SAFC®

Pharma & Biopharma Raw Material Solutions

MERCK

Cell Culture Media

supply robustness and control

Global Raw Material and Vendor Management Program

Consistent Manufacturing Network

Global Quality Systems

Introduction

Lack of consistency in cell culture media can create significant variation in your upstream process. To control cell culture media variability and ensure the quality of our products worldwide we have implemented a robust supply process that incorporates a global raw material and vendor management program, a consistent manufacturing network, and global quality systems.

We have developed a risk-based approach to manage our raw materials and assess change. We know the impact trace element impurities have on cell culture performance and protein quality, and we offer the right data to better understand this variability.

We require high standards from our suppliers which includes defining raw material quality attributes, classifying animal origin risks, and establishing change notification. We purchase the same approved cell culture media raw materials from the same approved supplier qualification list for use in all of our manufacturing sites. This gives you confidence that we are supplying the same high-quality products from any one of our manufacturing sites from all over the world.

We provide manufacturing redundancies for dry powder media in Europe and the United States. Two sister sites – with the same manufacturing technology, single source of raw materials and proven comparability. To ensure the highest level of quality for our cell culture media, our manufacturing facilities are governed by a comprehensive company-wide Global Quality Management System including harmonized certifications, and standard quality control testing.

To ease your regulatory efforts for risk assessment and accelerate your progress through regulatory requirements, we are expanding our Emprove® Program to include a number of catalog media.

The result? Providing you the highest quality in cell culture media, as well as the utmost confidence in consistent quality anywhere in the world.

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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.

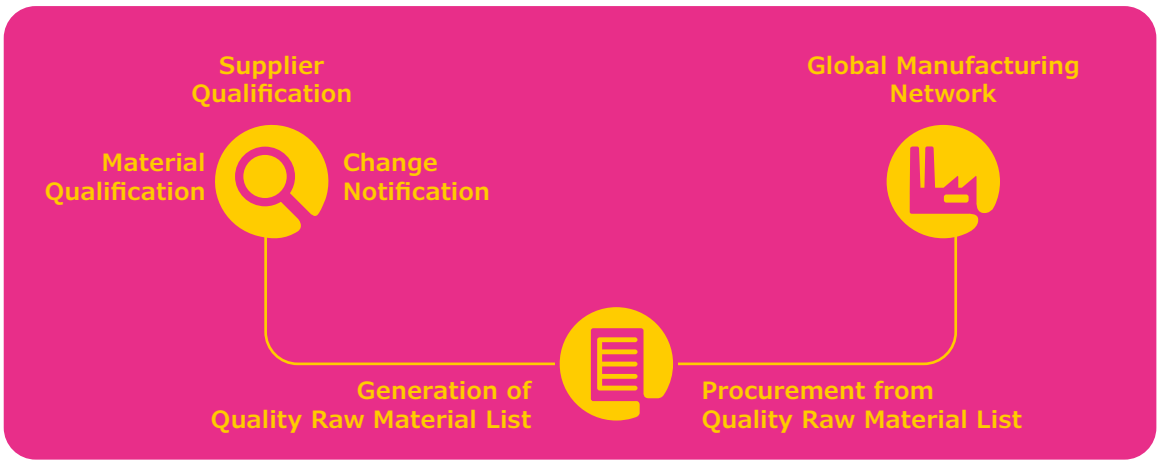


Figure 2. Procurement and inventory systems are managed locally as part of our global, unified supply chain management program.

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**).

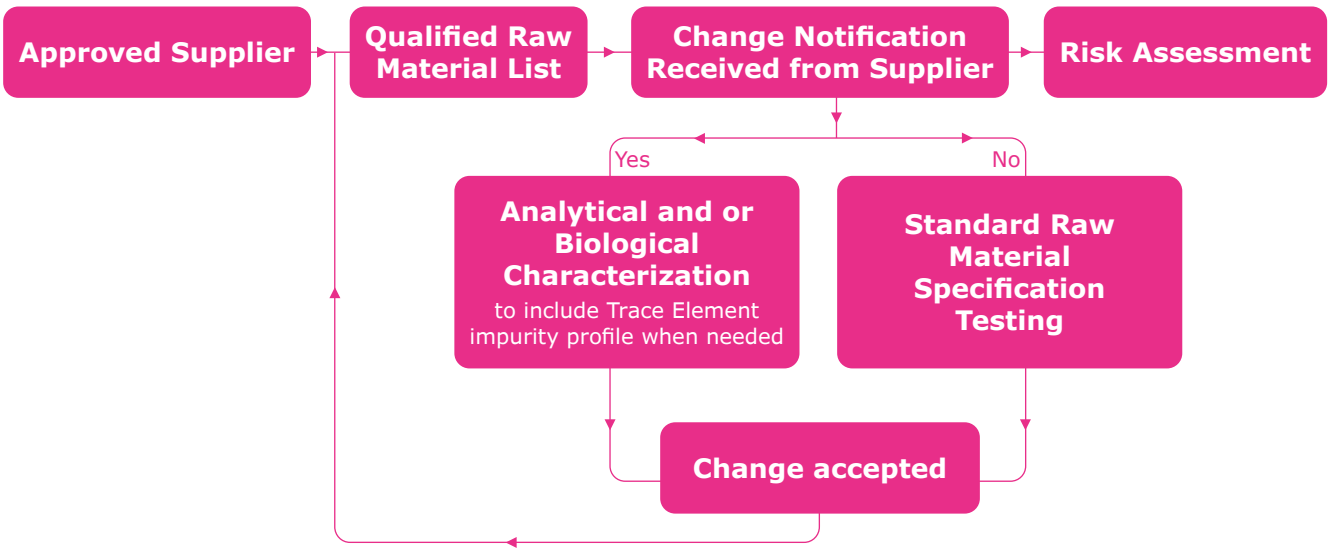


Figure 3. Integration of raw materials characterization with the global supplier quality initiative enables a risk-based approach to assess supply chains.

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” (Merck 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.

Transparency and comprehensive documentation with Emprove® CCM

Emprove® Dossiers for Cellvento® CHO cell culture media products in Biomanufacturing Upstream Processes

Raw materials and process aids used during drug substance manufacture have come under increased regulatory focus. Recent best-practice industry publications[1,2] broadened the scope of raw materials to be included in drug product risk assessments from excipients to the entire drug product production process, including Upstream Processing.

Cell culture media are of utmost importance to bio-pharmaceutical processes as they support cellular productivity and critical quality attributes of the final drug products. Therefore a high level of information for the media is needed to support the entire process risk evaluation.

With our new category Emprove® CCM we address the specific needs when selecting and qualifying products of our Cellvento® CHO cell culture media platform.

The platform consists of specially designed catalog media supporting the needs of process intensification in fed-batch and perfusion applications. The product formulations are chemically defined and of non-animal origin.

In line with the existing Emprove® product categories, detailed information is available in three different types of dossiers, supporting you throughout the different stages of your operations: material qualification, risk assessment, and process optimization.

Three Levels of Information for Material Qualification, Risk Assessment and Process Optimization

Material Qualification Dossier	Quality Management Dossier	Operational Excellence Dossier
• General information – Specification • Manufacture – Address, Manufacturing Flowchart, ISO Cert, GMP Statement – Homogeneity Statement • Characterization Statements – TSE/BSE, Virus Safety, GMO, Components of Interest • Control of CCM – CoAs, Label, Batch Numbering – Packaging Material – Stability	• Supply Chain Information • Product Quality Self Assessment • Site Quality Self Assessment • Supplier Managment • Stability data	• Trace Element Information • Origin of Raw Materials • Analytical procedures
Information to start a material qualification	**Answers questions during risk assessment**	**Supports process optimization**

Target Emprove® dossier for Cellvento® media

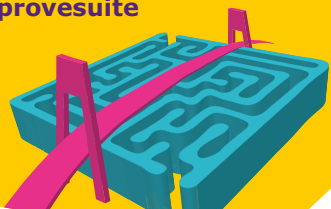
Product	Catalog Number
Cellvento® 4CHO-X COMP Expansion	103840
Cellvento® 4Feed COMP	103796
Cellvento® 4CHO	103795
Cellvento® CHO-200	101885
Cellvento® Feed-200	101883
Cellvento® CHO-220	102577
Cellvento® Feed-220	102578
Cellvento® CHO-210	102485
Cellvento® Feed-210	102488

Find out more on **MerckMillipore.com/emprove**

1. BioPhorum “Raw material risk assessments – A holistic approach to raw materials risk assessments through industry collaboration”, Sept 2019.
2. European Biopharmaceutical Enterprises, “Management and control of raw materials used in the manufacture of biological medicinal products and ATMPs”, Dec 2018.

Gain 24/7 online access to all your dossiers with our Emprove® Suite at:

MerckMillipore.com/emprovesuite



TRACE ELEMENTS

Data for Decisions

Cell Culture Media

There are many possible raw materials in a cell culture media formulation. Although the supply chain for these raw materials remains relatively unchanged over the last 40 years, the way we view the supply chain and the potential for variability on the bioprocesses has changed.

The role of trace elements and their impact on protein and product quality is well documented. As such, trace elements by formulation addition is critical. Variation in these same critical components has been linked to unintended impurities in the prevailing cell culture raw material supply chain. The first step in understanding and managing variability is acquiring reliable data on these critical trace elements.

As our organization is committed to developing industry leading products and capabilities, out of our Raw Material Characterization program we are able to offer on our cell culture products the following services.

Finished Product Testing

- Quantitative Testing by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) for these elements.
  - Copper, Manganese, Zinc, Molybdenum, Nickel, Vanadium, Aluminium, Selenium, Chromium, Cobalt
  - Results reported on the CofA are without specification limits. (data for informational purpose only)
- Testing performed on cell culture products from our Lenexa, KS, Irvine, Scotland, and St. Louis, MO (Broadway) facilities
- This testing is an additional charge, please consult with your sales representative regarding your product portfolio

Typical LOQ for a Chemically Defined Media

(LoQ's will vary based on media formulation)

Trace Element Symbol	Trace Element Name	LOQ for Liquids (mcg/L)	LOQ for Dry Powder (mcg/kg)
Cu	Copper	0.8	36
Mn	Manganese	0.8	36
Zn	Zinc*	80.0	3636
Mo	Molybdenum	0.8	36
Ni	Nickel	3.2	145
V	Vanadium	0.8	36
Al	Aluminium	4.0	182
Se	Selenium	6.4	291
Cr	Chromium	1.6	73
Co	Cobalt*	40.0	1818

* This formulation by design contains higher levels of Zinc and Cobalt. Lower LoQ's can be achieved. Note: Specification limits are not available

Customer Collaboration Projects

- Based on data generated from the finished product testing, customers can enter into collaboration projects with our R&D Team:
  - Our experienced team of scientists connected to our Raw Material Characterization Program
  - Data transparency for purpose of discovery
  - Strategy recommendations for managing trace element variability recognizing changes within the prevailing supply chain may not be possible
- Collaborations are defined and charged per a scope of work

Knowing your cell culture media

Lack of consistency in cell culture media can create significant variation in your upstream process. Our supply chain experts are committed to providing you with the highest quality and most consistent cell culture media — regardless of manufacturing site location.

RAW MATERIALS

Global Raw Materials Vendor Management Program

A cornerstone of our focus, our global program for the control, management, and procurement of raw materials provides the confidence you need for consistent, quality product.

Understanding Trace Element Variability

The role of trace elements and the impact on protein and product quality is well documented. We offer the right data to begin understanding this variability.

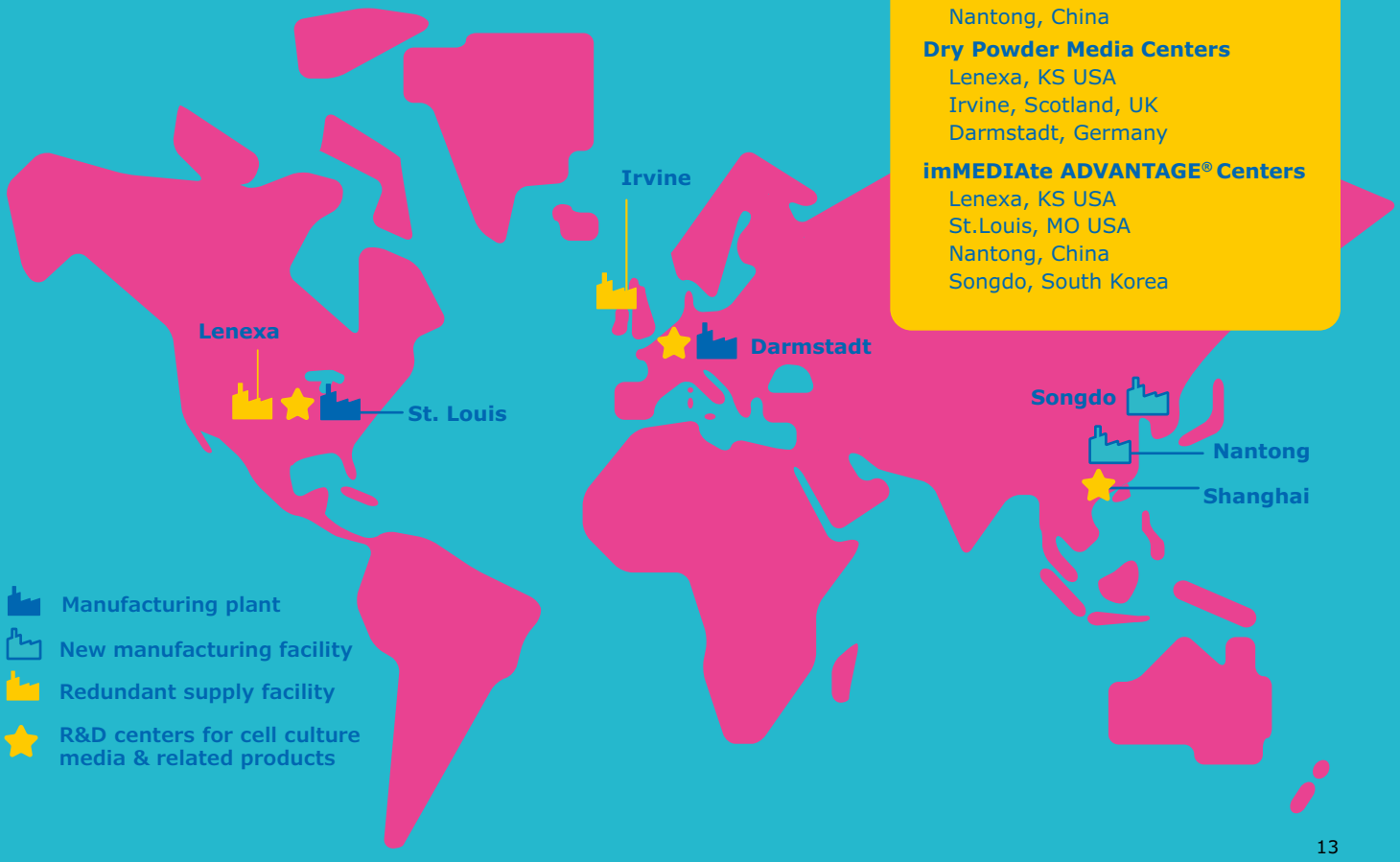
- Quantitative testing by ICP-MS
- Cu, Mn, Zn, Mo, Ni, V, Al, Se, Cr, Co
- Results reported on the CofA

MANUFACTURING LOCATIONS

Liquid Centers
St.Louis, MO USA
Irvine, Scotland, UK
Nantong, China

Dry Powder Media Centers
Lenexa, KS USA
Irvine, Scotland, UK
Darmstadt, Germany

imMEDIAte ADVANTAGE® Centers
Lenexa, KS USA
St.Louis, MO USA
Nantong, China
Songdo, South Korea



GLOBAL QUALITY MANAGEMENT

Global Quality Management System

NEW! IPEC-PQG compliance*

Our cell culture media sites are certified as ISO 9001:2015
* Voluntarily comply to the Joint IPEC-PQG Guide on Good Manufacturing Practices for Excipients and applicable sections of Annex 1 of the EU Guidelines to Good Manufacturing Practice for Medicinal Products. Apply to Lenexa, St. Louis-Broadway, Irvine, Darmstadt, and Nantong (liquid) sites.

Quality Control

Standard testing with options to add customized quality testing.

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)	•	•	•

Quality Services: Customer Inquiries

TIER 1
Front Line Contact
Product documentation, Q&A

TIER 2
Technical & Quality Workflows
Appropriate team support

TIER 3
Expert Support
Scientific or site expert support

NEW! Emprove® Cell Culture Media

High-quality products, comprehensive documentation, and superior customer support for qualification, risk assessment, and process optimization. Now available for a range of cell culture media.

www.MerckMillipore.com/emprove

MANUFACTURING CAPABILITIES

Our global network of manufacture sites are specifically designed and operate to exceed industry standards for cell culture media intended for bioprocesses.

Custom Capabilities Large Scale

- Clinical to commercial supply
- Liquid: 50 - 10,000 L batch sizes
- Dry powder: 25-6000 kg batch sizes

Custom Capabilities Small Scale imMEDIAte ADVANTAGE® Services

- Pre-GMP product intended for bioprocess development studies
- Liquid; 1-200L batch sizes
- Powder: 0.5 - 20kgs batch sizes

Raw Materials
Option to use unique, non-qualified raw materials for your experiments

Documentation to Support
Certificate of analysis and safety data sheet with each batch

Right Technology & Processes
Equivalent liquid and dry powder manufacturing methods as compared to large scale facilities

Design Support

Let one of our R&D teams or our designs specialist help you develop your custom cell culture media.

Redundant Supply Facilities

We know the challenges global biopharma companies can have with securing dual source of cell culture media. We provide the solution by offering two sister sites-same technology, single source of raw materials and global quality management to deliver dual sourcing from one supplier.

Lenexa, KS, US

Irvine, UK

Ensuring Consistency in the Supply of Cell Culture Media

Barb Martinez, Global Senior Product Manager Custom Cell Culture Media

Damon Talley, Head of Cell Culture Media Quality

Pascal Perrotey, Head of Cell Culture Media Operations

Continued growth of the biopharmaceutical industry, along with the remarkable expansion of new therapies, have increased the demand for cell culture media. As an essential component of upstream processes, the quality of the media, along with continuity of supply, are critical to minimize interruptions in manufacturing. The complexity of media formulations, which contain a variety of raw materials from different sources, can impact consistency and availability unless a robust supply chain and control measures to minimize variability are in place.

In this white paper, we describe the establishment of a robust, global manufacturing network for our cell culture media. This network enables consistent production of high quality media, supports capacity expansion to meet growing demand and provides product comparability for business continuity. This gives you confidence that you are receiving the highest quality and consistency from any of our manufacturing sites around the world.

Building A Flexible Manufacturing Network

We have established a global manufacturing network with multiple sites for liquid and powder media, all designed to deliver consistent quality product (**Figure 1**) and respond to a variety of needs, including:

- Custom and catalog media for both clinical and commercial application in batch sizes of 25 – 6000 Kgs for dry powder media and 50 – 10,000 L for liquid media.
- Custom sizes from 0.5 – 20 Kgs for dry powder and 1 – 200 L for liquid media for pre-GMP, bioprocess development studies.
- Available selections for raw materials, packaging and compaction.

With a network of temperature-controlled warehouses, we manage and deliver your product in the manner you choose. Common options include temperature controlled, temperature monitored, tracking and just-in-time-delivery.

Expansion of our manufacturing network with new facilities allows us to respond to the growing demand for cell culture media. We have added a new dry powder manufacturing facility to the existing Irvine, Scotland liquid media manufacturing site, and recently opened cell culture media small scale development services in Nantong, China and Songdo, South Korea. We are also increasing capacity in our European and American manufacturing plants. We continue to assess market trends and collaborate with customers to help further guide expansion plans and the development of our network of trusted suppliers.

Figure 1. A manufacturing network with multiple sites for liquid and powder, all designed to deliver consistent quality product.

Assuring Raw Material Supply and Minimizing Variability

Modern cell culture media typically consist of 70 or more components and the variety of components numbers well into the hundreds. Each component can be obtained from multiple sources – resulting in a complex network of suppliers and an increased potential for variability. It must be a priority of your cell culture provider to manage this complexity by developing a level of trust and transparency with suppliers and ensuring the right control of the raw materials is in place.

A cornerstone of our focus on business continuity for cell culture media is our *Global Raw Material and Vendor Management Program* which supports all our manufacturing locations (**Figure 1 and 2**). Local procurement teams and inventory systems are integrated on a global basis to help minimize the potential for supply disruptions. Our *Global Vendor Management Program* establishes and maintains close relationships with suppliers to ensure reliable supply and consistent quality. Supplier qualification includes a requirement for assessment of the supplier quality management system through questionnaires and on-site audit programs, open communication to include commitment for change notification, quality agreements and visibility to process and source material as needed. Our suppliers must also understand and be able to differentiate and segregate animal component containing materials from animal component free materials. Raw material qualification includes the right testing regiments based on the vendor certificate of analysis and the necessary fit for purpose required specification testing for bioprocess cell culture use.

Our procurement experts purchase the same approved cell culture media raw materials, from the same qualified suppliers, for use at all our manufacturing sites. This gives you confidence that we're supplying high-quality products from any one of our manufacturing sites from all over the world.

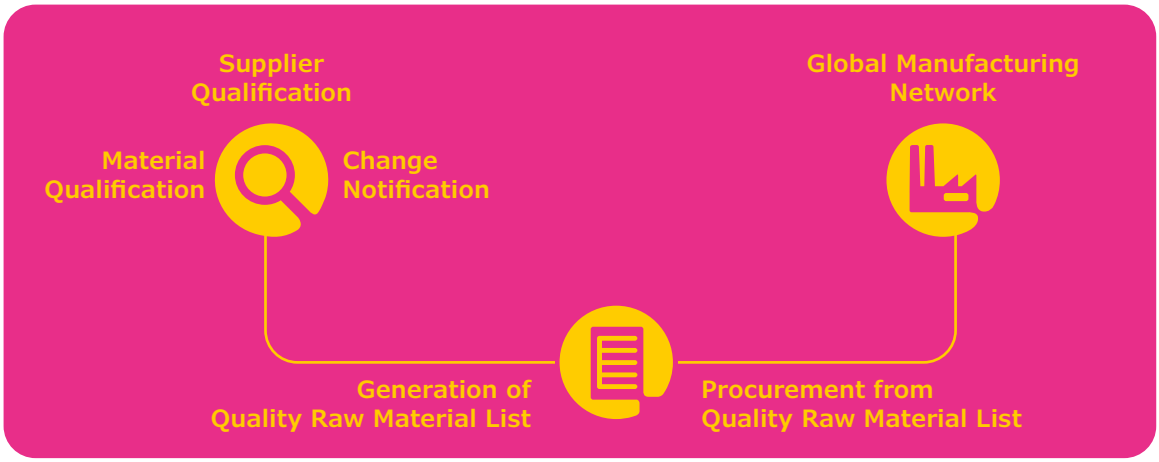


Figure 2. Our global raw materials vendor management program supports all of our manufacturing locations.

Raw Materials Characterization

More than a decade ago, we established a research and development team dedicated to raw materials that focused on the biological and analytical characterization of components used in our cell culture media. The team addressed fundamental questions about our components including their specific biological function and chemical-physical properties influencing media flowability and handling, stability, and other critical performance parameters. An important aspect of the raw material characterization program was to study and understand the inter- and intra-lot variability of our suppliers. We compared multiple lots of the same material from the same supplier, and multiple lots of the same material from different suppliers. We studied all aspects of the raw material which would cause variability in the use of the raw material, either biologically or analytically.

We also studied the impurity profile of raw materials which included trace elements. What we discovered were most of our raw materials were essentially pure, free of impurities and only a small subset posed a risk for trace element impurity and hence would be a source of trace element variability.

We integrated insight from this characterization program into our quality systems, enabling us to proactively prevent variability in raw material from impacting the quality of the final cell culture media product. We have developed a risk base approach to manage change; through this scoring system, we determine if any additional testing is needed to mitigate the change risk. We share our findings with our suppliers, and when we identify the need for an improvement to a raw material, we collaborate with the supplier to determine an approach to overcome it. Although we aim to eliminate all variability, there are instances where the prevailing supply chains are not able to be adjusted to remove the innate variability, and in these instances, our approach is to is offer information and choice for our customers.

Trace Element Analysis

Whether the trace element is an intentional component of the media formulation or an unintended impurity, the cumulative impact on the final medium composition can affect multiple pathways of the cells, contributing to the variability of harvested proteins. 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 metals are critical nutrient sources in their own right.

To avoid product quality issues, it is vital that biopharmaceutical companies understand the effect of elemental metals on a given bioprocess and determine the tolerances of their unique process.

Another output of our raw materials characterization program was to develop a qualified assay to measure and report the level of ten common cell culture trace elements as a service to our customers. The quantitative testing is by inductively coupled plasma mass spectrometry (ICP-MS) for copper, manganese, zinc, molybdenum, nickel, vanadium, aluminium, selenium, chromium and cobalt. The results of the trace element testing can be added to any custom cell culture product specification and results are provided on the customer certificate of analysis.

Controlling intentional addition of trace elements to a media formulation is the easy part of a complete trace element management process. Controlling or eliminating the trace impurities present in the cell culture supply chains is the more challenging task for the industry as the impurities have always been present. Sophistication in molecule characterization and analytical testing are enabling us to identify these cases. It will be through joint collaborations by 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 .

Leveraging a Global Quality Management System

Across our facilities, we have implemented a global quality management system as a holistic way to manage everything from incoming raw materials and other consumables, to operations and quality testing laboratories. This 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.

Our cell culture media facilities are covered under a comprehensive company-wide Global Quality Management System featuring:

- ISO 9001:2015 site certification
- Quality control testing aligned with industry standards
- A tiered approach for customer inquiries, facilitating a rapid and appropriate response

We also remain committed to staying at the forefront of all relevant guidelines and regulations. To facilitate your regulatory efforts for risk assessment and accelerate your progress through regulatory requirements, we have expanded and continue to further expand our Emprove® Program to include cell culture media. Additionally, our cell culture media sites now voluntarily comply with the Joint IPEC-PQG Guide on Good Manufacturing Practices for Excipients and applicable sections of Annex 1 of the EU Guidelines to Good Manufacturing Practice for Medicinal Products.

Establishing Dual Manufacturing

As a bio-manufacturer progresses to commercial stage for their product, the ability to safeguard against disruptions becomes vital. And as most commercial operations for bio-manufacturing utilize dry powder as the format for upstream cell culture, the targeted focus on a company's ability to provide security for dry powder becomes even more in focus. To augment our supply strategies, we added dry powder media manufacturing capabilities to our existing Irvine, Scotland liquid media manufacturing site. Addition of dry powder milling and blending capability to the facility completed a 5-year Capital Expansion Plan initiated as part of our long-term commitment to supporting customers in the growing industrial biopharmaceutical market.

This purpose-built manufacturing facility produces animal component free cell culture media and serves as redundant manufacturing capabilities to our facility in North America, located in Lenexa, Kansas. The dual US and UK manufacturing sites for dry powder media provide batch sizes ranging from 25 – 4000 kg and 25 – 6000 kg, respectively, for custom formulations and includes flexible packaging options.

Both sites use the same technology and comparable processes to deliver true cell culture media supply redundancy and reproducible chemical composition, particle size/bulk density, finished product specifications and cell culture performance (**Table 1**). Consistency and continuity in manufacturing is further enabled by use of the same raw materials, automated process controls, equivalent validation standards and documentation.

Description	Lenexa, KS, US	Irvine, UK
Animal component-free/non-animal origin manufacture	Yes	Yes
Segregated, animal component-containing manufacture	Yes	Not at Site
Manufacturing batch size range	25–4000 kg	25–6000 kg
Pin mill technology	Yes w/N_2	Yes w/N_2
Blending technology: Preblend Postblend	 Conical Blenders Conical Blenders	 Conical & Tumble Blenders Tumble Blenders
Global Raw Material Supply	Yes	Yes
GMP Quality Systems and ISO 9001:2015	Yes	Yes
Packaging capabilities: Standard packaging: Bottles, buckets and barrels EZ BioPAC® and right size weighing	 Yes Yes	 Yes Yes

Table 1. Both the US and UK site incorporate the same technology and comparable processes for their dry powder cell culture media production, offering proven product comparability. Additionally, each site voluntarily complies with the Joint IPEC-PQG Guide on Good Manufacturing Practices (GMP) for Excipients and applicable sections of Annex 1 of the EU Guidelines to Good Manufacturing Practice for Medicinal Products.

Conclusion

Cell culture media play a critical role in the development of biologics. In addition to selecting an optimized formulation, a consistent and reliable supply of the media is essential for successful development and manufacturing. To ensure this for our customers, we have implemented several programs across our global network to create a robust supply process including a global raw material and vendor management program, a global quality management system and robust manufacturing network with multiple sites. Through these programs, we deliver the stringent, consistent quality expected by our customers around the world. We will continue to build upon our established systems and operating procedures, applying innovative thinking and new strategies to remain at the leading edge of quality.

Learn more:

- **Tech bulletin Irvine to Lenexa Site Comparability Study**
- **White paper Irvine Dry Powder Media Facility – Validation Harmonization**
- **A New Era for Cell Culture Media, ebook, Medicine Maker**

Global Supply of Dry Powder Media

Clinical to Commercial Supply

We know your business is global and while most vendors will try to convince you of their strategies to mitigate supply disruption, we know the strongest strategy for the bioprocessing industry leaders is security of commercial supply through redundant manufacturing sites.

You do it, so we do it. Here's how we deliver:

Location

Key locations in the US and EU to service the global market.

Description	Lenexa, KS, US	Irvine, UK
Animal component-free/non-animal origin manufacture	Yes	Yes
Segregated, animal component-containing manufacture	Yes	Not at Site
Manufacturing batch size range	25–4000 kg	25–6000 kg
Pin mill technology	Yes w/N_2	Yes w/N_2
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GMP Quality Systems and ISO 9001:2015	Yes	Yes
Packaging capabilities: Standard packaging: Bottles, buckets and barrels EZ BioPAC® and right size weighing	 Yes Yes	 Yes Yes

Raw Materials

Same raw material supply chains and control system for both sites.

Single Global Raw Material Vendor Management Program

- Global Supplier Quality Management
  - Transparency (source materials, process, country of origin)
  - Documentation (Assess-Value-Manage)
  - Risk-based approach
- Supply Chain Procurement
  - Controlled globally
  - Managed locally
  - Integrated with Global Supplier Quality

Manufacturing

Manufacturing process which is scalable and reproducible.

Single Method for Manufacturing Comparable and Reproducible

- Scalable manufacturing technology (IA to GMP)
- Full range of batch sizes (0.5–6000 kg)
- Lot to lot consistent product and process
  - Redundant pin mill technology
  - Proven mixing for homogeneity
  - Automated process controls
  - Equivalent validation standards

Quality

Programs which deliver high quality product.

Global Quality Management System to Support GMP Manufacturing

Key Attributes

- Animal component-free policy
- Electronic document management
- Robust internal audit program
- Change control and notification
- Customer complaint process
- Non-conformance procedure with associated root cause analysis
- Corrective and preventive programs
  - Validation master plans
  - Vendor audit program

Technical Comparability Study

Proven product comparability.

Irvine to Lenexa Site Comparability Study – Dry Powder Media Manufacturing Process

The Comparability Study was performed to demonstrate the manufacturing processes and equipment used to produce cell culture media at the Irvine, Scotland (Irvine) site are comparable to those used to produce media product at the Lenexa, Kansas (Lenexa) site.

Study Conditions

- Single product formulation
- Identical batch size
- Identical raw material lots
- Identical sampling/testing/laboratories

Study Measures

- Chemical composition
- Particle size/bulk density
- Finished product specifications
- Cell culture performance

We used four scientific methods of evaluation. All results demonstrated both sites produce comparable product. Visit our webpage for full details of the Technical Comparability Study:
SigmaAldrich.com/technical-documents/articles/biology/dry-powder-media-manufacturing-process

We are the unique critical supplier for the bioprocess industry which provides two redundant sites for clinical to commercial supply of cell culture dry powder media. Our strategy aligns with your strategy to ensure security in global supply and a lower risk for supply disruption without compromising quality or reproducibility in lot to lot performance.

We also provide outstanding services in programs designed to support your end to end process. Come visit our website and see the solutions we offer:

- Biopharmaceutical Expression Systems
  SigmaAldrich.com/safc/biological-manufacturing
- imMEDIAte ADVANTAGE® and Bioservices
  SigmaAldrich.com/safc/bioprocess/immediate-advantage
- Raw materials for Bioprocessing
  SigmaAldrich.com/safc/bioprocess/pharmagrade
- Bulk Packaging in Liquid and Dry Powder Formats
  SigmaAldrich.com/safc/bioprocess/liquid-solutions
  SigmaAldrich.com/safc/bioprocess/bulk-powder-transfer-bags

imMEDIAte ADVANTAGE®

Small Volume Custom Media

Our imMEDIAte ADVANTAGE® service for pre-GMP, small scale custom media, feeds, supplements and buffers is one example of our support. This expedited service provides you the competitive advantage to complete your development work quicker and accelerate your molecule to market sooner.

We understand quick never replaces quality. Our centers are uniquely designed and equipped with manufacturing technology equivalent to our large scale GMP facilities. This ensures the reliable use and quality of our small volume products.

Key Features of Our IA Program

- **Raw Materials**

  Qualified, same source as our larger facilities with the option to use unique, non-qualified raw materials for your experiments.

- **Operational Management Systems**

  Master formulation management, batch management, controlled process procedures and trained team members.

- **Product Documentation**

  Certificates of Analysis and Safety Data Sheets for all products.

We also understand how valuable every experiment you do equates to time in the race to market. Our service has been developed with the right attributes to ensure the data you generate is trusted first time.

Attribute	Feature	Liquid	Dry Powder
Product	Batch size	1 to 200 L	0.5 to 20 Kg
Water quality	Milli-Q® Ultrapure Water System	✔	N/A
Weigh Requirements	Procedure defined weigh tolerances	✔	✔
Formulation	Defined raw material group rules and order of addition to the process vessel	✔	✔
Milling and blending controls	Designed to ensure homogeneous product. Flowability and bulk density measurements recorded.	N/A	✔
Mixing, Solubility and Filtration	Calibrated mixing tanks with procedure requirements for mixer placement. Formalized check to ensure solubility prior to filtration. Millipore® PES and PVDF membranes (0.2 micron for sterile filtration, 0.1 micron used as needed).	✔	N/A
Product use information	Hydration instructions developed in-house or with customer collaboration.	N/A	✔
Performance	Certificate of Analysis	Appearance, pH, osmolality, solubility, contamination clearance and conductivity (buffers only).	Appearance, pH, osmolality, and solubility.
Packaging	Standard Product Packaging	Sterilized PET bottles with tamper evident seals (100–2000 mL) Sterilized bags with standard connections (1–20 L)	Bottles with tamper evident seal Protective buckets with two liners, desiccant pouch and tamper evident seal

Site to Site Comparability

As your process development may require global involvement, we know the importance of ensuring all of our Centers operate to the same standards. All sites are managed locally with global program oversight and autonomy to ensure the global consistency you expect.

- Similar or same equipment design and execution
- Same procedures for operation and process boundaries
- Proven performance of product comparability

Our imMEDIAte ADVANTAGE® Centers are strategically located to support global process developers with needed access to small volume, expedited service, custom cell culture products.

- Lenexa, Kansas USA
- St. Louis, Missouri USA
- ***NEWLY OPENED*** – Nantong, China
- ***NEWLY OPENED*** – Songdo, South Korea

The work you do today defines the products of tomorrow. Our ability to support your bioprocess development activities is strengthened by more than 40 years of cell culture media formulation and manufacturing expertise. Let us be your trusted partner. Contact your sales representative or sales development personnel for how to order and a personalized quote.

SAFC®

Pharma & Biopharma Raw Material Solutions

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

Learn more
MerckMillipore.com/ccmsupply

For additional information, please visit **www.MerckMillipore.com**
To place an order or receive technical assistance, please visit **www.MerckMillipore.com/contactPS**

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