SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Leading the Edge of Innovation into Cell Culture Media Quality

Barb Martinez, Global Senior Product Manager Custom Cell Culture Media

Courtney Walston, Supervisor, Cell Culture Media Supplier Quality

Carol Krause, Project Manager

Damon Talley, Head of Quality for Cell Culture Media

Cell culture medium is the cornerstone of a successful upstream process and foundational for long-term commercial success of a biotherapeutic. Given its central role in biomanufacturing, a consistent supply of high-quality media is required to deliver the necessary titer and protein quality while ensuring an uninterrupted process.

Because complex media formulations can include a number of components, and hundreds of options, each with its own supply chain, ensuring quality of the final media product calls for a global raw material program integrating multiple disciplines. The program should encompass a detailed understanding and characterization of the raw components used in cell culture media, in combination with well managed and defined supply networks.

In this white paper, we highlight the breadth of programs implemented across our organization to safeguard the quality of the cell culture media that are used in our customer processes – from some of the world's highest grossing biologics to those produced on a patient-by-patient basis such as breakthrough cell therapies. Our programs represent a set of integrated disciplines focused on raw material characterization in conjunction with global supplier quality management and advanced procurement and inventory systems (**Figure 1**).

Figure 1. Our comprehensive cell culture media quality program is based on an integrated set of disciplines.

"We know the therapies our customers are manufacturing are lifesaving and we realize the importance of our work as related to the quality of our cell culture media. That's why our team is so dedicated and committed to making sure it's done the right way, the first time, every time."

Damon Talley, Head of Quality for Cell Culture Media

Raw Materials Management and Characterization

Reducing variability and ensuring the safety, quality and performance of raw materials used for manufacturing of cell culture media is our top priority. Stringent control of raw materials is essential as modern cell culture media typically consist of 70 to 100 components, hundreds of choices for the components, and each component can be obtained from any number of sources. This results in an intricate network of suppliers and the potential for variability. Given this complexity, establishing a robust supply chain with multiple suppliers of qualified materials to maintain continuity, built over time with a deep level of trust and collaboration, is critical.

"Our global quality management system ensures we are aligned in our raw materials and suppliers. Strong relationships with supplier ensure our quality requirements are met."

Courtney Walston, Supervisor, Media Supplier Quality

Production of Products Classified as Animal Component Free

Animal sourced materials are a primary concern for cell culture due to the possible presence of transmissible spongiform encephalopathy (TSE) and viral contamination. We reduce these risks by selectively sourcing raw materials which can provide the right documentation as to its origin. Suppliers have to be aligned to the industry standards for definition and understanding their raw materials as either animal derived or animal component free (ACF). At our cell culture media manufacturing locations, we dedicate and segregate facilities as either ACF or animal component containing (ACC). We have formalized procedures for people, material movement and control of incoming raw materials. All raw materials entering our facilities are stopped at the dock and held until we have the appropriate documentation and certifications to confirm the ACC or ACF status. Our procedures for control are aligned with global industry standards.

Raw Materials Vendor Management Program

An essential component of our ability to provide high quality for cell culture media is a global raw materials vendor management program which supports our manufacturing locations around the world (**Figure 2** and **4**). The program establishes and maintains close relationships with suppliers to ensure reliable supply and consistent quality. Our Global Supplier Quality team works with the appropriate internal team like Technical Operations, R&D and Quality Control to apply the right raw material specification, apply risk-based approach for change management, and collaboratively manage the raw materials and suppliers.

Supplier qualification includes a requirement for transparency regarding source of materials, the process used to manufacture the material as needed, the country of origin, complete documentation and proactive change notifications. Material qualification includes extensive characterization of a number of lots, and those attributes which would be a risk for cell culture media like trace element impurities. Local procurement teams and inventory systems are integrated on a global basis to help minimize the potential for supply disruptions and allow us to share batches for raw materials between sites.

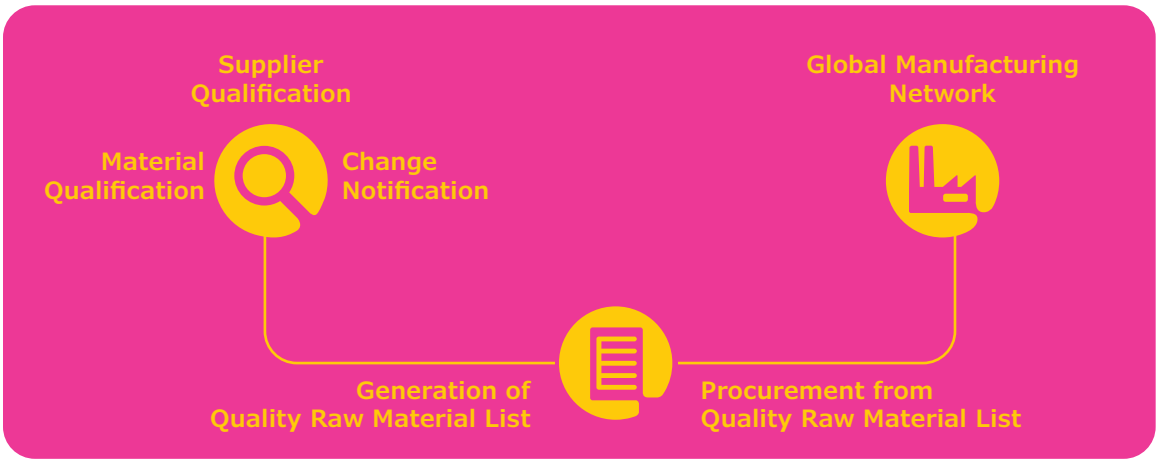

Figure 2. Procurement and inventory systems are managed locally as part of our global, unified supply chain management program.

Raw Materials Characterization

Our raw materials characterization program is an integral part of our larger raw material management organization. Analytical and cell culture scientists provide the scientific rationale for intelligent raw material specifications. This team also evaluates the inter and intra lot variability of suppliers and raw materials. Integration of this characterization program with our quality systems enables us to proactively prevent variability in raw material from impacting the quality of the final media product.

Overall, this internal program supports three critical functions:

- Defining intelligent and science based raw material specifications
- Conducting investigations or troubleshooting when needed by our customers or internal teams
- Managing change to understand and eliminate variability like trace element impurities

To further understand and address the changing nature of supply chains, our risk-based approach to evaluate raw materials risk integrates the raw materials characterization team with our global supplier quality initiative (**Figure 3**).

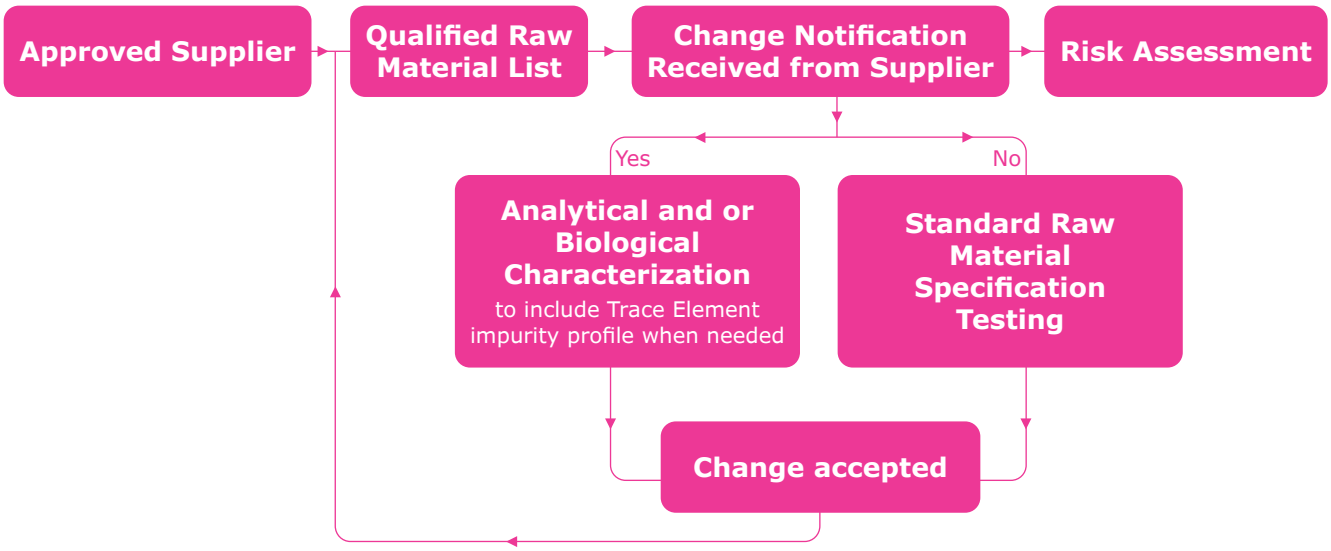

Figure 3. Integration of raw materials characterization with the global supplier quality initiative enables a risk-based approach to assess supply chains.

Trace Element Analysis

An important focus of our cell culture media program is to measure and report the level of ten common cell culture trace elements as a service to our customers. We conduct quantitative testing by inductively coupled plasma mass spectrometry (ICP-MS) for copper, manganese, zinc, molybdenum, nickel, vanadium, aluminium, selenium, chromium and cobalt.

Low levels of trace element impurities in media components can have a cumulative impact on the final medium composition and affect multiple pathways of the cells, contributing to the variability of harvested proteins. For example, some trace metals impact glycosyltransferases and can alter the protein glycosylation profile. Similarly, concentrations of trace elements like copper, manganese, zinc, and selenium have a direct impact on protein quality. Other trace metals are critical nutrient sources in their own right.

Whether the trace metal is an intentional component of the media formulation or an impurity, trace components have different effects and their ideal concentrations may vary according to a specific process. To avoid product quality issues, it is vital biopharmaceutical companies understand the effect of elemental metals on their bioprocess. Receiving the ICP-MS results for cell culture products is one key piece of information in the ability to manage variability.

It is through our supplier collaborations in which the major contributors of impurities will be reduced or eliminated, with the ultimate goal of driving the impurity level to one of tolerance or total elimination. Developing new supply chains to replace ones which have historically contained impurities may present a secondary challenge in terms of cost.

Global Quality Management System

Our media facilities operate under a comprehensive global quality management system focused on ensuring the safety, quality and performance of our products. This global approach ensures that product from our media manufacturing sites are comparable in terms of performance and have the same level of quality. As a result, customers can more effectively manage variability in their processes and minimize risk associated with inconsistency.

"We have a living, breathing quality system that is adapted across cell culture media sites to ensure we meet our customers' needs around the world."

Carrie Krause, Project manager of bulk production materials and co-manager of the M-Clarity™ program

Within this global system we have harmonized a set of critical Quality Systems and processes including:

- Design control
- Validation and qualification requirements for facilities, utilities, equipment and processes
- Validation and verification of quality control assays
- Stability program
- Training program
- Raw material and supplier management
- Finished product storage and distribution
- Change control and notification
- Deviation and CAPA program
- Complaint management
- Business continuity

Figure 4. Our cell culture media manufacturing network

Each of our media facilities have on-site quality control laboratories. Standard quality control assays for media are conducted using harmonized current compendia methodologies. Other non-compendial assays require validation to ensure fit for use for cell culture media as shown in **Table 1**.

Finished Product Testing	Methodology	NA	EU	China
Appearance	Uniformity/color	•	•	•
pH	USP 791	•	•	•
Osmolarity	USP 785	•	•	•
Bioburdon (Powder)	USP 61	•	•	•
Sterility (Liquid)	USP 71	•	•	•
Endotoxin	USP 85	•	•	•
	(Kinetic, Chromogenic, Gel clot LAL)			

Table 1. Standard quality control testing for cell culture media is harmonized across our manufacturing sites.

All our cell culture media sites are certified as ISO 9001:2015 and we are expanding and evolving our quality program to provide you the highest quality in cell culture media, as well as the utmost confidence in consistent quality anywhere in the world.

At the Leading Edge of Innovation

Ensuring the quality of a complex product that is integral to the manufacture of biotherapeutics requires innovative thinking. We challenge ourselves to constantly expand and evolve our quality initiatives. The following programs exemplify this commitment to remain at the leading edge of quality innovation.

Harmonized Quality Standards

Unlike other aspects of drug manufacturing, there are no regulations that speak specifically to cell culture media. In light of this, we have proactively applied quality standard for all of our cell culture media manufacturing sites of Lenexa USA, St Louis Broadway USA, Irvine UK, Darmstadt Germany, and Nantong China. We voluntarily comply with the Joint IPEC-PQG Guide on Good Manufacturing Practices for Excipients and applicable sections of Annex 1 of the EU Guidelines for Good Manufacturing Practice for Medicinal Products.

In addition, we are partnering with the leadership of a non-profit organization that owns and manages oversight of an independent third-party certification scheme available to pharmaceutical excipient manufacturers and distributors worldwide. Given their experience with the biopharmaceutical industry with regards to excipients, we consider them to be an exceptional partner for collaborative development of guidelines for auditing cell culture media sites and certification for GMP.

M-Clarity™ Program

Our M-Clarity™ program defines product quality levels throughout our broad life science portfolio, classifying products into six “MQ” (MilliporeSigma Quality) levels – from MQ100 to MQ600 (**Table 2**). These levels help customers select products to meet their specific needs with respect to:

- Compliance with the appropriate quality and regulatory standards
- Portfolio transparency
- Change control notification support
- Documentation support

The program supports our customers in their process of choosing components and raw materials, allowing for comparison of quality support and documentation, and ultimately minimizing costs and delays. The MQ levels provide transparency in terms of the attributes of materials needed to support regulatory requirements. The decision regarding the most relevant quality profile is driven by the customer’s specific needs for controlled and verified or validated processes.

	Quality Segments					
	MQ100	**MQ200**	**MQ300**	**MQ400**	**MQ500**	**MQ600**
Application scope	For non-regulated applications with no change notification requirements	For non-regulated applications with limited change control requirements	For products used in applications requiring enhanced change control and quality agreement	For critical products and applications driven by high expectations and requiring verified process control or manufacturing control	For regulated applications	For highly-regulated applications under authority surveillance
Discriminating features	Standard control	Increased control	Enhanced control	Driven by customer expectation	Driven by authority regulations	Driven by authority regulations and surveillance
Quality systems	ISO 9001	ISO 9001	ISO 9001	ISO 9001	IPEC GMP and/or HACCP, FSSC 22000 and/or ISO 17025 and/or ISO 13485	ICH Q7 or 21 CFR medical device
Quality attributes (e.g. specifications, Certificate of Quality)	●	●	●	●	●	●

	Quality Segments					
	MQ100	MQ200	MQ300	MQ400	MQ500	MQ600
Basic change control		●	●	●	●	●
Enhanced level of control			●	●	●	●
Verified process				●	●	●
Certified/validated process					●	●
Highly regulated application						●

Emprove® Program

We recently expanded our Emprove® Program to include Cellvento® CHO cell culture media. With this addition, customers get access to comprehensive documentation to facilitate qualification, risk assessment and regulatory filings. Addition of Cellvento® CHO media to the Emprove® Program eliminates the time-consuming process normally required to compile information about media including product specifications, characterization and supply chain information. Three dossiers are available for each media product included in the Emprove® Program:

- The Material Qualification Dossier accelerates media qualification and supports regulatory filing preparation. It includes content related to product specifications, manufacturing and characterization such as TSE/BSE and virus safety. Certificates of analysis, batch numbering, packaging material and stability are also included.
- The Quality Management Dossier supports quality risk assessment by offering extended information on the supply chain, product and site quality self-assessments, supplier management and stability data.
- The Operational Excellence Dossier supports process optimization efforts as well as extended and safety risk assessment. The dossier contains information on trace elements, the origin of raw materials and analytical procedures.

An Unwavering Commitment to Quality

The central role of cell culture media in the development and manufacturing of drugs demands that comprehensive and proven quality control measures are embedded throughout our organization. As outlined in this white paper, we have established a dynamic, global quality program for our cell culture media portfolio that has the depth and breadth required to deliver performance, quality and ensure a robust supply chain.

We are gratified to be entrusted by both emerging companies and industry leaders for their cell culture media needs. We will continue to explore innovative initiatives to further protect the quality of raw materials, protect supply chains and reinforce our relationships with trusted suppliers.

Learn more
EMDMillipore.com/ccmsupply

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

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