Enhanced Quality Product Documentation

Cysteamine hydrochloride
PharmaGrade, manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical production
Product Number 08901

Contents
• Product Regulatory Datasheet
• Buchs Quality Overview
• Buchs Site and Supply Chain Security Overview

Related Documents
• Buchs ISO 9001:2008 Certificate
• Buchs Management System Overview

Revision 1, July 2015
Product Regulatory Datasheet

1. General Product Information

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Cysteamine hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name</td>
<td>PharmaGrade, manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical production</td>
</tr>
<tr>
<td>Product Number</td>
<td>08901</td>
</tr>
<tr>
<td>Quality Level</td>
<td>ELITE</td>
</tr>
<tr>
<td>Disclaimer</td>
<td>For further (non-TSCA only use in US) manufacturing uses only. Not intended for direct use in humans or animals.</td>
</tr>
<tr>
<td>Related documents</td>
<td>Buchs Quality Overview</td>
</tr>
<tr>
<td></td>
<td>Buchs Site and Supply Chain Security Overview</td>
</tr>
</tbody>
</table>

2. Manufacturing, Packaging, Release Site and Supplier Information

- Site of manufacturing, packaging and product release:
  Sigma-Aldrich Production GmbH, Industriestrasse 25, 9470 Buchs (SG), Switzerland
- Standard sites of storage and dispatch:
  - Sigma-Aldrich Production GmbH, Industriestrasse 25, 9470 Buchs (SG), Switzerland
  - Sigma-Aldrich Chemie GmbH, Industriegebiet Sued, Kappelweg 1, 91625 Schnelldorf, Germany
- This product is manufactured in multi-purpose equipment.

3. Physico-chemical Information

3.1 Synonyms
- β-Mercaptoethylamine hydrochloride
- 2-Mercaptoethylamine hydrochloride
- 2-Aminoethanethiol hydrochloride
- Decarboxycysteine hydrochloride
- Thioethanolamine hydrochloride

3.2 Structural Formula
\[
\text{HS} \quad \overset{\text{HCl}}{\text{\longrightarrow}} \quad \text{NH}_2
\]

3.3 Molecular Formula
- \( \text{C}_2\text{H}_7\text{N}_1\text{S} \cdot \text{HCl} \)

3.4 Molecular Mass
- 113.61

3.5 CAS Number
- 156-57-0

3.6 Origin
- The product is manufactured by chemical synthesis.
- Starting materials of synthetic and microbial fermentation origin are used.
- There are procedures in place to avoid cross-contamination with other materials or residues of animal, human, GMO origin or allergen materials.

3.7 Manufacturing process
- Recrystallization of Cysteamine hydrochloride > centrifugation > drying > homogenization > bulk filling
## 3.8 Specification

<table>
<thead>
<tr>
<th>Analytical items</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPEARANCE (COLOR)</td>
<td>White to Off White</td>
</tr>
<tr>
<td>APPEARANCE (FORM)</td>
<td>Powder or Crystals or Powder with Chunk(s) or Crystals with Chunk(s)</td>
</tr>
<tr>
<td>ARGENTOMETR. TITRATION</td>
<td>30.6 - 31.8 %</td>
</tr>
<tr>
<td>PURITY (GC AREA %)</td>
<td>≥ 98.0 %</td>
</tr>
<tr>
<td>ASSAY (GC WEIGHT %)</td>
<td>98 - 102 %</td>
</tr>
<tr>
<td>GC MINOR COMPONENT 1 (AREA %)</td>
<td>Cystamin ≤ 2.0 %</td>
</tr>
<tr>
<td>SOLUBILITY (COLOR)</td>
<td>Colorless</td>
</tr>
<tr>
<td>SOLUBILITY (TURBIDITY)</td>
<td>Clear</td>
</tr>
<tr>
<td>SOLUBILITY (METHOD)</td>
<td>3.408 G IN 30 ML H2O (1 M)</td>
</tr>
<tr>
<td>LOSS ON DRYING</td>
<td>≤ 1.0 %</td>
</tr>
<tr>
<td>PROTON NMR SPECTRUM</td>
<td>corresponds to reference</td>
</tr>
<tr>
<td>HEAVY METALS</td>
<td>≤ 20 mg/kg</td>
</tr>
<tr>
<td>METAL TRACE ANALYSIS (ICP)</td>
<td>CORRESPONDS TO REQUIREMENTS</td>
</tr>
<tr>
<td>ALUMINIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>BARIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>BISMUTH (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>CALCIUM (ICP)</td>
<td>≤ 10 mg/kg</td>
</tr>
<tr>
<td>CADMIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>COBALT (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>CHROMIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>COPPER (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>IRON (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>POTASSIUM (ICP)</td>
<td>≤ 50 mg/kg</td>
</tr>
<tr>
<td>LITHIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>MAGNESIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>MANGANESE (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>MOLYBDENUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>SODIUM (ICP)</td>
<td>≤ 50 mg/kg</td>
</tr>
<tr>
<td>NICKEL (ICP)</td>
<td>≤ 50 mg/kg</td>
</tr>
<tr>
<td>LEAD (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>STRONTIUM (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>ZINC (ICP)</td>
<td>≤ 5 mg/kg</td>
</tr>
<tr>
<td>RESIDUAL SOLVENTS (GLC-HS)</td>
<td>Ethanol ≤ 5000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>tert-Butylmethyl ether ≤ 5000 mg/kg</td>
</tr>
</tbody>
</table>
3.9 Batch results
• Certificates of Analysis are available for each lot.

4. Regulatory Information

4.1 Compendial compliance
• Not applicable.

4.2 Master file
• Drug Master File (DMF) or EDQM Certificate of Suitability or other master file is currently not available.
• Please contact Sigma-Aldrich for further regulatory support.

4.3 BSE/TSE and viral risk statement
• The product is manufactured from synthetic and microbial fermentation starting materials.
• This product is neither partly nor fully of human or animal origin.
• The manufacturing process does not involve any raw materials, sourcing materials or reagents that are of human or animal origin.
• This product is derived from non-animal sources. Therefore this product complies with the requirements stipulated in EMEA/410/01 as Negligible Risk for BSE/ TSE (Bovine Spongiform Enzephalopathy/Transmissible Spongiform Encephalopathy).
• The product poses no risk concerning viral contamination.

4.4 Allergen information
• The product is a pure substance and contains no additives.
• No allergens have been used during manufacture as listed in
  – Directive 2003/89/EC, Annex IIa, or
• No Gluten materials have been applied during manufacture.

4.5 GMO information
• The product is GMO free and is not produced using GMOs.

4.6 Residual solvents information
• Class 1 solvents according to CPMP/ICH/283/95: none
• Class 2 solvents according to CPMP/ICH/283/95: none
• Class 3 solvents according to CPMP/ICH/283/95: Ethanol ≤ 5000 ppm tert-Butylmethyl ether ≤ 5000 ppm
• Other solvents: none

4.7 Metal catalyst and metal reagent residues
• The product is produced without use of metal catalysts or metal reagents.
• Contact surfaces during production are Glass, HDPE, enamel, steel, Hastelloy® and PTFE.

4.8 Kosher/Halal status
• No status.

4.9 Melamine statement
• This product is Melamine-free.
• This material does contain Nitrogen.
• The purity and assay information are not based on methods based on Nitrogen content. Therefore, additional testing of the material to establish Melamine absence is not necessary.
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 45 to 59 kg.
- Each received batch is identified by a specific, unique batch number.
- The batch number consists of 4 characters, followed by four digits and optionally a ‘V’:
  
  BCXY1234(V)

  BC  Site identifier for Buchs
  XY1234 Serial alphanumeric number according to goods receipt, running from BB0001 to ZZ9999
  V If applicable, identifier for GHS compliant labelling

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

- 48 months from date of manufacture.
- The retest date is based on historical data from Sigma-Aldrich’s catalog product grades.

5.3 Stability information

- If stored in the original unopened containers, no significant change of the material can be observed.
- Storage and shipping conditions:
  - Store in cool place. Keep container tightly closed in a dry and well-ventilated place.
  - Recommended storage temperature 2 - 8 °C
  - Moisture sensitive
  - Shipping on wet ice

5.4 Packaging

- Standard pack sizes of 100 g and 1 kg:
  - Packaged under Argon in 250 mL and 2500 mL amber glass bottles with polypropylene cap having tamper evident seal and a PTFE-coated PE foam liner

6. Revision History

- Revision 1, July 2015
  - This document is valid for lots released after May 2015.
  - It is customer’s responsibility to check validity of this document for specific lots.
- 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 world-wide offices

Veronika Kalberer  QA Specialist/ EQP Site Lead  Sigma-Aldrich Production GmbH, Buchs, Switzerland
Harald Sucker  QA Compliance Service  Sigma-Aldrich Production GmbH, Buchs, Switzerland
Buchs Quality Overview

The SAFC® Buchs facility adapts its supply chain and quality management systems to support your raw materials supply for industrial use.

Buchs provides procurement, manufacturing, quality control, packaging, quality assurance and customization beyond expectation. This creates a supply chain designed to serve the needs of industry customers for SAFC®. SAFC® is the custom manufacturing unit of Sigma-Aldrich® and has 30 manufacturing sites worldwide.

1. Facility overview

1.1 Scope
- Sigma-Aldrich Production GmbH, Industriestrasse 25, 9470 Buchs (SG), Switzerland

1.2 Corporate ownership
- Sigma-Aldrich Production GmbH is a 100 % subsidiary of Sigma-Aldrich Corporation, St.Louis, USA

1.3 Customer audit policy
- Customers who purchase our Elite PharmaGrade products are welcome to audit our Buchs site.
- Depending on the business value, an audit fee may be charged.

1.4 Site details
- General site information:
  - 17040 m² building surface, 109364 m² site surface, ~500 employees
  - Production operates in 2 shifts, seven days/week
- Site activities conducted:
  - Chemical manufacture, packaging, distribution, testing, chemical R&D
- Primary applications of products manufactured:
  - Products for laboratory use, pharmaceutical raw materials, intermediates, APIs and excipients, fine chemicals for other industry applications
- No production of antibiotics, steroids or hormone products is commenced in the facilities where pharmaceutical raw materials are manufactured.
- Responsible for product release (Elite PharmaGrades) is the local Quality Control and Quality Assurance. Please inquire about our organizational chart.
- Sub-contractors are used in the areas of preventive maintenance and microbiological testing.

2. Compliance Evidence

2.1 ISO registration number and certificates
- ISO 9001:2008, SQS Registration No 16368
- Please download the ISO certificate on sigmaaldrich.com/safc

2.2 Elite PharmaGrade production
- Manufacturing, including packaging and quality control, is in full compliance with ISO 9001.
- The batch processing and packaging are reviewed by QA for compliance with Elite quality level requirements prior to release.
- Final release according to internal requirements for raw materials for pharmaceutical production is of customer’s competence.

2.3 Other certifications
- cGMP
- ISO 13485:2012
- ISO 17025:2005/ ISO Guide 34
3. Compliance Details

3.1 Quality Management Systems

- **General**
  - Sigma-Aldrich Production GmbH has established a comprehensive Management System covering all aspects of its business.
  - The management system is certified to ISO 9001:2008 and includes all relevant regulatory requirements concerning cGMP production.
  - Responsibilities of Quality Assurance functions are explained in detail.

- **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, date of issue, next review date and distribution.
  - All activities connected to the manufacturing and testing of a batch (batch record), and the used equipment (logbooks), are stored as required by the internal Elite guidelines and archived for at least ten years after production date.

- **Change Control**
  - A formal change control system covering all quality relevant changes is in place.
  - Approval of changes is in the competency of Quality Assurance.
  - 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 regarding the production of pharmaceutical raw materials and to provide adequate resources. This is laid down in the Corporate Quality Policy and in the local Management System

- Adequacy of the quality system is assessed by Key Performance Indicators, which include e.g. audit observations, CAPAs, customer complaints, failed batches & recalls.

- The responsibilities of the quality unit are defined in the Management system. Release or rejection of pharmaceutical raw material batches is the responsibility of Quality Control and Quality Assurance. Quality Assurance is independent from production and reports directly to the site manager.

- Regular management reviews are performed to assess continuing compliance of the system with customers and regulatory requirements. Appropriate actions are defined to address issues of concern.

3.3 Resource Management

- All facilities and equipment comply with Elite requirements as applicable. 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 pharmaceutical raw materials.

3.4 Product Realization

- Planning of product realization is performed by the planning and scheduling group and is supported by the ERP system (SAP)

- Customer-related processes are defined in processes C10, P15, P40 and S30 of the management system.

- Design and development is defined in processes C40 and P40 of the management system. Appropriate processes and documents are in place to ensure compliance with the requirements of ISO and Elite quality level.

- Purchasing operations are defined in Process P20 of the management system.

- Production and service provision are designed to ensure safe and compliant manufacture of pharmaceutical raw materials. Details are defined in processes P15, P40, P50, S20 and S30 of the management system.

- Control of measuring and monitoring devices
  - All measuring and control devices are controlled and calibrated on a regular base.
  - The process and requirements are defined in process S70 of the management system and related documents.
3.5 Measurement, Analysis and Improvement

- Key Performance Indicators are designed and implemented for all relevant processes. It is management’s responsibility to control and analyse these data and compare with corporate business targets and/or with legal/customer requirements.
- Regular management reviews are performed to assess continuing compliance of the system with customer and regulatory requirements. Appropriate actions are defined to address issues of concern.
- Clear guidelines are in place to prevent, identify and control nonconforming products. All non-conformance cases are defined and classified. Corrective actions and preventive actions are defined to prevent reoccurrence.
- All Key Performance Indicators are analyzed and assessed on a regular base during management review meetings. 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 and economic improvements in all areas of our business and operations.

4. Revision History

- Revision 3, February 2015
  - Amendment of ISO 14001/OHSAS 18001 certification
  - Update of process numbers
- Revision 2, October 2013
  - Change of EQP Site Lead
- Revision 1, February 2013
  - First edition

5. Contact Information

Please contact your local Sigma-Aldrich representative for more information:
SAFC world-wide offices

Veronika Kalberer
QA Specialist/ EQP Site Lead
Sigma-Aldrich Production GmbH, Buchs, Switzerland

Harald Sucker
QA Compliance Service
Sigma-Aldrich Production GmbH, Buchs, Switzerland
Buchs Site and Supply Chain Security Overview

1. Scope
   - Sigma-Aldrich Production GmbH, Industriestrasse 25, 9470 Buchs (SG), Switzerland
   - Corporate ownership
     Sigma-Aldrich Production GmbH is a 100 % subsidiary of Sigma-Aldrich Corporation, St.Louis, 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:
   - All packing/labelling operations are performed onsite.
   - All Elite PharmaGrade 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 certified.

3. Security Information
   3.1 Scope of Security Plan
   - Head of EHS department is responsible for site security.
   - All relevant procedures and policies are part of our management system.
   - 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
     - Major areas are security-fenced.
     - Only a few buildings are not within the fence but equipped with an electronic locking system.
     - Ingress/egress of employees is followed up through the electronic badge system.
     - Ingress/egress of suppliers/contractors via central gate, which is manned with external security service.
     - Sensitive areas within the fence are additionally locked with mechanical or electronic locking system. Some areas are observed with CCTV.

   3.2 Personnel Security
   - Pre-employment background checks.
   - Background checks on temporary and contract personnel.
   - Each employee receives initial and ongoing training regarding safety, health and environment.
   - Individual employee badges are collected upon leaving the company to avoid unapproved access to the site. Contractors only receive temporary badges which need to be returned daily.

4. Environmental Health & Safety Program (EHS)
   - Tracking of official notes by the EHS manager; membership in associations, implementation of new requirements into the existing integrated management system, including quality and EHS.
   - Annual goals and Key Performance Indicators are approved & communicated by site management; achievement is tracked by the EHS manager; actual status is visible for all employees; monthly reports & quarterly review from EHS manager within site management meeting.
   - The site is certified according to ISO 14001 and OHSAS 18001.
   - There are no registrations to Responsible Care or others.
   - A documented emergency response plan consists of clear responsibilities and defined processes in case of events related to EHS.
5. Revision History

- Revision 3, February 2015
  - Update of ISO 14001/ OHSAS 18001
- Revision 2, October 2013
  - Change of EQP Site Lead
- Revision 1, February 2012
  - First edition

6. Contact Information

Please contact your local Sigma-Aldrich representative for more information:
SAFC world-wide offices

Veronika Kalberer
QA Specialist/ EQP Site Lead
Sigma-Aldrich Production GmbH, Buchs, Switzerland

Harald Sucker
QA Compliance Service
Sigma-Aldrich Production GmbH, Buchs, Switzerland