Erythropoietin Hormone

Erythropoietin Hormone (Molecular model)

Erythropoietin (EPO) is a hormone produced by the kidneys to stimulate the production of oxygen-carrying red blood cells (erythrocytes), as well as to regulate overall blood oxygen levels in the body. When blood oxygen levels are low (hypoxia), EPO is released and travels to the bone marrow, which in turn, stimulates red blood precursor cells to maturity. As blood oxygen levels increase, EPO production decreases.

1989

Amgen received approval for the first recombinant human erythropoietin product (Epogen®) for the treatment of anemia associated with chronic kidney failure. It is also marketed by Johnson & Johnson under the trade name Procrit®. Epogen® would later be approved for anemia due to cancer chemotherapy, anemia due to treatment with certain HIV drugs, and for the reduction of the need for transfusions associated with surgery.
Why Choose SAFC?

“What you do in your business every day impacts the lives of real people. You never forget quality and experience are the building blocks of what you deliver to make lives better. What you count on from people you work with is their expertise and responsiveness.”

SAFC’s industry focus remains the same: continue to build and responsiveness.”

Our goal is to deliver high-quality products and services that drive the end performance of our customer’s products. Our desire is to help make a difference.

Legacy of Expertise

Global cell culture-based manufacturing operations for vaccine, biotherapeutic and diagnostic products have relied on SAFC as a primary supplier since 1971. This long-standing presence in the biopharmaceutical industry as a leading developer and manufacturer of critical raw materials has positioned SAFC to meet the ever changing demands associated with raw material supply.

SAFC continues to focus on:
- Secure ongoing capacity
- Reduced variability and increased safety
- Improved supply efficiencies

An Evolution: Biopharmaceuticals and SAFC
Our media manufacturing sites are Centers of Excellence, established as part of a long-term capital expansion plan. Each facility is designed to support industry capacity and supply requirements well into the next decade. Our dry powder media facilities are strategically located in the established biopharmaceutical regions of North America and Europe. They provide simplified and sustainable supply logistics, as well as expanded flexibility to serve the continued growth in biopharmaceutical manufacturing.

SAFC provides value to an industry that relies on having the highest levels of confidence in a raw material supplier. SAFC has fortified a long-term business continuity plan that focuses on the continuous improvement of the safety, quality and consistency of industrial cell culture media supply. Forward-looking and selective investments show commitment to growing with the industry it serves.

### Media Supply Strategy
**Ensuring Business Continuity**

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### Global Dry Powder Media Redundancy

<table>
<thead>
<tr>
<th>INDUSTRY NEED</th>
<th>SAFC FEATURE</th>
<th>BENEFIT</th>
</tr>
</thead>
</table>
| Clinical-to-Commercial Capability | • Redundant Manufacturing  
• Scalable Technology  
• Legacy of Global Supply | • Secure capacity  
• Reproducibility at scale  
• Manufacturing, warehousing, and cold-chain logistics underpinned by experience |
| Safety, Quality and Performance | • Global Quality Systems and Controls  
• Single Raw Material Management and Sourcing Strategies  
• Raw Material Characterization | • Demonstrated comparability of material supply across sites  
• Batch-to-batch consistency and reproducibility  
• Formulations and specifications driven by “Quality by Design” approach for optimized performance |
| Responsive and Flexible Supply | • Manufacturing in Key Regions (North America and Europe)  
• Modular Manufacturing  
• Electronic In-process Data Monitor and Capture | • Efficiency in supply logistics  
• Shortened lead times / Efficient through-put  
• Real-time transparency of sourcing and manufacturing data |

**TRUE SUPPLY REDUNDANCY**

- 1. Dry Powder Media Redundant Manufacturing
- 2. Liquid Media Dual Manufacturing
- 3. Single Raw Material Supply
- 4. Global Quality Systems and Controls
SAFC dry powder manufacturing sites are strategically located in North America and Europe enabling increased supply efficiencies as well expanded flexibility and capacity in support of the continued growth in biopharmaceuticals. Modern facilities, progressive technologies and more than 40 years of experience is SAFC's commitment to reliable global supply.

Due to the complex nature of cell culture media, SAFC has a multi-dimensional approach in managing the risks most commonly associated with media and by extension, biopharmaceutical manufacturing process. Confirming batch-to-batch consistency with proven processes and well qualified raw materials is crucial to eliminating product variability. Ensuring efficiency and flexibility of:

### Reproducibility
- Scalable Manufacturing Technology
- Single Global Raw Material Program
- Raw Material Characterization Program

### Comparability
- Redundant Pin Mill Equipment
- Global Quality System
- Aligned Local Quality and Supply Chain Programs

### Capability and Capacity
**SAFC Dry Powder Media**

<table>
<thead>
<tr>
<th>North America (Lenexa, KS)</th>
<th>Europe (Irvine, Scotland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal GMP Capacity</td>
<td>&gt; 1000 metric tons per annum</td>
</tr>
<tr>
<td>Production Line Batch Sizes (Kg)</td>
<td>ACF Line 1 (300–4000 Kg)</td>
</tr>
<tr>
<td></td>
<td>ACF Line 2 (25–1000 Kg)</td>
</tr>
<tr>
<td></td>
<td>ACC (15–2100 Kg)</td>
</tr>
</tbody>
</table>

**Production Line Batch Sizes**
- ACF Line 1 (300–4000 Kg)
- ACF Line 2 (25–1000 Kg)
- ACC (15–2100 Kg)

**General Mill Processing**
- ACF Manufacturing Lines (9)
  - Pin Mill
  - Tumble Blenders

**Process Controls**
- Product Temperature During Milking
- CIP/COP (ULS/P Purified Water)
- Electronic Component Bar-code and Weighting
- Planning and Inventory Management Systems (SAP)

**imMEDIAte Advantage® Services**
- Liquid/Powder

**Flexibility**
- Shortening lead times is a driver for all stakeholders in the biopharmaceutical industry. SAFC’s facility design accommodates modular manufacturing for increased efficiencies in throughput.
  - Modular Manufacturing
  - Decoupled Packaging
  - Improved Mill Cycle Time

**Progressive Manufacturing**
- Current regulatory guidelines have placed an increasing amount of accountability on the drug manufacturers themselves for their third party sourcing.
  - Electronic Data Transfer
  - Monitored OSI PI data historian
  - In-line Data Monitoring Capability During Process

**MULTI-FACETED SUPPLY**
- Global
- Secure
- Flexible
Packaging and Logistics
SAFC Dry Powder Media

Packaging and delivery of end product is as important as the manufacturing process itself. SAFC has a flexible approach to both, while maintaining the highest levels of safety and compliance. Manufactured products are stored in GMP-controlled warehouses before shipment. SAFC has the global reach to get product WHERE you need it and WHEN you need it.

Packaging
SAFC provides a range of qualified primary and secondary packaging as well as customization options in consultation with the SAFC Packaging Engineering Team:
- Range of Hard-Walled Containers
- Powder Transfer Bags
- Tamper Evident Seals
- Stability for Custom Container/Closure Options

Logistics and Cold Chain Warehousing
With a network of GMP temperature controlled warehouses in North America, Europe and Singapore, SAFC has the capability to offer a range of shipping and storage options to meet your needs:
- Temperature-controlled Freight
- Temperature Monitoring and Tracking Options
- Just-In-Time Delivery Capable

Global Quality Systems

SAFC media facilities are covered under a comprehensive company-wide Global Quality Management System focused on ensuring the safety, quality, and performance of our products. SAFC is committed to staying at the forefront of all relevant guidelines and regulations. Our client audits, customer complaint process, ISO audits, and Internal Audits drive a culture of continuous improvement of all elements of our Quality Systems.

Key Attributes
- Animal Component-Free Policy
- Electronic Document Management System
- Robust Internal Audit Program
- Change Control and Notification
- Customer Complaint Process
- Non-conformance Procedure – Associated root cause analysis investigation
- Global Vendor Audit Program
- Validation Master Plans
- Corrective and Preventive Program

SAFC GLOBAL QUALITY SYSTEMS

<table>
<thead>
<tr>
<th>Lenexa Facility (NA)</th>
<th>Irvine Facility (EU)</th>
<th>Broadway Facility (NA)</th>
</tr>
</thead>
</table>

Customer Audits
At SAFC, we encourage customer audits. During your audit we invite you to review and evaluate our many Quality System programs designed to maintain product control and allow us to produce high quality products consistently lot after lot. To schedule an audit, please contact your Account Representative.

Quality Control Testing
The SAFC media facilities each have on-site Quality Control laboratories. Standard quality control assays for media are conducted using harmonized current compendia methodologies as shown below.

STANDARD QUALITY CONTROL TESTING FOR CELL CULTURE MEDIA

<table>
<thead>
<tr>
<th>Tested Parameter</th>
<th>Methodology</th>
<th>North America</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Uniformity / color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>USP 791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolarity</td>
<td>USP 785</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioburden (Powder)</td>
<td>USP 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterility (Liquid)</td>
<td>USP 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>USP 85 (Kinetic Chromogenic, Gel clot LAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Growth</td>
<td>Multi-passage, minimum density, and % control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SAFC Supply Chain and Supplier Quality Management teams work in a coordinated effort to support the sourcing and management of our Global Raw Material Management Program, ensuring the program is robust, controlled, and provides sustainable consistent material supply. These groups within SAFC have two primary initiatives:

1. **ENSURING SECURITY OF SUPPLY**
2. **MAINTAINING ACTIVE DIALOG AND RELATIONSHIP WITH SUPPLIERS**

### Integrated Disciplines

#### RAW MATERIAL CHARACTERIZATION
(by SAFC Cell Sciences and Development)

- **Supply Chain Procurement and Inventory Systems**
- **Global Supplier Quality Management**

#### Global Supplier Quality Management

Reducing variability and ensuring the safety, quality, and performance of raw materials used for further manufacturing of cell culture media is our top priority. The Global Supplier Quality team uses a risk-based approach to assess quality and manage the materials, manufacturers, and suppliers. Here are some key approaches:

- **Transparency** (Source Materials, Process, Country of Origin)
- **Documentation**
- **Risk-based approach** (Assess – Value – Manage)

#### Supply Chain Procurement and Inventory Systems

SAFC procurement and inventory systems are managed locally coordinating as part of the global supply chain management program:
- **Controlled Globally**
- **Managed Locally**
- **Integrated with Global Supplier Quality**

- **Irvine Facility (EU)**
- **Lenexa Facility (NA)**
- **Broadway Facility (NA)**

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#### RAW MATERIAL CHARACTERIZATION

Initially an internal effort to study variability across the qualified materials used for cell culture media, the Raw Material Characterization Program by SAFC Cell Sciences and Development has now evolved into an integral part of our larger raw material management organization. Our team of analytical and cell culture scientists provide the scientific rationale for intelligent raw material specifications. This internal program is directly linked to our Global Supplier Quality Vendor Management Program and supports three critical functions:

- **Specifications / Change Notification**
- **Investigations / Troubleshooting**
- **Trace Element Initiative**

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### Trace Element Initiative

Complex and undefined raw materials are a well-known source for potential variability within cell culture media manufacturing processes. Recent trends have revealed a concern due to trace element impurity profiles of composite media formulations, because of the impact these impurities can have on cell/glycoprotein and protein quality. SAFC Cell Sciences and Development teams established the Trace Element Initiative to study these impurities, often a result of starting materials or manufacturing processes. Detection methods include ICP-MS and ICP-OES.
Scale-up and Support Service
Small Volume Custom Media: imMEDIAtE ADVANTAGE®

The work you do today defines the products of tomorrow. SAFC global development and support services are underpinned by more than 40 years of cell culture media manufacturing expertise to help you deliver high quality performing products.

FEASIBILITY – SCALABILITY – MANUFACTURABILITY
Complex materials such as cell culture media are often a significant source of process variability. Our imMEDIAtE Advantage® laboratories in Lenexa, Kansas, St. Louis, Missouri, Irvine, Scotland and Singapore are dedicated to supporting the study and development of this critical component in your process. These labs are uniquely equipped to support developers and manufacturers alike with access to non-GMP small volume custom media with expedited timing. All media formulations are produced using comparable compounding methods and qualified raw materials where possible to provide the consistency in your development studies. With over 40 years of manufacturing experience, SAFC process and analytical scientist understand the need for scalability and routinely support efforts across all stages of development and manufacture.

- Scale-down powder mill and blend process equipment (Lenexa, Kansas)
- Use of Qualified Raw Materials
- Formulation derivatives tracked and archived for reference

VALIDATED SCALE-DOWN PROCESS EQUIPMENT
The imMEDIAtE Advantage® Pin Mill is the same stainless steel pin mill design as the larger full-scale cGMP counterparts.

- Process flow: pre-blend, pin mill, post-blend
- Nitrogen gas: utilized to cool the mill and transport components after particle size reduction
- Milling temperature: criteria is monitored: <40 °C
- Lot size range: 0.5–20.0 Kg

PROCESS SUPPORT
Small volume custom powder and liquid media formulations provided within ten (10) business days1 ideal for:
- Prototyping / Troubleshooting / Scale-up Studies
- Upstream / Downstream Materials
- Powder / Liquid / Liquid Concentrates

ANALYTICAL SUPPORT
Reliable component analysis from SAFC peer material and development scientists who are available to consult on results within 15 business days or less.1
- Material Science Support
- Formulation Optimization
1 Does not include shipping

ASSAY DESCRIPTION (ASSAY NUMBER)

<table>
<thead>
<tr>
<th>Lipids / Phatty Acids (88101-1EA)</th>
<th>Lipids, phospholipids, free fatty acids, triglycerides, cholesteral esters, and total protein analysis by gas chromatography. (Results reported in mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (88102-1A)</td>
<td>Cholesterol analysis performed by reverse phase HPLC. (Results reported in mg/mL)</td>
</tr>
<tr>
<td>Free Amino Acids (88103-6A)</td>
<td>Amino Acids separated and analyzed by HPLC. (Results are reported as mg/L)</td>
</tr>
<tr>
<td>Standard Element – ICP (88118)</td>
<td>Standard elemental analysis by ICP-OES. Standard Elements: Calcium, Magnesium, Sodium, Sulphate, Potassium and Phosphates. (Results reported in g/L)</td>
</tr>
<tr>
<td>Trace Element – ICP (88119)</td>
<td>Trace elemental analysis by ICP-OES. Trace Elements: Barium, Bismuth, Cadmium, Cobalt, Copper (II), Lead, Mercury, Manganese, Nickel, Silver, Strontium, and Tellurium. (Results reported in ppm or mg/L)</td>
</tr>
<tr>
<td>Vitamin B12 w/ Folic Acid (88128-1EA)</td>
<td>Water soluble vitamins, including B12, through B12, analysis by HPLC. (Results reported in mcg/mL)</td>
</tr>
<tr>
<td>Glucose (88202)</td>
<td>Glucose measured by the hexokinase test method. (Results reported in mg/dL)</td>
</tr>
<tr>
<td>Endotoxin (88204)</td>
<td>Endotoxin determined by kinetic, chromogenic Limulus Amoebocyte Lyase method. (Results reported in EU/mL or EU/g)</td>
</tr>
<tr>
<td>Osmolality (88206)</td>
<td>Osmolality determined by freeze-point depression. (Results are reported in mOsm/kg H2O)</td>
</tr>
<tr>
<td>pH (88207)</td>
<td>pH measured with a pH meter. (Results reported to nearest tenth)</td>
</tr>
<tr>
<td>Bioburden (88208)</td>
<td>Standard USP test for Bioburden using membrane / filtration. (Results reported as CFU/g or CFU/100mL)</td>
</tr>
<tr>
<td>Appearance (88210)</td>
<td>Appearance determined by a standard operating procedure with consistent requirements for visuals. (Results are reported as satisfactory or unsatisfactory with a description of observation)</td>
</tr>
</tbody>
</table>

Additional testing may be available upon request.
Contact your Account Representative for further assistance.

SAFC Global Dry Powder Media: Redundant Supply

SAFC Global Development and Support Services

1 Formulation Optimization

Monoclonal Antibody
An antibody is produced by a single clone of cells or cell line and consisting of identical antibody molecules. Monoclonal antibodies made in large quantities are a cornerstone of biotechnologic manufacturing. There are multiple types of monoclonal antibodies and each is developed to bind specifically to a particular substance in the body.

sigma-aldrich.com/safc