early stage in the journey to align the supply base with biopharma’s requirements to improve patient well-being by assuring product safety and meeting ever-increasing regulatory demands. This requires increased understanding, monitoring and control of raw materials. Patient well-being is best assured by reducing or eliminating variability of the finished drug product, and this can be achieved, in part by targeted reduction and/or elimination of variation in raw materials. Our challenge is to align the supply system to the patients' needs. Leading global Biopharmaceutical Manufacturers have been working together within the Biophorum Operations Group (BPOG) and collaborating to create an industry endorsed and supported guidance package. The areas of best Practice are categorized into 10 key topics:

1. Patient-Centered Organizational Culture:
   Patients have a right to expect to receive safe and effective medicines as intended by the Biopharmaceutical manufacturers. The patient’s needs should be at the center of all decisions made by all parties along the supply chain.

2. Control and Elimination of Sources of Variation:
   Collaboration is required across the supply chain to understand the impact of, and then reducing, raw material variability which can have a detrimental impact on process performance and product safety and efficacy and therefore patient well-being.

3. Good Manufacturing Practice (cGMP):
   An appropriate level of cGMP compliance, dependent on material, should be applied across the whole supply chain to ensure the control of manufacturing operations and assure that the drug produced is safe and effective and meets specific requirements for identity, strength, quality, and purity.

4. Fit-for-Purpose Specifications:
   Setting specifications based on the materials’ intended use.

5. Change Notification and Early Warning:
   Having agreed criteria for change notification and then robust change control processes to minimize the impact on the patient (shortages and/or risks to safety and efficacy).

6. Risk Management:
   A structured approach to assessing and managing risk along the whole supply chain to minimize the impact on the patient (shortages and/or risks to safety and efficacy).

7. Traceability, Transparency, and Trust:
   A partnering culture which builds trust and promotes transparency, effective risk planning and issue resolution.

8. Technical Due Diligence and Audits:
   Structured assessments to deepen the understanding of design inputs, controls and systems that are in place to assure control of manufacturing operations, to help support risk planning and providing opportunities to pro-actively identify areas for improvement.

9. Root Cause Investigations:
   Shared ownership of the problem and the exchange of the right information at the right time to enable quick issue resolution.

10. Data Management:
    Capturing and sharing the required data across the supply chain to enable effective performance management & root cause analysis.
The biopharma industry invests significant resources to the management of raw material quality and testing for consistency. This approach includes a focus on the materials themselves with respect to material qualification, specifications setting and maintenance, and the sampling, testing and release of materials, along with documentation of change control and quality issue investigations/resolutions. Biopharmaceutical Manufacturers also qualify suppliers by periodic audits and through the management of quality/service/change control agreements.

Suppliers who specialize in supplying raw materials into biopharmaceutical manufacturing should be familiar with these requirements. Suppliers for whom biopharmaceutical manufacturing is not their main customer segment may be less familiar with the specific needs of the biopharmaceutical industry and view the biopharmaceutical manufacturer demands as an unnecessary burden.

This White Paper is intended to complement the work already being done across the industry to help suppliers understand the biopharmaceutical industry and the key standards being asked for by Regulatory Agencies and patients, and Biopharmaceutical Manufacturers. The BPOG membership encourages participation in, and adoption of the various standardization initiatives that have been delivered or are in development across the industry such as: joint auditing, standardized questionnaires, change control processes, quality agreements and data formats by Rx-360, Bio-Process Systems Alliance (BPSA) Pharmaceutical Process Analytics Roundtable (PPAR), ASTM, BioPhorum Operations Group (BPOG) and other industry organizations.

Together with the supply chain partners we aim to establish consistent definitions and terminology, a common understanding of critical supply chain issues, a common understanding of the impact of raw material variability on drug product quality (safety and efficacy) and a foundation for collaborative working to jointly manage risks and resolve issues that adversely affect Biopharmaceutical Manufacturing and thereby patient well-being.
Patients expect their medicines to be delivered to them at the right quality and trust the supply chain to deliver them uncompromised. Products manufactured by the biopharma industry address serious medical needs of patients and these products must be safe and efficacious. Raw material quality can have a direct impact on the safety and efficacy of those medicines. It is vital that all parties involved in manufacturing and delivering products to meet the patients' needs adopt a patient-centric organizational culture, wherein all activities and decisions are made with the patient in mind.

1. PATIENT-CENTERED ORGANIZATIONAL CULTURE

Patients expect their medicines to be delivered to them at the right quality and trust the supply chain to deliver them uncompromised. Products manufactured by the biopharma industry address serious medical needs of patients and these products must be safe and efficacious. Raw material quality can have a direct impact on the safety and efficacy of those medicines. It is vital that all parties involved in manufacturing and delivering products to meet the patients' needs adopt a patient-centric organizational culture, wherein all activities and decisions are made with the patient in mind.

This patient-centered approach does not just lie within the Biopharmaceutical Manufacturer but should extend the length of the supply chains. Biopharmaceutical Manufacturers invest significant resources to design, monitor and control their own operations to assure identity, strength, quality, and purity of drug products. These key requirements ensure patients' needs are met, and adoption of the areas of best practice identified in this paper will help ensure compliance with industry regulations and guidelines. Raw materials are recognized as a key contributor to drug product quality and supply, but Biopharmaceutical Manufacturers have not historically focused as heavily on the manufacturing that takes place outside their own facilities. This needs to change. Through close partnership with Suppliers, there is an opportunity to identify and explore opportunities to improve the supply chain in an efficient, effective and sustainable manner.

For biologics, “the process is the product” describes the complex inter-relationships linking the biologic drug manufacturing processes to the final drug quality. While small molecule compounds can typically be completely characterized, i.e. they can be fully tested, the final products in biological manufacturing are more difficult to fully characterize, placing additional importance on carefully defining the manufacturing process in question. Introducing raw materials of the wrong quality can have huge costs in terms of out-of-specification drug product lots, product recalls, rework, reputation, and, most severe of all, patient health. These costs have led the biopharma industry to realize that the “process as product” concept extends beyond their own manufacturing and into the processes operated by their Suppliers.

The Biopharmaceutical Manufacturers have a responsibility to clearly articulate the needs of the industry to help create this link between Suppliers and patients. Biopharmaceutical Manufacturers can assist Suppliers to create their own patient-centered organizational cultures by providing information on the connection between supplier products and patient outcomes. Examples include sharing patient stories and product pipeline information for biopharma products impacted by the Supplier’s materials. A thorough understanding of the role these raw materials play in the manufacturing process enables Suppliers to better assess their responsibilities and a greater sense of their contributions to patient well-being. Ensuring that Suppliers are always aware (while respecting confidentiality) of the intended use of the medicinal and therapeutic products manufactured using their raw materials is key to Suppliers adopting and embedding best practice principles.

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Biopharmaceutical Manufacturers have a key role to help connect the supply chain with the patient and effectively communicate current and future supply chain needs. This can include providing clarity to ongoing R&D and commercial activities that may impact future sourcing and supply strategies and helping suppliers plan and invest in supply chain innovation. Substantial biopharma investment into discovering and developing treatments for chronic diseases and cancer, including viral & cellular therapies, vaccines, will require agile and innovative supply chains.
In a 2011 survey of 820 non-federal, short-term acute care hospitals conducted by the American Hospital Association, 44% of hospitals reported 21 or more drugs in short supply over the previous six months. Over 80% of the hospitals described treatment delays resulting from these shortages; patients receiving a less effective drug or not receiving recommended treatment at all were reported by 69% and 63% of hospitals, respectively. Over one-third of the hospitals noted patients experiencing adverse outcomes related to drug shortages.
2. CONTROL AND ELIMINATION OF SOURCES OF VARIATION

Variability in raw material properties can impact patient safety and efficacy, product quality, and process performance. Management and control of raw material variability is essential for assuring product quality and patient safety.

Strong collaboration between Suppliers and Biopharmaceutical Manufacturers is critical to achieve supply chain reliability. This approach supports continuous improvement of raw material products and the processes that deliver them. Suppliers and Biopharmaceutical Manufacturers must collaborate in the design of fit for purpose tools and metrics to monitor and control variation. Best practice concepts such as statistical process control, process capability, critical material attributes, and critical process parameters need to be adopted by both parties.

Variability in the raw material manufacturing process may affect the quality attributes of the raw material and hence impact biopharma products. Where possible, Biopharmaceutical Manufacturers must be clear about which variations are impactful to their processes and then actively partner with Suppliers to develop fit-for-purpose specifications and controls supporting those specifications. The best way to understand, manage, and minimize sources of variation is via mutually-beneficial partnerships between Suppliers and Biopharmaceutical Manufacturers. Benefits to Suppliers include improvements to their manufacturing efficiency through better process and raw material control. Biopharmaceutical Manufacturers can reduce risk to patients and achieve manufacturing consistency by partnering closely with Suppliers. Most importantly, better raw material and process control benefits patients using Biopharma products.

The ICH Q8 Guideline entitled Pharmaceutical Development states that the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product (ICH Guideline for Pharmaceutical Development). Because raw material variability can impact product quality and process performance, raw material variability should be evaluated to determine if it is a critical parameter to the manufacturing of biopharma products. Variability can have many sources and effects. For example, variability of cell culture media components may affect cell growth and, therefore product titers (productivity) and media effects on cell metabolism may alter glycosylation patterns or other aspects of product quality. Any such variability can impact product quality (patient safety and efficacy). Variation in residual peroxides or metal ions in raw materials may increase oxidation rates of end products, thereby impacting product titers and stability (product quality over its shelf life).
Process development: Variability of Peptone used for yeast culture

- Media prepared with different lots of the same peptone reference

In examining the overall factors that can influence the variability in raw material, it is important to recognize that the large number of components and Suppliers represents an undeniable challenge to control of variation in raw material. Approximately 80% of the active pharma ingredients (APIs) used in drugs manufactured in the US are sourced from more than 150 countries (source: http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm).

The span and complexity of the supply chains for these ingredients in terms of the variety of sources, distributors, shippers, methods of transportation, and warehousing does not facilitate traceability. In addition to variability related to a complex supply chain, some raw materials, e.g., those derived from natural sources (i.e. plant or animal), are inherently variable.

Figure 2: An example of raw material variability where variability of peptone quality had an impact on yeast growth as shown by the different colored liquids and growth curves.
The above piece illustrates how supply chain issues can be reported in the media. The editorial does not include all the facts of this particular case.

Regulatory agencies are providing more stringent enforcement of raw material standards as a result of some recent high profile incidents, with “supplier management” being listed as one of the top observations in recent warning letters (http://www.fda.gov/ICECI/Inspections/ucm481432.htm#Biologics). The Drug and Device Accountability Act of 2009 requires Biopharmaceutical Manufacturers to file information on all sites involved in drug preparation, and health authorities including the FDA and MHRA are conducting their own audits of the raw material supply chain at the Supplier level.

For Suppliers to effectively control and reduce variability of critical raw materials, detection and control systems must be strengthened by routine use of best practice analytical tools and validation packages/regulatory support files to control sourcing of ingredients used in raw material production. Suppliers must implement increasingly rigorous scientific standards and shift from testing to demonstrate raw material quality to an approach of designing quality into the manufacturing process. The latter approach requires Suppliers to have a deep understanding of their raw materials, manufacturing processes, and analytical test methods. This also means that the supplier has a robust supply chain themselves, with raw materials qualification and validation methods and systems in place for incoming raw materials. Such knowledge is key to understanding how changes to the process may affect raw material attributes, as well as assessment of quality risks and identification of critical parameters.
3. GOOD MANUFACTURING PRACTICE

While the foundation of the biopharma industry is a patient-centered organizational culture, the guiding principles for its operation are found in the regulations comprising current Good Manufacturing Process (cGMP), the code of practices that assure the proper design, monitoring, and control of manufacturing processes and facilities.

In biopharmaceutical manufacturing, cGMP is the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled as required by product specifications using quality standards appropriate to their intended use. Regulatory authorities such as the FDA and EMA produce guidances and guidelines, respectively, that outline current thinking and approaches that Biomanufacturers should undertake. In the USA, a set of regulations is found in the Code of Federal Regulations Title 21, and in the European Union it is the EudraLex; other regions and countries follow their own similar guides and standards. These manufacturing regulations also address how Biopharmaceutical manufacturers make certain that incoming raw materials are compliant with requirements of their intended use (“fit for purpose”).

**Code of Federal Regulations Title 21**

“the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products”

**Eudralex**

“Documented prior knowledge and risk assessment can help identify and justify the material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates)”
Biopharmaceutical manufacturers comply with cGMP standards by:

1. Ensuring materials received are what they are claimed to be and that they meet the specifications agreed upon with the Supplier. This is confirmed by testing the materials using compendial methods (i.e. methods that are described in the United States, European, or Japanese Pharmacopeia) or by using pre-defined test methods that produce accurate and repeatable results.
2. Putting in place and maintaining systems that guarantee traceability of raw materials in order to link raw material lots to end product lots.
3. Auditing Suppliers’ facilities to establish and maintain qualification of these sites as sources for given raw materials and rely on Suppliers auditing their Suppliers.
4. Implementing appropriate quality, supply, and change control agreements with Suppliers relevant to specific raw materials and Suppliers. Consistency of incoming materials is safeguarded by tracking any and all changes related to the raw materials. These include any change to the identity of Suppliers or their processes, starting materials, packaging, etc. Per cGMP guidance, Biopharmaceutical Manufacturers must be aware of any and all of these changes that might impact the raw materials.

Different risk categories are assigned to raw materials based on their criticality to the process e.g. the constraints may be more stringent for materials used in cell culture media that more significantly impact product quality than those used in purification processes. For example, raw material risk management focuses on not only careful documentation of animal–derived materials in particular, but also the tracking of residual solvents, heavy metals and the results of Class VI testing and extractables and leachables of plastic single-use materials. Such levels of scrutiny and documentation are considered minimum requirements. At the same time, while it is clear that Suppliers are not required by law to adhere to GMP, there are nevertheless minimum standards that need to be met by Suppliers, and these minimum standards may be more rigorous and prescriptive for certain raw materials. A list of best practices for Suppliers is found in Table 1.

As previously described, it is likely that the supply chain includes Suppliers who do not specialize in supplying the biopharma industry and may supply certain raw materials that have their primary use outside of the biopharma industry. Biopharmaceutical Manufacturers and Suppliers should work together and apply a cGMP approach (i.e. apply cGMP principles) to the non-GMP manufacture and work towards minimum cGMP manufacture where possible.
Table 1: cGMP Best Practices for Suppliers

<table>
<thead>
<tr>
<th>BEST PRACTICE</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>Quality management system</td>
<td>ISO 9001 regarded as baseline; Suppliers may need to follow specific cGMP practices in some cases</td>
</tr>
<tr>
<td>Documentation management</td>
<td>Manufacture and analyze according to predefined procedures and methods; production and analytical data logged per defined methods</td>
</tr>
<tr>
<td>Deviation management</td>
<td>Deviations from defined procedures/methods investigated appropriately; Suppliers should have documented investigation process for their supply chains</td>
</tr>
<tr>
<td>Change management</td>
<td>Change permitted but must be made via controlled process using robust change control and notification systems</td>
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<tr>
<td>Complaint management</td>
<td>There should be documented processes in place to manage complaints, including adequate response times and meaningful feedback from corrective and preventative action (CAPA) processes</td>
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<tr>
<td>Recall management</td>
<td>There should be documented processes in place to manage product recalls</td>
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<tr>
<td>Specification management</td>
<td>There should be documented processes in place to manage specifications</td>
</tr>
<tr>
<td>Audit management</td>
<td>Supplier facility audits are required as well as a review of (Tier 1) Suppliers' audit programs of their Suppliers</td>
</tr>
<tr>
<td>Raw material quality attribute testing and release</td>
<td>Test methods must be suitable for their purpose, consistent, and reproducible</td>
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<tr>
<td>Stability management</td>
<td>Material storage conditions must be well defined and include expiry justification when required</td>
</tr>
<tr>
<td>Supply Chain management</td>
<td>Appropriate quality and supply agreements relevant to the raw material must be in place</td>
</tr>
<tr>
<td>Production oversight</td>
<td>Raw materials must be traceable and emerge from qualified and consistent manufacturing process; careful documentation of animal derived materials; tracking of residual solvents and extractables/leachables</td>
</tr>
<tr>
<td>Facilities, utilities, and equipment</td>
<td>Equipment must be cleaned appropriately between batches and especially at changeover between products using validated procedures and preventive maintenance systems bearing appropriate documentation; use of controlled/validated sterilization processes/procedures, as applicable</td>
</tr>
<tr>
<td>Training system</td>
<td>Training of operators and analysts on raw material manufacturing procedures and methods documented</td>
</tr>
<tr>
<td>Shipping/Transport:</td>
<td>Security of shipments guaranteed with tamper-evident seals, appropriate packaging, e.g., no cardboard or timber heat-treated pallets</td>
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</table>
4. FIT- FOR-PURPOSE SPECIFICATIONS

Setting specifications for raw materials is an important element of the overall strategy for controlling their properties and quality. Best practice involves Suppliers working closely with Biopharmaceutical Manufacturers to align a given raw material's specifications with the material's intended use. Wherever possible, Suppliers and Biopharmaceutical Manufacturers should also jointly pursue "smart" specifications, i.e., setting appropriate tolerances for the material based on the process sensitivity to those raw material attributes.

The term “fit for purpose” does not imply that such specifications are custom. Although raw material specifications should be based on the material's intended use, Biopharmaceutical Manufacturers should seek to maximize use of standard specifications and minimize use of custom specifications whenever achievable via use of standardized tests, test methods, acceptance criteria, lot sizes, packaging, etc. as custom materials are often more expensive and can have longer lead times, and standardization can help address business risks and quality concerns.

Of course, standard specifications may have to be adjusted to reflect actual needs, i.e. to detect potentially unacceptable lots of raw material for a specific application of the raw material. In such cases, it is incumbent upon Biopharmaceutical Manufacturers to clearly communicate any modifications required to the standard specifications. Implementation of fit for purpose specifications requires Biopharmaceutical Manufacturers to fully share necessary product and process knowledge with Suppliers (subject to appropriate confidentiality considerations). Although Biopharmaceutical Manufacturers are not required to specify the tests that Suppliers use to check that material is within specifications, such Suppliers test methods should at least be known to Biopharmaceutical Manufacturers. For example, in microbial control testing of non-sterile powdered media materials, Biopharmaceutical Manufacturers expect Suppliers to test these materials for both bioburden and endotoxin, and to have processes in place to meet established specifications, even if these are not conducted under sterile conditions.

As an additional example, Biopharmaceutical Manufacturers have struggled with issues surrounding removal of “particles” (e.g. steel fragments, paper, fibers, etc.) from their raw materials. Appearance of particles can involve expensive investigations, rejection of lots and disruption of manufacturing process schedules. Best practice for Suppliers around particles involves understanding why Biopharmaceutical Manufacturers need to drive towards zero particles in particular raw materials. Biopharmaceutical Manufacturers must communicate the reasons for maintaining a zero particles target by sharing risk assessments and other rationales for limiting particles. Suppliers can help Biopharma manufacturers understand how the material source (e.g. mined versus crystallized) can impact the ability to minimize "particles".

While Suppliers should strive for the zero-particle goal, Biopharmaceutical Manufacturers must be prepared to deal with the reality of Technically Unavoidable Particles when these are encountered. Use of Technically Unavoidable Particle Profiles (TUPPs) can clarify Suppliers’ constraints in efforts to remove particles and help Biopharmaceutical Manufacturers understand what could be considered “normal” for a given raw material. An ideal situation would be to extend the International Pharma Excipient Council's TUPP guidance to all raw materials. Aligning TUPPs with Food & Chemical Codex (FCC) recommendations would also be helpful, although because most biologics are injectables, FCC guidance is not entirely applicable.
5. CHANGE NOTIFICATION AND EARLY WARNING

Ensuring a reliable supply chain of raw materials requires effective management of the inevitable changes to product and process that will occur over time. Effective and timely communication is essential. Suppliers at all points in the inbound supply chain must have procedures in place for notifying downstream users of changes occurring in the Supplier’s raw material manufacturing process. The timing of such notification should allow Biopharmaceutical Manufacturers to fully evaluate and plan for the impact of the change. Change is defined as anything that could potentially affect the quality of the raw material or the Biopharmaceutical manufacturer’s product (and therefore patient outcomes), including availability or manufacturability of the material. Change notification should include both planned (foreseen) and unplanned changes, e.g. deviations.

Most biopharmaceutical manufacturing companies have their Suppliers send change notifications to an email platform or central desktop where these notifications can be routed for stakeholder review and feedback. Such a platform enables Biopharmaceutical Manufacturers to make inquiries to Suppliers on issues concerning an announced change and in the event of post-announcement discrepancies. Supplier Change Notifications (SCNs) are assessed by Biopharmaceutical Manufacturers for impact and severity, then tracked using a change control solution, typically a software-based system designed to manage change controls. Categorization of these changes then determines the process to follow. Close collaboration across internal departments of the Biopharmaceutical Manufacturers, e.g., Procurement, Supply Chain, Quality, Technology, Manufacturing, and Regulatory, is often required to determine which Biopharma products and manufacturing sites could be affected by an announced change in the raw materials and/or the supply chain. This cross-functional assessment of the change is essential to identify, plan, and execute the activities that will be required to support the raw material change. Depending on the nature of the change and its potential impact on the biopharma product, a significant amount of time and resources may be required to support the change. Such support can include filing of regulatory updates or performance of experimental studies to evaluate pre- and post-change raw materials.

The Biopharmaceutical manufacturer should be notified of a planned significant change a minimum of twelve (12) months prior to the change becoming effective or distribution of the modified material or component, however, earlier notification is always preferable. In cases of unexpected or unplanned changes, Biopharmaceutical Manufacturers and Suppliers must work closely together to negotiate a path forward, which may include sourcing of the raw material from alternative sources or agreeing to other solutions e.g. Supplier makes a one-time final buy of a key raw material and/or Biopharmaceutical organization makes a strategic buy to cover demand until qualification and validation is completed.

Suppliers sometimes do not know what impact a change will have on the Biopharmaceutical manufacturing process, resulting in either over- or under-notifying of changes. Over notification places a resourcing burden on Biopharmaceutical Manufacturers and Suppliers must work closely together to negotiate a path forward, which may include sourcing of the raw material from alternative sources or agreeing to other solutions e.g. Supplier makes a one-time final buy of a key raw material and/or Biopharmaceutical organization makes a strategic buy to cover demand until qualification and validation is completed.

Overall, SCNs must be assessed, and if deemed to have an impact on the process, then the change must be managed via a change control process. SCNs to Biopharmaceutical Manufacturers must include the full scope of the change along with data sufficient for Biopharmaceutical Manufacturers to determine the resulting risk, accompanied by a justification.
6. RISK MANAGEMENT

Biopharmaceutical manufacturing’s recommended approach to assessing the integrity of the raw materials entering the supply chain is to apply a robust risk management process. The evaluation of these risks must be based on good scientific knowledge of the raw materials and their manufacturing process and controls. Ultimately, these factors are linked to the protection of patients via the safety and efficacy of the Biopharma product. The level of effort, formality, rigor, and documentation applied to the risk management process should be commensurate with the overall level of risk involved.

It is expected that Suppliers should have robust risk management processes in place to evaluate and manage risks in their own businesses and how their own risk mitigation plans and any specific steps in their process could impact the Biopharmaceutical Manufacturer’s supply chain and risk management plans. Ideally, there are readily available common tools and International Standards (e.g. ISO 22301 Business Continuity Management) to make such assessments in order to drive consistency across the industry and create a common approach to risk assessment and management. All parties should take every opportunity to proactively participate in risk assessments at technical and business levels to ensure mutual understanding and mitigation of risk.

Risk management can not only be a complex process, but can also be relatively subjective. There are guidelines e.g. EU Guideline on formalized risk assessment for excipients standards, processes, and tools that can be used to help assess and manage risk. Biopharma’s guideline for risk management is provided by ICH module Q9, Quality Risk Management. In addition to open communication between Suppliers and Biopharmaceutical Manufacturers, gathering input from Biopharma functional areas including Operations, Quality, Technical and Procurement is critical to the process of Risk management. The ICH Q9 principles are illustrated in Figure 4.

Figure 4: ICH Q9 Principles Source: http://www.ich.org/products/guidelines/quality/q9-briefing-pack/briefing-pack.html
Risk management requires Suppliers and Biopharmaceutical Manufacturers to each assess their own supply chains to ensure basic understanding and ranking of the inherent risks. Risks may be of scientific, quality, supply chain security, or business continuity in nature. Each of these areas should be assessed individually, as the associated risks are often very different. Suppliers and Biopharmaceutical Manufacturers should work together to assess risks in their supply chains. An integrated and collaborative approach is strongly advised to ensure an aligned and agreed understanding of risks and mitigation strategies. Supply chain mapping exercises can be particularly effective in ensuring that both parties have visibility to the sources of materials in the supply chain. Such exercises enable Suppliers and Biopharmaceutical Manufacturers to jointly determine the points at which risks are most likely to be introduced and what risk mitigation plans may be necessary.

Some raw materials are of special importance or may require specific information from the Supplier provided on a Certificate of Analysis. In these situations, Biopharmaceutical Manufacturers must clarify the nature of the risk for the Supplier by explaining why a particular raw material is of specific concern. This may help Suppliers better understand the needs of Biopharma Manufacturer and what information Suppliers should seek to address such needs. After mapping the supply chain and assessing risks, Suppliers and Biopharmaceutical Manufacturers should work together to coordinate risk mitigation actions. Both parties benefit from a collaborative process of risk mitigation that requires their combined knowledge and capabilities to succeed.

Table 2 below includes examples of tools that may be used to assess and control risks. The selection of the most effective tool should be based on the intended purpose and the nature of the risk to be analyzed. Technical due diligence is a key input for several of these tools, although details in the applications and management of these tools will vary. Change control processes should include updated risk assessments of the material being changed.

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<tr>
<th>RISK ASSESSMENT</th>
<th>RISK CONTROL</th>
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<td>Quality Function Deployment (QFD)</td>
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<tr>
<td>Hazard Analysis and Critical Control Points (HACCP)</td>
<td>Hazard Analysis and Critical Control Points (HACCP)</td>
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<tr>
<td>Hazard Operability Analysis (HAZOP)</td>
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<tr>
<td>Six Sigma/Lean methods –Process mapping, fishbone analysis, etc.</td>
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</tr>
<tr>
<td>Statistical Process Control–Data trending, control charts, Cpk/ Ppk, etc.</td>
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<tr>
<td>Preliminary Hazard Analysis (PHA)</td>
<td>Criticality Analysis and Control Strategies</td>
</tr>
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<td>Failure Mode Effects (and Criticality) Assessment (FMEA or FMECA)</td>
<td></td>
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</tbody>
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Table 4: Example tools for the assessment and control of risk
7. TRACEABILITY, TRANSPARENCY AND TRUST

Biopharmaceutical Manufacturers produce medically important products used by patients all over the world; so disruptions to raw material inputs may mean interruptions in supplies of critical medicines, endangering the health of patients. Therefore, Biopharmaceutical Manufacturers need the ability to appropriately plan for and mitigate potential disruptions to drug supplies. Supply chain mapping exercises are critical to ensuring that potential disruptions are identified, assessed, and managed well before impact is realized. In an ever-dynamic global supply chain network, it is essential to have the ability to readily trace the supply chain. For example, material origin data and lot traceability are critical for investigations related to incoming material that has been determined to be Out Of Specifications (OOS). Suppliers of raw materials that are distributors rather than manufacturers should understand the criticality of tracing batch information from their upstream Suppliers on through to Biopharmaceutical Manufacturers.

Although full transparency of the manufacturing process further up the supply chain may not always be possible, it is nevertheless critical for Suppliers to ensure that they understand their own processes and starting materials. Working in partnership to map the supply chain across nodes that include raw material manufacturers, Biopharmaceutical Manufacturers, component suppliers, packagers, etc., is critical in the current and future regulatory environment.

There should be a bilateral openness and willingness to engage in collaborative supply chain mapping exercises to increase transparency and visibility, despite the effort required to gather and maintain the information and the reluctance to share sensitive information. Biopharmaceutical Manufacturers should share the intended use of raw materials with Suppliers to harmonize material sources and specifications, and Biopharmaceutical Manufacturers should be clear on why information requests to Suppliers are being made.

Key supply partnerships between Suppliers and Biopharmaceutical Manufacturers can further increase the level of transparency. Where appropriate, strategic/preferred supplier programs and global/key account programs for Suppliers that require joint investment by both Biopharmaceutical Manufacturers and Suppliers can deliver additional strategic value to the partnership. The creation of strategic partnerships between Suppliers and Biopharmaceutical Manufacturers should be pursued as an ideal in the relationship.

Collaboration occurs when companies work together to achieve common objectives. Such behavior requires a shift away from the traditional transactional relationship of customer/supplier. Collaborative relationships between Biopharmaceutical Manufacturers (customers) and Suppliers can create value for both parties. However, establishing and maintaining collaborative relationships require significant investments in time, effort, and/or capital from both sides. Close cooperation between customer and supplier also includes extensive sharing of information, integration of processes, and coordinated decision-making.

Strategic partnering can offer significant benefits to both parties and some are listed in Table 3.
Table 3: Potential Benefits of Strategic Partnering

A key factor in maintaining the types of business relationships that enable traceability and promote transparency is trust. Trust between individual Suppliers and Biopharmaceutical Manufacturers is often only earned over time. Trust is a pre-requisite for openness; an attitude of openness from all parties in the raw material supply chain is required for problems to be identified and resolved most quickly. It is recognized that trust between corporations is underpinned by a clear understanding of each party's obligations as defined by formal legal agreements.
8. TECHNICAL DUE DILIGENCE AND AUDITS

Technical due diligence and audits are similar but distinct activities performed by Biopharmaceutical Manufacturers on their suppliers. Performance of technical due diligence by Biopharmaceutical Manufacturers on Suppliers is a key component of effective risk management in Biopharmaceutical manufacturing. This due diligence by Biopharmaceutical Manufacturers requires close collaboration with Suppliers in order to focus on the scientific elements of the application for which the raw material is required. Due diligence includes a mutual review by Biopharmaceutical Manufacturers and Suppliers of essential material attributes of the raw material for its intended application. Due diligence also involves critical assessment of Supplier manufacturing processes, including raw material controls, process flow diagrams, equipment design and operation, and description of procedural controls (e.g., batch records, SOPs, operator instructions) and critical process parameters.

Audits of Supplier facilities and processes by Biopharmaceutical manufacturing are necessary to the maintenance of robust raw material supply chains. Audits of Supplier controls focus on identification and implementation of effective strategies for controlling the quality of the Supplier raw materials. However, audits also include examination of the methods used by the Supplier for processing and analysis of the raw materials, as well as those for packaging, storage, and shipping. Supplier audits are led by quality representatives from the Biopharma Manufacturer company. Facilities audited include warehouses, manufacturing areas, and equipment involved in the processing of raw materials flowing from the Supplier receiving department, through manufacturing, packaging and on to shipping/distribution, including overall quality systems (e.g. documentation, change control, deviation process). Audits of Suppliers also include review of personnel, procedures, and training. Of particular interest to Biopharmaceutical Manufacturers are the specifications and release testing procedures used by the Supplier company, and how these processes are validated, including the qualification of laboratory facilities appropriate for testing a given raw material. Other key areas of interest in audits are the processes surrounding change management and notification to Biopharmaceutical Manufacturers. Based on the importance of the raw materials used in the Supplier processes and their potential impact upon the final biopharma product, Biopharmaceutical Manufacturers recommend that similar due diligence be carried out by Suppliers on their own supply chains. This audit system and scheme is also part of the Biopharmaceutical Manufacturer’s audit.

<table>
<thead>
<tr>
<th>Supplier Performance Rating</th>
<th>Material and Supplier Risk Rating</th>
<th>Single-Source and Business Risk 30%</th>
<th>Product Quality Risk 30%</th>
<th>Requirement Definition Risk 20%</th>
<th>Spend 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal</td>
<td>Audits every four years</td>
<td>Audits every four years</td>
<td>Audits every four years</td>
<td>Audits every four years</td>
<td>Annual audits</td>
</tr>
<tr>
<td>Standard</td>
<td>Audits every four years</td>
<td>Audits every three years</td>
<td>Audits every two years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>Audits every three years</td>
<td>Audits every two years</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Figure 5 Example - Risk Factors and Supplier Performance driving audit frequency
9. ROOT CAUSE INVESTIGATIONS

Audits of Supplier facilities by Biopharmaceutical Manufacturers are necessary to assess the integrity of raw materials flowing into Biopharmaceutical manufacturing. A highly collaborative exchange of information and knowledge during technical due diligence ensures that technical risks are identified and then controlled based on a mutual understanding of the critical material attributes and their process controls. In the event of an issue with the material, then the incident should be fully investigated to identify the root cause and an action plan developed to minimize impact of the current issue and avoid it happening again in the future. Biopharmaceutical Manufacturers expect that Suppliers have their own robust, documented internal issue investigation processes in place.

Successful root cause analysis is critical to the timely resolution of undesired raw material related effects on the product quality and process performance of Biopharma products. Timely communication is imperative, and Biopharmaceutical Manufacturers are responsible for making clear to Suppliers the priority of the issue at hand.

The expediency and manner in which root cause analyses are conducted is dependent on the exact nature and urgency of the problem at hand, e.g., whether a recall is required, if any interruption in finished product is involved, etc. A strong relationship between Suppliers and Biopharmaceutical Manufacturers will ensure a successful root cause investigation is carried out quickly. Strong relationships are built upon;

1. Shared accountability and commitment across the supply chain between Biopharmaceutical Manufacturers and Suppliers; this may extend several steps up the supply chain.
2. A clear and timely definition of identified issues (e.g., OOS issues or other deviations, contamination of material, etc.) is mandatory and must be followed by close collaboration between Biopharma Manufacturer and Supplier representatives from each entities’ quality, technical/scientific, and supply chain departments in defining, analyzing, and correcting root causes.

Due to the complex nature of some supply chains it is crucial for Supplier Companies to maintain the capabilities, tools, and processes for participating in multi company root cause analyses and investigations. Transparency is especially important to ensure effective communication and documentation of findings between the parties. This may also include relevant information from the Biopharmaceutical Manufacturers, e.g. process data, for help suppliers deepen their understanding of the downstream impact of their material(s) on the process, product and/or patients and thereby aid issue resolution.

The processes that drive investigations and root cause analyses are standard, and follow consistent methods and use familiar tools to properly identify root causes, e.g., Six Sigma, fishbone analysis, 5 Why’s, IS/IS NOT, DMAIC principles, etc. Principles of change control are applied for notification of updates to established methods, along with standard reporting methods that include periodic updates. Suppliers should have clearly-defined rules in place to account for continued processing, production, and/or shipping while investigations are ongoing.

In terms of consequences once a root cause for an incident has been determined, Suppliers and Biopharmaceutical Manufacturers should apply the principles of Corrective and Preventive Action (CAPA). CAPAs contain clearly-defined actions for each party involved along with expected outcomes and reasonable deadlines while avoiding open ended commitments. Interim progress is communicated and documented by all parties, demonstrating commitment to a timely resolution. CAPAs are closed after appropriate demonstrations of the corrective action’s effectiveness and documentation, including review and approval by the quality representatives.
10. DATA MANAGEMENT

Data integrity is critical to GMP compliance and is a major concern for both the industry and the regulators. The analysis and trending of manufacturing process and product related data has resulted in numerous product improvements and process optimizations. More recently, advancements in data capture and information technologies have enabled important improvements in data sharing, and have provided more opportunities to apply these approaches. A better understanding of how data is captured (e.g. paper and/or electronic, batch records, in-line monitoring, lab testing) in their manufacturing process can be a source of value and competitive advantage for Suppliers. Enhanced data capture and monitoring enables Suppliers to better evaluate their manufacturing processes by allowing comparisons between the variations observed during processing and final product attributes, ultimately leading to manufacturing performance optimization. Advanced data trending technologies are capable of detecting even weak signals of emerging quality issues in order to proactively head off threats to quality. When such data and trending are not available, non-conformances and risks to product quality increase.

Data contained in a certificate of analysis (CoA) represents the minimum requirements of Biopharmaceutical Manufacturers and is often not the most relevant data for studying variation. Additional data is needed to identify opportunities for continuous improvement in raw material supply chains. Availability of the relevant data on the ongoing status of raw material in the supply chain helps both parties identify sources of variation. Such data also provides a means of quickly determining whether such variations represent clues to a change in either raw material quality or process performance. Taking advantage of advances in the flow of electronic data across the Supplier-Pharma Manufacturer interface represents an important opportunity for both Suppliers and Biopharmaceutical Manufacturers.

Biopharmaceutical Manufacturers need Supplier information on raw material quality attributes, in-process controls (IPC), and other process data to help establish such correlations. As a result, data exchange and adherence to data format standards (e.g. PPAR and other organizations are developing best practices and data standards) constitute best practice in quality agreements between Suppliers and Biopharmaceutical Manufacturers. An enabler for data exchange is use of confidential disclosure agreements (CDAs). In the event of intellectual property concerns arising despite having CDAs in place, Suppliers or Biopharmaceutical Manufacturers can blind particularly sensitive data, but ideally the blinding process ensures that both parties are still capable of trending and analyzing data usefully. Sharing of data is an increasingly critical aspect of relationships between Suppliers and Biopharmaceutical Manufacturers, and is necessary for achieving true strategic collaboration between Suppliers of critical raw materials and Biopharmaceutical Manufacturers of those materials.

Supplier data acquisition/data management tools and methods must be sufficiently robust to accomplish agreed-upon raw material quality goals. Ideally, IPCs and other operating parameters are well understood in the Supplier's manufacturing process. Appropriate databases and laboratory information systems must also be in place. Data exchange standards must be established to minimize data format variability. Best practice involves Suppliers providing data in a given standard electronic format for transfer to Biopharmaceutical Manufacturers. Adherence to standard electronic format minimizes the total cost of data ownership for both parties. A common electronic data format is not only much more cost-effective and easier than developing new format for each request, but also makes the data integration needed for trending and reporting much more straightforward and sustainable. Biopharmaceutical Manufacturers are required to provide certified or verified data to regulatory authorities to ensure data integrity; similar rigor is expected from Suppliers. Data integrity codes of conduct as offered by the PDA (www.pda.org/codeofconduct) and data format standards are being developed across the industry. (e.g. http://www.astm.org/COMMIT/SUBCOMMIT/E55.htm)
CONCLUSION

The Biopharma industry sees continuous improvement as a critical commitment for building effective partnerships with raw materials Suppliers. This commitment involves the sharing of scientific and technical expertise by Suppliers with Biopharma companies and regulators to improve product understanding. Biopharma’s patient-centered organizational culture, guided by the principles of cGMP, forms the basis of Biopharmaceutical manufacturing.

Best practices in the areas of change control and risk management are fundamental to the management of incoming raw material quality and minimizing variability. Biopharmaceutical Manufacturers are focused on performing technical due diligence on their sources of raw materials, on conducting audits of Supplier facilities, and on mandating traceability to protect patients from shortages or quality issues. Such an approach is best accomplished in an atmosphere of transparency and trust. Both Suppliers and Biopharmaceutical Manufacturers must constantly strive for robust data management and monitoring technology for such investigations to succeed. Best practices in data management are also required to achieve continuous progress toward the goal of reducing raw material variability in the Biopharma industry.

While safeguarding patient health is the guiding principle behind these activities, it is also clear that application of the principles described in this paper should also deliver mutual benefits for both Suppliers and Biopharmaceutical Manufacturers. Effective partnering and collaboration enhances process knowledge and product understanding across the supply chain, resulting in improved quality and process efficiency. Partnering also reduces costs associated with deviations, rejections, rework, and recalls that result in product loss, lowered utilization of facilities, and expensive investigations. In addition to these advantages, partnering between Suppliers and Biopharmaceutical Manufacturers increases the level of confidence regulatory authorities have in the integrity of the supply chain, potentially decreasing the length and frequency of audits and inspections. Overall, the application of the principles, concepts, approaches, and tools outlined in this white paper provides a framework for ensuring continual improvement in the overall quality and reliability of the supply chains that provide novel and life-saving medicines to patients worldwide.