SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Ensuring Consistency in the Supply of Cell Culture Media

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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.

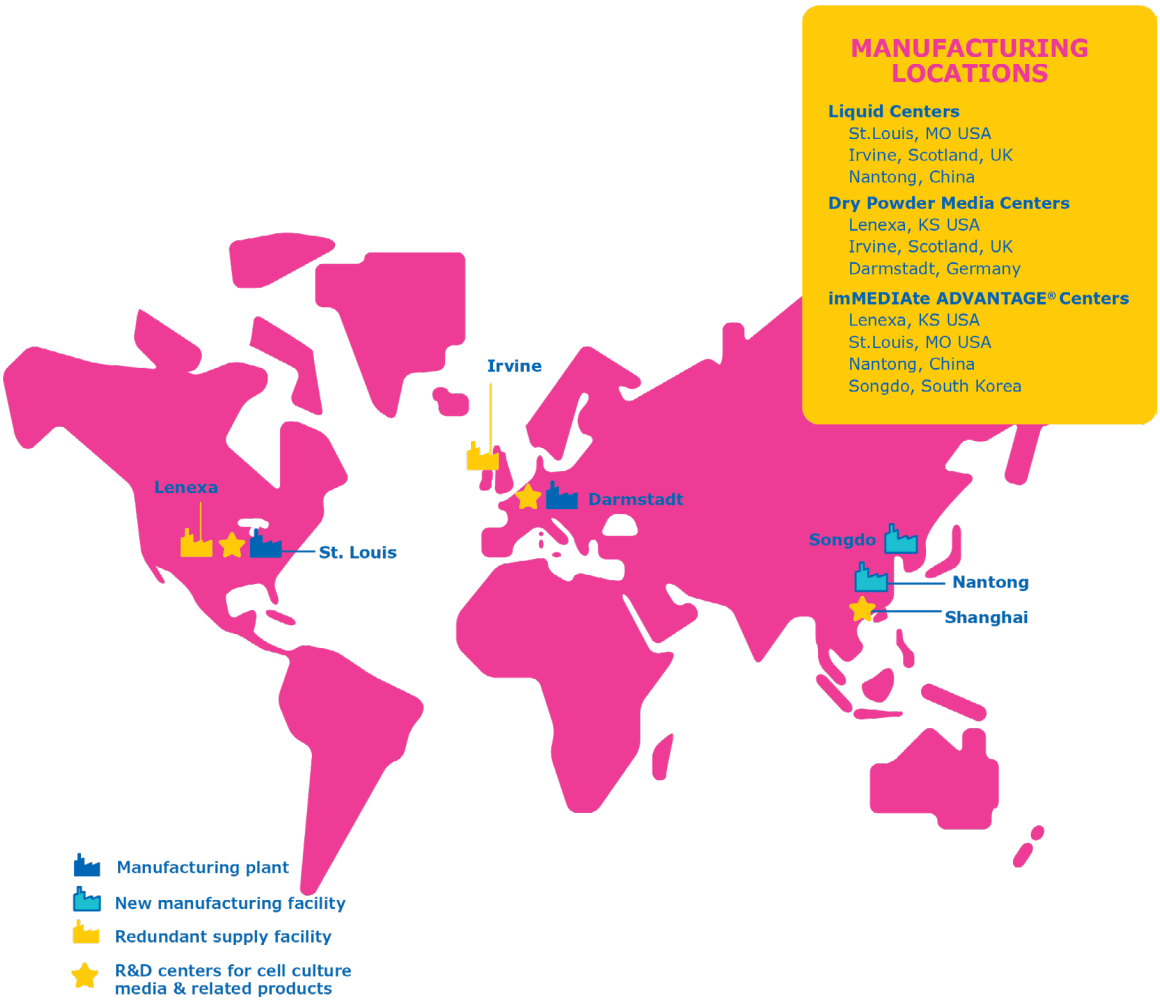

Figure 1. A manufacturing network with multiple sites for liquid and powder, all designed to deliver consistent quality product.

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.

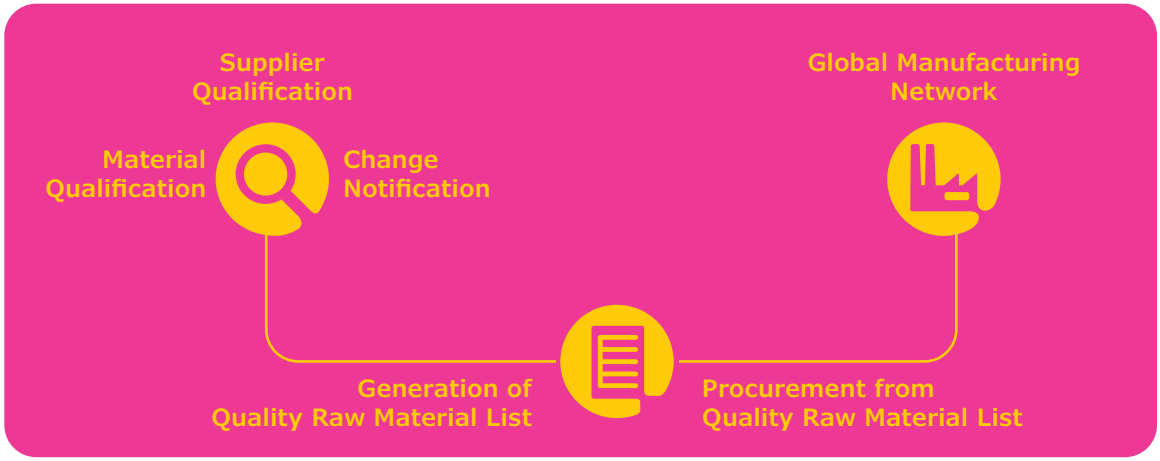

Figure 2. Our global raw materials vendor management program supports all of our manufacturing locations.

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**

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