# Enhanced Quality Product Documentation

Tricine
PharmaGrade, Manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical production, Suitable for cell culture.

Product Number RES3077T-A7

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- Product Regulatory Datasheet
- SAFC Cleveland Quality Overview
- SAFC Cleveland Site and Supply Chain Security Overview
- SAFC Cleveland ISO9001:2008 Certificate

# Product Regulatory Datasheet

## 1. General Product Information

| Product Name | Tricine |
|---|---|
| Product Number | RES3077T-A7 |
| Qualifier | PharmaGrade, Manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical production, Suitable for cell culture. |
| Quality Level | Elite |
| Related documents | SAFC Cleveland Site Quality Overview<br>SAFC Cleveland Site and Supply Chain Security Overview<br>SAFC Cleveland Site ISO 9001:2008 Certificate |

## 2. Manufacturing, Packaging, Release Site and Supplier Information

- Site of manufacturing, testing, packaging and product release:
  SAFC, 4353 East 49$^{th}$ Street, Cleveland, Ohio 44125 USA
- This product is manufactured using multi-purpose equipment.

## 3. Physico-chemical Information

### 3.1 Synonyms

- N-Tris(hydroxymethyl)methylglycine

### 3.2 Molecular Formula:

- C6H13NO5

### 3.3 Molecular Mass

- 179.2

### 3.4 CAS Number

- 5704-04-1

### 3.5 Origin

- The product RES3077T-A7 is manufactured synthetically. Only raw materials of synthetic origin are used.

### 3.6 Manufacturing process

- Chemical synthesis utilizing crystallization, isolation and purification processes.
- Typical contact surfaces during production are glass, stainless steel, polyproplyene and teflon.
- Equipment cleaning is verified.
- Revision controlled master batch records are used.

### 3.7 Specification *

| Analytical items | Specifications |
|---|---|
| Appearance | White crystalline powder |
| Solubility | Clear, colorless solution |
| Melting Point | Meets requirements |
| Infrared | Must conform to known reference |
| Cytotoxicity | Passes test |
| DNase - Endonuclease/Exonuclease | Passes test |
| DNase - Nickase | Passes test |
| RNase | Passes test |
| Protease | Passes test |

| | |
|---|---|
| Assay | >=99.0% |
| Water Content | <=1.0 % |
| Ultraviolet Absorbance A(260 nm) | <=0.04 Abs unit |
| Ultraviolet Absorbance A(280 nm) | <=0.02 Abs unit |
| Trace Metal Analysis Aluminum | <=5.0ppm |
| Trace Metal Analysis Antimony | <=5.0ppm |
| Trace Metal Analysis Arsenic | <=3.0ppm |
| Trace Metal Analysis Barium | <=5.0ppm |
| Trace Metal Analysis Bismuth | <=5.0ppm |
| Trace Metal Analysis Cadmium | <=5.0ppm |
| Trace Metal Analysis Calcium | <=10.0ppm |
| Trace Metal Analysis Chromium | <=5.0ppm |
| Trace Metal Analysis Cobalt | <=5.0ppm |
| Trace Metal Analysis Copper | <=5.0ppm |
| Trace Metal Analysis Iron | <=15.0ppm |
| Trace Metal Analysis Lead | <=5.0ppm |
| Trace Metal Analysis Lithium | <=5.0ppm |
| Trace Metal Analysis Magnesium | <=5.0ppm |
| Trace Metal Analysis Manganese | <=5.0ppm |
| Trace Metal Analysis Molybdenum | <=5.0ppm |
| Trace Metal Analysis Nickel | <=5.0ppm |
| Trace Metal Analysis Sodium | <=50.0ppm |
| Trace Metal Analysis Zinc | <=5.0ppm |
| Bioburden | <=100 CFU/g |
| Endotoxin | <=50 EU/g |
| Yeast & Mold | <=100 CFU/g |

- * Current specification can be accessed from website.

### 3.8 Batch results

- Certificates of Analysis are available for each lot produced.

## 4. Regulatory Information

### 4.1 Compendial compliance

- Not applicable.

### 4.2 Master file

- Drug Master File (DMF) is not available for this product.
- EDQM Certificate of Suitability is not currently available for this product.
- Please contact Sigma-Aldrich for further regulatory support.

### 4.3 BSE/TSE and viral risk statement

- This product is not produced using any components of animal origin (bovine, ovine or caprine) and is considered BSE/TSE free.

### 4.4 Allergen information

- This product is not produced with any known major food allergens (as defined by the FDA and WHO).

### 4.5 GMO information

- The product is GMO free and not produced using GMOs.

**4.6 Residual solvents information**

- The product is produced using Class 2 residual solvent Methanol.

**4.7 Metal catalyst and metal reagent residues**

- The product is produced without use of metal catalyst or metal reagent.

**4.8 Kosher/Halal status**

- No status.

**4.9 Melamine statement**

- This product is Melamine-free.

## 5. Miscellaneous Product Information

**5.1 Explanation of the lot/batch numbering system**

- The product is manufactured in a batch process.
- Batch size is approximately 445kg.
- Each produced batch is identified by a specific, unique batch number.
- The batch number has a first letter corresponding to a year, 5 sequential global counter digits, a dash and the Julian date.
- E12345-13022
- (E) = 2013  (12345) = Serialized global counter  (13022) = January 2, 2013

**5.2 Expiration date and/or recommended re-evaluation interval**

- Recommended retest date is 730 days from the date of manufacture.

### 5.3 Handling, Shipping Conditions and Long-term Storage Recommendation

- If stored in the original unopened containers under specified conditions, no significant change of the material can be observed.
- Storage and shipping conditions:
  - Store at room temperature.
  - Ship at ambient temperature.

### 5.4 Packaging

- SAFC Cleveland can accommodate various package sizes.
- Typical materials of construction consist of:
  1. Retail sizes HDPE plastic containers.
  2. Bulk quantities HDPE Plastic Drums or Fiber Drum with double lined LDPE liners.

## 6. Revision History

- Revision 1.0, February 2013

## 7. Contact Information

- Please contact your local Sigma-Aldrich representative for more information.

# SAFC Cleveland Quality Overview

**Statement 1 - General**

SAFC Cleveland is a leading supplier of high purity biochemicals for use in molecular biology, diagnostics, cell culture, pharmaceuticals, biopharmaceuticals, life sciences and biotechnology.

## 1. Facility overview

### 1.1 Scope

4353 East 49$^{th}$ Street, Cleveland, Ohio 44125 USA

### 1.2 Corporate ownership

SAFC Cleveland is a wholly owned subsidiary of Sigma-Aldrich Corporation, St. Louis, Missouri, USA.

### 1.3 Customer audit policy

SAFC Cleveland welcomes customer audits.

### 1.4 Site details

General site information:

- 12 buildings covering 90,000 ft$^2$ on 10 acres of property.
- ~70 employees
- Production can operate in 2 shifts, up to 7 days/week.
- Site activities conducted:
  SAFC Cleveland supplies a product line that includes biological buffers, reagent biochemicals, molecular biology grade products, enzyme substrates, fluorescent compounds, amino acids and derivatives, ACS reagents, USP and FCC products, neurochemicals and plant tissue culture reagents. Custom synthesis services.
- Each in-process and batch lot is tested to conform to internal and customer specifications. Lot specific certificates of analysis are available for each lot.
- QC testing capabilities include aqueous, non-aqueous, redox, complexometic and argentometric titrations, Karl Fisher titrations, melting point, UV-Vis analysis, infrared, identification, conductivity, elemental analysis, GC and HPLC. TMA is conducted on all biological buffers and applicable reagent biochemicals.
- Primary applications of products: Chemicals used in diagnostic, biopharma, cell culture and life science disciplines.
- There is no production or use of antibiotics/steroids/hormones at SAFC Cleveland.
- SAFC Cleveland monitors processes to ensure conformance to specifications and procedures. Quality inspects all batch lots, utilizes statistical process controls and adheres to ISO standards in equipment qualification, product testing, method validation, change control, impurity profiles and stability studies. Quality tests and authorizes release of product.
- SAFC Cleveland uses approved sub-contractors for preventative maintenance and calibration services.

## 2. Compliance Evidence

### 2.1 ISO registration number and certificates

ISO 9001:2008, Management Certification of North America, Registration No. 0002025

### 2.2 GMP inspections by competent authorities (Regulatory Agencies):

SAFC Cleveland does not operate as a GMP facility per ICH Q7.

### 2.3 Other certifications / registrations

SAFC Cleveland does not have other certifications.

## 3. Quality Management Systems Compliance Details

SAFC Cleveland operates to current ISO guidelines and also uses IPEC-PQG GMP guidance document for continuous improvement activities for the biopharmaceutical market.

### 3.1 Quality Management Systems

**General**

- Sigma-Aldrich has established a Corporate Quality Policy and SAFC Cleveland has a comprehensive Quality Manual.
- The management system is certified to ISO 9001:2008. Internal audits of the Quality Management System are conducted annually per the management approved schedule to ensure ISO conformance.
- Monitor the effectiveness of the Quality Management System and develops strategic continuous improvement plans and goals, in compliance with ISO 9001:2008 standards;
- Manage internal and external audit program.
- Prepare and host customers during customer audit.
- Manage Supplier Qualification/Approval status.
- Manage Customer Specifications.
- Manage CAPA System and Change Management System.
- MRP system part number input, obsolescence and maintenance, Bill of Material accuracy, inventory corrections, and sampling and lot requirements of part numbers.
- Document and maintain control records associated with manufacturing and quality control.
- Document control related to ISO 9001:2008 documentation and training.
- New employee quality related training.
- Disseminate controlled documents to distribution locations and archive obsolete documents.
- Complete trend and data review for MRB and Management Review.

**Documentation**

- Written procedures and approved work instructions are maintained to control documents and data used for the manufacture and verification of SAFC Cleveland products in accordance with the requirements of ISO 9001:2008.
- Quality is responsible for controlled documents and databases, which identify the current revision, effective date and revision history of the document. The database also provides an electronic link to the controlled documents.
- All activities are defined in Standard Operating Procedures, Manufacturing Procedures and other supportive documents.
- All documents have a unique identifier, revision number and effective date.
- All activities connected to the manufacturing and testing of a batch (batch record) and the equipment logs are stored electronically, for a minimum of 5 years, after verifying there is no inventory.

**Change Control**

- Quality reviews and acknowledges all process variations and deviations. Change control requirements of the customer are evaluated. Manufacturing and Quality evaluate change requirements prior to manufacture and/or release to customers. Quality is responsible for change approval and customer notification. Customer notification on changes is possible provided that a specific agreement is established between Sigma-Aldrich and the customer, and per previously established requirements.

### 3.2 Management Responsibility

- First and foremost, management emphasizes the importance of meeting customer needs as well as statutory and regulatory requirements. Customer focus is what we do best at SAFC Cleveland. Site goals are aligned with the quality policy.
- Verification of the Quality System is confirmed through audits.
- Customer needs and product requirements are part of our SOPs and specifications. We can exchange and adopt customer test methods.
- Trends and control charts are used to assess goals.
- CAPA and non-conforming product SOPs help analyze and advance processes.
- Management review is conducted quarterly to review company and departmental goals. Vendor metrics, qualification status, complaints, rejections inventory and cycle counts, processing issues, customer report cards, new products and corrective and preventive actions are reviewed at this time.
- Customer satisfaction is gauged not only by meeting specifications, supplier scorecards but also in the perceptions relayed back to SAFC Cleveland when interacting with customers.

### 3.3 Resource Management

- Management assigns resources and responsibility where needed to ensure that the quality management system operates efficiently.
- All equipment is subject to written preventive maintenance procedures and qualification programs, if required.
- Work environment is defined and maintained to ensure safe and compliant manufacture of products.
- Facilities Meetings are scheduled to discuss resource and facility needs.

### 3.4 Product Realization

- Planning: Make to stock based upon First In, First Out (FIFO) or make to order.
- Design and Development: New product offer or custom.
- Purchasing: Global Supply Chain capabilities with vendor management per quality, delivery, pricing, and compliance to regulatory requirements.
- Production and Service: Original manufacturer and/or repackager with quality control and quality assurance. Pre and post-sales technical and compliance services. Global distribution capabilities.
- Measuring and Monitoring Devices: Calibration and preventive maintenance is completed per schedule.

### 3.5 Measurement, Analysis and Improvement

- Corrective and Preventive processes The CAPA process defines steps to review the non-conformance, determine the root cause, evaluate the need for action to prevent recurrence, implement action, record action, and review trends and effectiveness.
- Internal Audit Internal audits are completed to verify compliance of the quality management system with the planned arrangements, customer requirements, good manufacturing practice requirements and the requirements of the ISO 9001:2008 standard.
- Nonconforming product controls, electronic, physical segregation, designated areas with signage and within our MRP system, product resides in a quarantine/inspection status “I” until Quality Control determines it to be non-conforming. Once determined to be non-conforming, product is moved to "H" hold or reject status. No product can be shipped from the MRP system in a "H" Hold status. Non-conforming product and/or raw material are physically segregated from other product.
- Continuous Improvement, 5S programs Key performance indicators, quality objectives and goals are discussed and re-aligned at Management Review and Material Review Board meetings. These guide the continuous improvement of our business and operations.

## 4. Miscellaneous Site Information

- Statement: social responsibility our sustainability program is a combination of environmental, social, and economic considerations and compliance to all regulations is the foundation.
- Batch explanation: The batch number has a first letter corresponding to a year, 5 sequential global counter digits, a dash and the Julian date.
  E12345-13022
- (E) = 2013 (12345) = Serialized global counter (13022) = January 2, 2013
- Double De-ionized reverse osmosis water with UV treatment is monitored and used in production processes
- The Enhanced Quality Program (EQP) is an initiative to provide quality assurance activities that are above what is expected of standard research products. The SAFC EQP provides clearly defined quality traits across a four-level value system: Standard, Premium, Elite and GMP. These tiers reflect various levels of product quality and documentation, according to the application for the product. SAFC Cleveland participates in Standard, Premium and Elite Quality tier products. For more information about EQP, please visit www.safcsupplysolutions.com/eqp.
- SAFC Cleveland has redundancy in its processing equipment to allow for proper PM activities and applicable shutdowns. A segregated packaging area exists with separate rooms with isolated ventilation, air handling and dust control systems.
- Please contact your local Sigma-Aldrich representative for more information.

# SAFC Cleveland Site and Supply Chain Security Overview

## 1. Scope

- SAFC Cleveland 4353 East 49th Street, Cleveland, Ohio 44125 USA
- Corporate ownership:
- SAFC Cleveland is a wholly owned subsidiary of Sigma-Aldrich Corporation, 3050 Spruce Street, Saint Louis, MO 63103 USA.

## 2. Supply Chain Security

The following controls are executed to ensure the integrity and security of the product in transit from SAFC Cleveland to the end user:

- All packing/labeling operations are performed onsite.
- All products are packed in tamper evident packaging.
- Environmental controls can be implemented during transport (e.g. to control cold chain, if applicable).
- Intermediate storage locations are monitored and reviewed on a routine bases. Cold storage units are mapped and revalidated on a two year interval. Full inventory audits occur at least once a year.
- Only new ISPM 15 certified heat treated wood pallets or plastic pallets are used during shipment.

## 3. Security Information

### 3.1 Scope of Security Plan

- Multidisciplinary team consisting of IT, HR and Quality.
- Site access control
  - Perimeter fencing around facility property.
  - Employees are issued key FOBs and approved by quality for access.
  - 24 hour internal network based DVR system accessible from the outside via secure VPN access.

### 3.2 Personnel Security

- Pre-employment background checks.
- Background checks on temporary and contract personnel.
- Individual employee electronic key FOB and keys are collected upon leaving the company to avoid unapproved access to the site. Contractors use temporary electronic key FOB which is returned daily.

## 4. Environmental Health & Safety Program (EHS)

- Implementation of new requirements into the existing integrated management system, including quality and EHS.
- Each employee receives initial and ongoing training regarding safety, health and environment.
- Management of Pest control program with relation to GMPs
- There are no registrations to ISO 14001, OHSAS 18001 and/or Responsible Care.
- A documented emergency response plan consists of clear responsibilities and defined processes in case of events related to EHS.

## 5. Miscellaneous site Information

- Documented integrated contingency plan for business continuity.

## 6. Contact Information

Please contact your local Sigma-Aldrich representative for more information.

# CERTIFICATE OF REGISTRATION

Management Certification
MCNA
of North America

This is to certify that the
Quality Management system of:

## Research Organics, Inc., DBA SAFC Cleveland

**4353 East 49th Street**
**Cleveland, OH 44125**
**USA**

has been assessed and found complying with the requirements of

## ISO 9001:2008

Approval is hereby granted for registration providing the
Certification rules and conditions are observed at all times.

**Certification Scope:**

**Manufacturer and Innovator of High Purity Bio-chemicals**

**Certificate Number:** 0002025

**Issue Date:** 10-Nov-2012

**Audit Date:** 13-Oct-2012

**Original Registration Date:** 15-Sep-2000

**Expiration Date:** 11-Nov-2015

Thomas W. Harris

On Behalf of:
**Management Certification NA**

ANAB ACCREDITED

This certificate is non-transferable and remains the property of Management Certification of North America, The Woodlands, Texas, to whom it must be returned upon request.