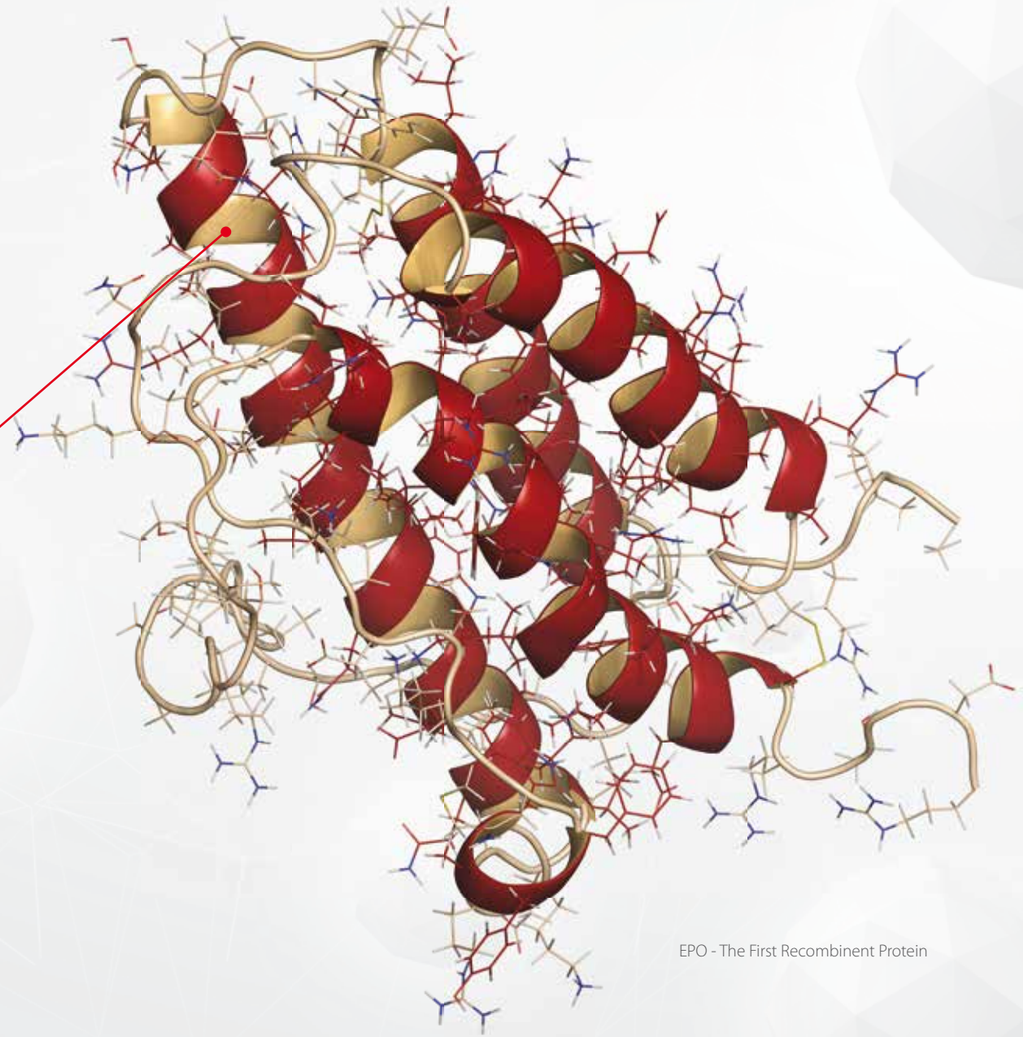
SAFC®

DRY POWDER MEDIA
GLOBAL SUPPLY

SIGMA-ALDRICH®

DRY POWDER MEDIA
GLOBAL SUPPLY



EPO - The First Recombinent Protein

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 erythropoetin 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.

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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 Biosciences Expertise & Responsiveness, 2006

SAFC's industry focus remains the same: continue to build scientific knowledge, invest in capabilities and find solutions to the challenges in an ever-evolving marketplace.

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.

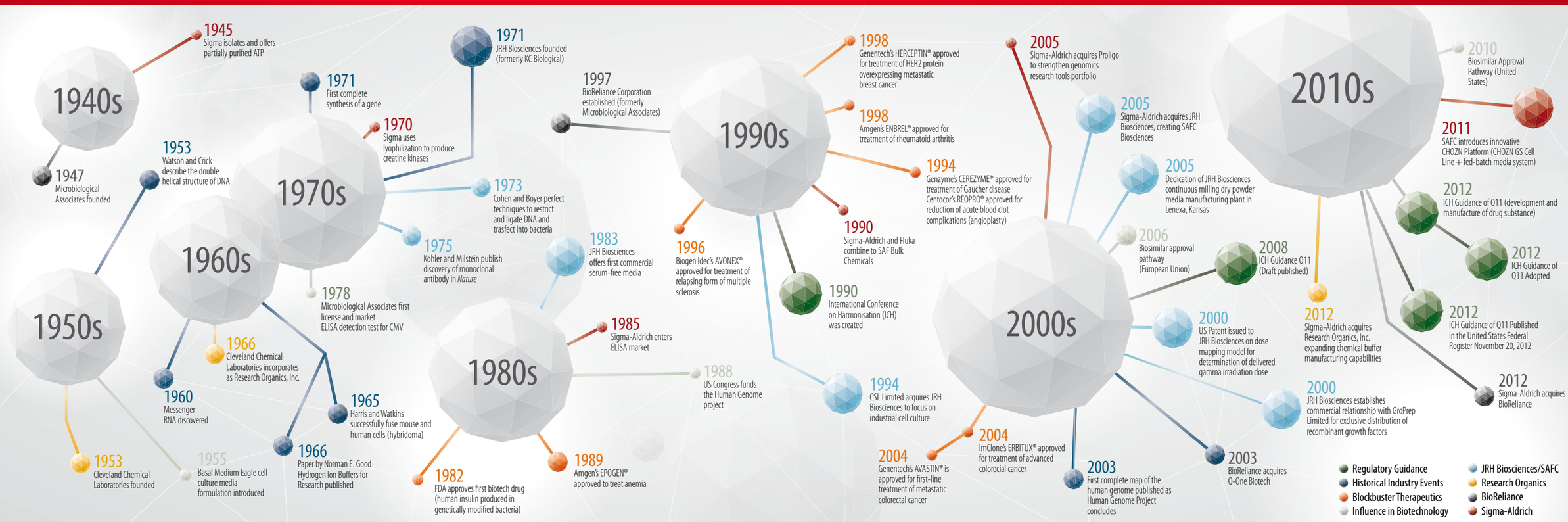
Legacy of Expertise

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



Media Supply Strategy

Ensuring Business Continuity

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.

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**

Global Dry Powder Media Redundancy

INDUSTRY NEED	SAFC FEATURE	BENEFIT
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

Capability and Capacity

SAFC Dry Powder Media

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

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

	North America (Lenexa, KS)	Europe (Irvine, Scotland)
Facility		
Nominal GMP Capacity	> 1000 metric tons per annum	> 1000 metric tons per annum
Production Line Batch Sizes (KG)	ACF Line 1 (300–4000 Kg)	ACF Line 1 (600–6000 Kg)
	ACF Line 2 (25–1000 Kg)	ACF Line 2 (25–750 Kg)
	ACC (10–2100 Kg)	
General Mill Processing		
ACF Manufacturing Lines (#)	2	2
Pin Mill	●	●
Blending Type	Conical Blenders	Tumble Blenders
Closed Process Unit Operations	●	●
Semi-automated Packaging	●	●
Process Controls		
Product Temperature During Milling	●	●
CIP/COP (USP/EP Purified Water)	●	●
Electronic Component Bar-code and Weighing	●	●
Planning and Inventory Management Systems (SAP)	●	●
imMEDIAte Advantage® Services	Liquid/Powder	Liquid

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
REACH

AMERICAS | EUROPE | ASIA PACIFIC

SAFC Global Dry Powder Media: Redundant Supply

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

Lenexa Facility (NA)	Irvine Facility (EU)	Broadway Facility (NA)
• ISO 9001: 2008 • 21CFR820	• ISO 9001: 2008 • ISO 13485: 2003 • 21CFR820	• ISO 9001: 2008 • 21CFR820

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

Finished Product Testing	Methodology	North America	Europe
Appearance	Uniformity / color	●	●
pH	USP 791	●	●
Osmolarity	USP 785	●	●
Bioburden (Powder)	USP 61	●	●
Sterility (Liquid)	USP 71	●	●
Endotoxin	USP 85 (Kinetic Chromogenic, Gel clot LAL)	●	●
Cell Growth	Multi-passage, minimum density, and % control	●	●

Raw Materials

SAFC Dry Powder Media

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**

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.

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

Material Qualification | **Supplier Qualification** | **Change Notification**

Generation of Qualified Raw Materials List

Single Global Raw Material Vendor Management Program

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

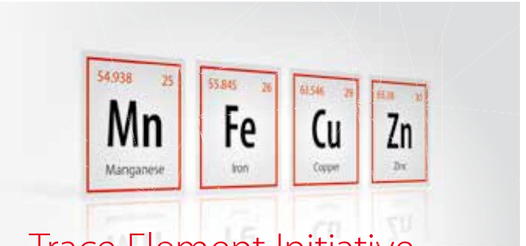
Irvine Facility (EU) Powder / Liquid | **Lenexa Facility (NA)** Powder | **Broadway Facility (NA)** Liquid

Procurement from Qualified Raw Materials List

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



Trace Element Initiative

Complex and undefined raw materials are a well known source for potential variability within biomanufacturing processes. Recent trends, however, show a rising concern due to trace element impurity profiles of composite media formulations because of the impact these impurities can have on glycosylation patterns and protein quality. SAFC Cell Sciences and Development team 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

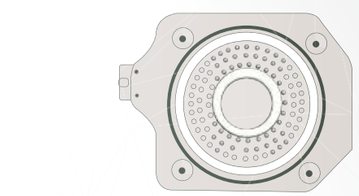
Complex materials such as cell culture media are often a significant source of process variability. Our imMEDIAte Advantage® laboratories in Lenexa, Kansas, St. Louis, Missouri, Irvine, Scotland and Singapore are dedicated to supporting the study and development of this critical component in your process. 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

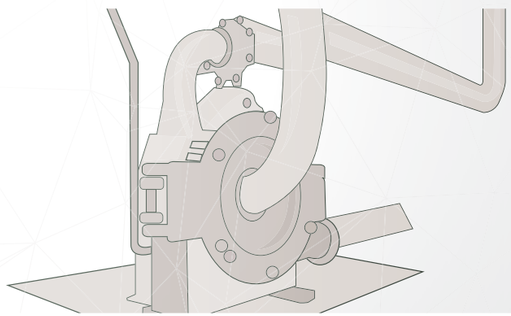
VALIDATED SCALE-DOWN PROCESS EQUIPMENT

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



Front View:
Pin Mill Disk



TIME MATTERS

RIGHT TOOLS + RIGHT SUPPORT = BETTER DECISIONS

ASSAY DESCRIPTION (ASSAY NUMBER)
Lipids / Fatty Acids (88101-1EA) Lipids, phospholipids, free fatty acids, triglycerides, cholesterol esters, and total protein analysis by gas chromatography. (Results reported in mcg/mL)
Cholesterol (88102-1EA) Cholesterol analysis performed by reverse phase HPLC. (Results reported in mcg/mL)
Free Amino Acids (88103-EA) Amino Acids separated and analyzed by HPLC. (Results are reported as mg/L)
Standard Element – ICP (88119) Standard elemental analysis by ICP-OES. Standard Elements: Calcium, Magnesium, Sodium, Sulphur, Potassium and Phosphate. (Results reported in g/L)
Trace Element – ICP (88120) Trace elemental analysis by ICP-OES. Trace Elements: Barium, Bismuth, Cadium, Cobalt, Chromium, Copper, Iron, Lithium, Manganese, Molybdenum, Nickel, Lead, Stronium, and Zinc. (Results reported in ppm or mg/L)
Vitamin B_{12} w/ Folic Acid (88128-1EA) Water-soluble vitamins, including B_1 through B_{12}, analysis by HPLC. (Results reported in mg/L)
Glucose (88202) Glucose measured by the hexokinase test method. (Results reported in mg/dL)
Endotoxin (88204) Endotoxin determined by kinetic chromogenic Limulus Amoebocyte Lysate method. (Results reported in EU/mL or EU/g)
Osmolality (88206) Osmolality determined by freeze-point depression. (Results are reported in mOsm/kg H_2O)
pH (88207) pH measured with a pH meter. (Results reported to nearest tenth)
Bioburden (88208) Standard USP test for Bioburden using membrane filtration. (Results reported as CFU/g or CFU/100mL)
Appearance (88210) Appearance determined by a standard operating procedure with consistent requirements for verbiage.
Solubility (88211) Solubility determined by a standard operating procedure with requirement of soluble at 30 minutes at 25 °C , clear and free of particulate. (Results are reported as satisfactory or unsatisfactory with a description of observation.)

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

Process Support

Small volume custom powder and liquid media formulations provided within ten (10) business days[1] ideal for:

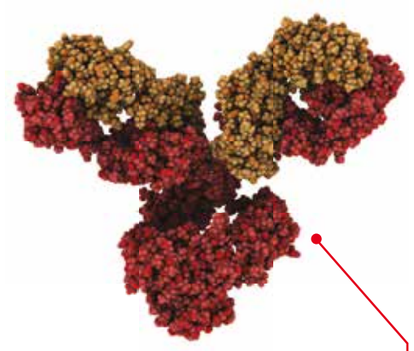
- Prototyping / Troubleshooting / Scale-up Studies
- Upstream / Downstream Materials
- Powder / Liquid / Liquid Concentrates

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



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 biotherapeutic manufacturing. There are multiple types of monoclonal antibodies and each is developed to bind specifically to a particular substance in the body.

SAFC®

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