



Enhanced Quality Product Documentation

HEPES

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

Product Number PHG0001

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Product Regulatory Datasheet



1. General Product Information

Product Name	HEPES
Product Number	PHG0001
Qualifier	PharmaGrade, Manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical productions, suitable for cell culture.
Quality Level	Elite
Related documents	Cherokee Buffers Site Quality Overview Cherokee Buffers Site and Supply Chain Security Overview

2. Manufacturing, Packaging, Release Site and Supplier Information

- Site of manufacturing, packaging and product release: Sigma-Aldrich Corporation, 3300 S. Second St., St. Louis, MO 63118 USA, internally referred to as the Cherokee site.
- Site of testing: Sigma-Aldrich Corporation, 3500 Dekalb St., St. Louis, MO 63118 USA,
- This product is manufactured under appropriate controls to be used in pharma or biopharmaceutical production.
- This product is manufactured using multi-purpose equipment.

3. Physico-chemical Information

3.1 Synonyms

- 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
- N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)

3.2 Linear Formula:

- $\text{CH}_2\text{OHCH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{SO}_3\text{H}$

3.3 Molecular Formula:

- $\text{C}_8\text{H}_{18}\text{N}_2\text{O}_4\text{S}$

3.4 Molecular Mass

- 238.30 g/mol

3.5 CAS Number

- 7365-45-9

3.6 Origin

- The product PHG0001 is manufactured by organic synthesis. Only raw materials of synthetic origin are used.

3.7 Manufacturing process

- Formation of HEPES from raw materials by organic synthesis and subsequent purification by ion-exchange chromatography, charcoal filtration and crystallization.
- Contact surfaces during production are mainly Glass, Stainless Steel and PTFE (Teflon), with some Pliosyn™ Ultra-High Molecular Weight Polyethylene (UHMWPE) and Clear Specular® Cross-Linked Polyethylene (XLPE) hoses, and Enduraflex rubber blend column lining.
- Equipment cleaning is verified.
- While this product does not officially fall under ICH Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients, manufacturing process design is based on this standard and uses Failure Modes and Effects Analysis (FMEA) process where Critical Quality Attributes and Critical Control Points controlling them are identified. Any changes to these parameters, or deviations around them, are appropriately evaluated.

3.8 Specification (Current specification can be accessed from website)

Analytical items	Specifications
Appearance (Color)	White
Appearance (Form)	Powder
Solubility (Color)	Colorless
Solubility (Turbidity) 1.0 M in H ₂ O	Clear
Infrared Spectrum	Conforms to Structure
Water (by Karl Fisher)	≤ 0.5%
Assay (anhydrous basis)	≥ 99.5%
pH 1% in H ₂ O	4.7-5.3
Residue on Ignition (Ash)	≤ 0.1%
UV Absorbance 260 nm 1.0 M H ₂ O	≤ 0.05
UV Absorbance 280 nm 1.0 M H ₂ O	≤ 0.04
Aluminum (Al)	≤ 5.0 ppm
Bismuth (Bi)	≤ 5.0 ppm
Lead (Pb)	≤ 5.0 ppm
Barium (Ba)	≤ 5.0 ppm
Cadmium (Cd)	≤ 5.0 ppm
Copper (Cu)	≤ 5.0 ppm
Zinc (Zn)	≤ 5.0 ppm
Cobalt (Co)	≤ 5.0 ppm
Calcium (Ca)	≤ 30.0 ppm
Chromium (Cr)	≤ 5.0 ppm
Magnesium (Mg)	≤ 5.0 ppm
Manganese (Mn)	≤ 5.0 ppm
Iron (Fe)	≤ 5.0 ppm
Lithium (Li)	≤ 5.0 ppm
Molybdenum (Mo)	≤ 5.0 ppm
Nickel (Ni)	≤ 5.0 ppm
Arsenic (As)	≤ 3.0 ppm
Antimony (Sb)	≤ 5.0 ppm
DNAse, Exonuclease Detection	Pass
NICKase, Endonuclease Detection	Pass
Rnase Detection	Pass
Protease Detection	Pass
Endotoxin	≤ 50 EU/g
Total Aerobic Microbial Count	≤ 100 CFU/g

Total Yeast and Mold	≤ 100 CFU/g
Cytotoxicity	Pass
Recommended Retest Period	4 Years

3.9 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 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 components from animal species (bovine, ovine or caprine) known to harbor BSE/TSE, and is therefore considered of negligible risk. The buffers facility and its equipment are animal-component 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 not produced using GMOs and is considered GMO free.

4.6 Residual solvents information

- The product is produced using methanol, a Class 2 residual solvent, and tested by GC analysis to show that Methanol content is <3000 ppm.

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 material is not assayed by a test that detects nitrogen. This product is considered negligible risk for melamine contamination.

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 2000 kg.
- Each produced batch is identified by a specific, unique batch number.
- The batch number consists of 4 characters followed by four digits, e.g., SLBB1234.

5.2 Expiration date and/or recommended re-evaluation interval

- The recommended retest period of 4 years is based on re-examination of stock material from the date of initial release.

5.3 Handling, Shipping Conditions and Long-term Storage Recommendation

- If stored in the original unopened containers under the specified conditions, no significant change of the material can be observed over the retest period.
- Storage and shipping conditions:
 - Storage at ambient temperature in a dry storage place

- Shipping at ambient temperature

5.4 Packaging

- SAFC Cherokee can accommodate various package sizes.
- Typical material of construction consist of 1. Retail sizes HDPE plastic containers. 2. Bulk quantities HDPE Plastic Drums with double lined LDPE liners.

6. Revision History

- Please note that updates are communicated to customers with Change Notification Agreements only.

7. Contact Information

Please contact your local Sigma-Aldrich representative for more information: SAFC worldwide offices.

Sigma-Aldrich Cherokee Site Biological Buffers Facility Quality Overview

The Sigma-Aldrich group includes SAFC® facilities that are able to adapt their supply chain and quality management systems to support your raw materials supply requirements for manufacturing use.

The Sigma-Aldrich biological buffers facility at the Cherokee site is the world's largest manufacturer of biological buffers. Our buffers are fully scalable regardless of need or requirement and are manufactured under stringent quality systems that meet your regulatory needs. Packaging, testing and labeling can be customized to your specific requirements.

1. Facility overview

1.1. Scope

- Sigma-Aldrich biological buffers facility, 3300 S. Second St., St. Louis, MO 63118 USA, internally referred to as the Cherokee site, T-West building, buffers manufacturing site.

1.2. Corporate ownership

- The buffers facility at the Cherokee site is a wholly owned subsidiary of Sigma-Aldrich, 3050 Spruce St., St. Louis, MO 63103
- See <http://www.sigmaaldrich.com/customer-service/about-us.html> for Corporate Fact Sheet (brand and customer base information), Annual Report, etc.

1.3. Customer audit policy

- Customers are welcome to audit our sites depending upon the business value.
- All inspections are planned, coordinated and accompanied by Quality Assurance; a thirty-day notice and confidentiality agreement may be required.

1.4. Site details

- General site information:
 - 390,000 ft² (36,000 m²) total for site; 35,000 ft² (3,300 m²) for buffers
 - ~250 employees for site; 8,000 Sigma-Aldrich employees in 38 countries
 - o ~20 in manufacturing for buffers
 - o ~20 Quality Assurance for site
 - o ~35 Quality Control for site (70 Quality at Dekalb site for buffers testing)
 - Buffers manufactured since 1970; manufactured at this site since 1986
 - Manufacturing operates continuously, seven days/week (24/7), with biannual preventive maintenance shutdowns
- Site activities conducted:
Chemical manufacture, special testing (such as cell culture and microbial testing), packaging, raw material and bulk storage. Packaging at the Cherokee site includes some products not manufactured at the site. Routine specification testing is conducted at the Sigma-Aldrich Dekalb site (e.g. aqueous, non-aqueous, redox, complexometric and Karl Fisher titrations, melting point, UV-Vis analysis, infrared, elemental analysis, optical rotation, ICP, GC, NMR, HPLC and endotoxin).
- Primary applications of products manufactured:
Buffers for laboratory use, pharmaceutical raw materials or other industry applications.
- No production or packaging of antibiotics, toxins, steroids or hormone products at the buffers facility.
- 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.
- Processes are monitored to ensure conformance to specifications and procedures. Quality Assurance is responsible for raw material approval, manufacturing batch and packaging record review, and product release of buffers with EQP (Enhanced Quality Program) classification of Elite. Quality Control is responsible for product release of buffers of Standard EQP. QA reporting is independent of Manufacturing. Organizational charts are available.
- Sub-contractors are qualified as part of our internal service supplier qualification program and used in some instances of preventive maintenance, calibration and pest control, and may be contracted for special validation or testing requests if not met by our in-house capabilities.

2. Compliance Evidence

2.1. ISO registration number and certificates

- Quality Systems governing the SAFC Biological Buffers manufacturing operations are based on selected elements of ICH Q7A as applicable to buffers for manufacturing use. Customer audits by pharma companies have concurred that this ensures adequate control for producing biological buffers.
- Support activities (testing, packaging, warehouse, maintenance, distribution, purchasing and customer support): ISO 9001:2008, Registration No QSR-825. Can be downloaded at <http://safcglob.com/safc-global/en-us/home/quality-management-systems/iso-certificates.html>

2.2. GMP Inspections by competent authorities (Regulatory Agencies):

- Not applicable to the Biological Buffers facility. FDA Registration Number 1937990 applies to other SAFC manufacturing facilities within the Cherokee site.

2.3. General GMP and compliance statements

- GMP not applicable to the Biological Buffers facility portion of this site.
- Quality Systems governing the SAFC Biological Buffers manufacturing operations are based on selected elements of ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients with support activities under ISO 9001:2008.

2.4. Other certifications or external audit programs:

- MSD - Metropolitan St. Louis Sewer District – quarterly routine compliance inspections
- City of St. Louis - Air Pollution Control Division – annual random compliance inspections
- MDNR (Missouri Dept of Natural Resources) – EPA compliance

3. Quality Management Systems Compliance Details

IPEC-PQG GMP compliance not applicable for the biological buffers.

3.1. Quality Management Systems

- General
 - Sigma-Aldrich has established a comprehensive Management System covering all aspects of its business and has a Corporate Quality Policy.
 - A Quality Manual for biological buffers describes the policies and systems to ensure that the quality of our products meet customer expectations.
 - Internal and external audits, Process Improvement programs and nonconformances from the CAPA system are reported to Executive Management.
 - Responsibilities of Quality Assurance functions are clearly defined.
 - Customer specifications can be managed on a custom basis.
- Documentation
 - The system and rules regarding document control and management are detailed in the management system description.
 - Administration and control of documents is QA responsibility.
 - All activities are defined in Processes, Standard Operating Procedures (SOP), Operating Procedures (OP), Manufacturing Procedures and auxiliary documents.
 - All Documents have a unique identifier, revision number, effectiveness date, next review date and distribution date.
 - All activities connected to the manufacturing and testing of a batch (batch record), and the equipment (logbooks), are stored with protected access and archived for at least ten years after production date.
 - Customers are provided with Specifications, Certificates of Analysis and Certificates of Origin.
- Change Control
 - A change control system covering all quality relevant changes is in place.
 - Quality and Manufacturing evaluate change requirements prior to manufacture and/or release to customers. Quality is responsible for change approval and customer notification. Change control requirements of the customer are evaluated. Customer notification on changes is possible provided that a specific agreement is set up between Sigma-Aldrich and customer.

3.2. Management Responsibility

- Sigma-Aldrich management is committed to fulfill all customer and regulatory requirements, and to align site goals with the quality policy.

- Adequacy of the quality system is assessed by Key Performance Indicators, which include, e.g., audits and review of metrics on CAPAs, customer complaints, failed batches & recalls. Executive Management review occurs yearly.
 - Management is responsive to customer perceptions as relayed back from customer interactions and supplier scorecards.
- 3.3. Resource Management
- Management assigns resources and responsibility where needed to ensure that the quality management system operates efficiently.
 - Personnel are qualified and trained on procedures and processes relevant to their function.
 - Equipment is subject to written preventive maintenance procedures and qualification programs, if required.
- 3.4. Product Realization
- For EQP Elite, raw materials and their suppliers are qualified.
 - For EQP Elite, process critical control points have been established by FMEA, with in-process testing as needed for verification.
 - Process Equipment Qualification and commissioning is undertaken on all new equipment installations. Retrospective Installation Qualification and Operations Qualification were performed on original equipment.
 - Equipment is designed for cleanability and to provide non-reactive product contact surfaces. Any multiuse equipment is cleaned per verified procedure and cleaning results are reviewed by QA.
 - Equipment used in manufacturing and testing are under a preventive maintenance and calibration program.
 - For EQP Elite, the Master Packaging Formulation (MPF) details the labeling and packaging procedures, components and accountability.
 - No animal-sourced materials, latex or GMO materials are used in the buffers facility.
 - All measuring and control devices are controlled and calibrated on a regular basis.
 - Quality Control Testing
 - Test methods are not validated (except compendial). Depending on customer requirements, method development activities up to and including method verification may be undertaken.
 - For EQP Elite, shelf life is established as a recommended retest date on the Certificate of Analysis.
 - Retained samples are kept for 1 year after release. For EQP Elite, samples are retained for a minimum of 2 years.
 - Planning: Make to stock based upon First In, First Out (FIFO) or make-to-order.
 - Purchasing: Global Supply Chain capabilities with vendor management per quality, delivery, pricing, and compliance to regulatory requirements.
 - Service: Pre- and post-sales technical and compliance services. Global distribution capabilities.
- 3.5. Measurement, Analysis and Improvement
- Key Performance Indicators are designed and implemented for all relevant processes. Regular management reviews are performed to assess continuing compliance of the system with customer and regulatory requirements.
 - Nonconforming product controls are electronic; the SAP MRP system prevents product in a quality rejected status from being shipped.
 - Corrective and Preventive processes: Data relevant for product quality are trend analyzed to detect potential drifts and corrective/ preventive actions are implemented as appropriate.
 - Continuous improvement represents an essential part of the strategy of the Sigma-Aldrich corporation. All employees are highly motivated to participate in various local and corporate improvement programs. These programs focus on quality, safety, 5S programs and economic improvements in all areas of our business and operations.
4. Miscellaneous Site Information
- Social Responsibility - Sigma-Aldrich is committed to serving the communities where we live and work, to a safe and fair work environment where our employees can grow and enrich themselves in the diversity that this worldwide organization offers, and to sustainability programs.
 - Sigma-Aldrich Foundation began in 2004 and has contributed large and small gifts to over 250 worthwhile charitable organizations. See <http://www.sigmaaldrich.com/customer-service/about-us.html> for Global Citizenship and Corporate Giving.

- A batch is a specified quantity of material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacture order during the same cycle of manufacture. Each batch is uniquely identified with one lot number. For products manufactured since late 2011, the lot format is SL followed by 2 more letters, 4 numbers, and an optional "V".
- Environmental controls and monitoring: Cold weather protection (heat supplied) and make-up air is coarse-filtered to remove large particulates. The process equipment remains closed throughout the process so that environmental factors do not affect final product quality. Water used in manufacture is deionized and port is monitored to ensure conformance to established specifications.
- Buffers with similar characteristics are manufactured in shared equipment. Cleaning is verified per established procedures to prevent cross-contamination.
- Sigma-Aldrich Enhanced Quality Program (EQP)
 - EQP is an internal four-level classification system for our products: STANDARD, PREMIUM, ELITE and GMP. These tiers are set up to reflect the various levels of product quality and support documentation as outlined at: <http://safcglob.com/safc-global/en-us/home/eqp.html>The Cherokee site Biological Buffers facility participates in Standard- and Elite-tier products.
- The site has a business continuity plan for disaster recovery in order to mitigate any potential supply interruptions to our customers.

5. Contact Information

Please contact your local Sigma-Aldrich representative for more information:
[SAFC world-wide offices](#)

Cherokee Biological Buffers Site Supply Chain Security Overview

1. Scope

- Sigma-Aldrich Corporation, 3300 S. Second St., St. Louis, MO 63118 USA, internally referred to as the Cherokee site.
- Corporate ownership: The Cherokee facility 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 manufacturer to end user:

- Products are packed in tamper-evident packaging. All packing/labeling operations are performed on-site or at Sigma-Aldrich Switzerland (the latter for routine Eurasian distribution).
- Environmental controls can be implemented during transport (e.g., to control cold chain).
- Intermediate storage locations are partnered warehouses that utilize approved procedures provided by Sigma-Aldrich Corporation. They are monitored and reviewed on a routine bases. Full inventory audits occur at least once a year.

3. Security Information

3.1 Scope of Security Plan

- The Environmental Health and Safety department is responsible for site security.
- All relevant procedures and policies are part of our management system. The overall system is internally audited at least once every three years.
- All employees receive regular training regarding security and safety.
- Procedures for data and computer system protection are in place and part of the management system.
- Site access control
 - Facility is security-fenced and has closed-circuit TV surveillance at a central security station.
 - Ingress/egress of employees is controlled through manned security checkpoints or electronic badge system.
 - Ingress/egress of suppliers/contractors is monitored via a central gate, which is manned with an external security service.
 - Sensitive areas within the facility are additionally locked with mechanical or electronic locking systems.

3.2 Personnel Security

- Pre-employment background checks are performed on all employees.
- Background checks are performed on temporary and contract personnel.
- Each employee receives initial and ongoing training regarding safety, health and environment.
- Individual employee badges are collected upon permanent leave of the company to avoid unapproved access to the site. Contractors receive temporary badges which are returned daily.

4. Environmental Health & Safety Program (EHS)

- Develops programs and procedures to implement EHS regulatory and principle requirements.
- Develops and delivers EHS training.
- Monitors and reports site EHS performance.
- Investigates significant EHS incidents.
- Provides continuous improvement in EHS Performance through periodic and organized Management Systems Reviews.
- Provides an annual review of the facility management systems for assuring compliance with applicable EHS laws, regulations and Corporate EHS Principles and Policies.
- There are no registrations to ISO 14001, OHSAS 18001 or others.
- A documented emergency response plan consists of clear responsibilities and defined processes in case of events related to EHS.

5. Miscellaneous site information

- The Business Continuity Plan utilizes the vast Sigma-Aldrich raw material/chemical supply chain and potential transfers of projects to other Sigma-Aldrich facilities in the US and Europe in order to mitigate potential supply interruptions.
- Medical, fire and HAZMAT teams are on-site. Procedures exist for emergency shut-downs, utilities and information systems. An Emergency Operation Center coordinates internal mitigation and recovery activities, and liaisons with external emergency agencies.
- The initiatives at Sigma-Aldrich Corporation promote greater environmental responsibility and support energy conservation, natural resources conservation, material reuse, reduction and recycling, and the application of green chemistry into our processing operations worldwide.

6. Contact Information

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

[SAFC world-wide offices](#)