Enhanced Quality Product Documentation

Tropolone
PharmaGrade, Manufactured under appropriate controls for use as a raw material in pharma or biopharmaceutical production
Product Number 15702

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- Product Regulatory Datasheet
- Buchs Quality Overview
- Buchs Site and Supply Chain Security Overview

Related Documents
- Buchs ISO 9001:2015 Certificate
- Buchs Management System Overview

Revision 5, July 2018
Product Regulatory Datasheet

1. General Product Information

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Tropolone</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>15702</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 Buchs Site and Supply Chain Security Overview</td>
</tr>
</tbody>
</table>

2. Manufacturing, Packaging, Release Site and Supplier Information

- Site of manufacturing, testing, 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
  - Aldrich Chemical Company, Inc, 6000 N. Teutonia Avenue, Milwaukee, WI 53209-3645, USA
- This product is manufactured under ISO 9001 plus other controlled processes defined for Elite quality level.
- This product is manufactured in multi-purpose equipment.

3. Physico-chemical Information

3.1 Synonyms
- 2-Hydroxy-2,4,6-cycloheptatrien-1-one

3.2 Structural Formula

3.3 Molecular Formula:
- C₇H₆O₂

3.4 Molecular Mass
- 122.12

3.5 CAS Number
- 533-75-5

3.6 Origin
- The product 15702 is manufactured by chemical synthesis.
- Only raw materials of synthetic, plant, natural-organic and natural-inorganic 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.
- Lot specific Certificates of Origin are available on the Sigma-Aldrich web site and upon request.

3.7 Manufacturing process
- Chemical synthesis with subsequent isolation, distillation and homogenization.
3.8 Specification

<table>
<thead>
<tr>
<th>Analytical items</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPEARANCE (COLOR)</td>
<td>White or Colorless to Yellow and Faint Beige to Beige</td>
</tr>
<tr>
<td>APPEARANCE (FORM)</td>
<td>Solid or Powder or Crystals or Chunks</td>
</tr>
<tr>
<td>PURITY (GC AREA %)</td>
<td>≥ 98.0 % rel</td>
</tr>
<tr>
<td>REMARKS ON GC</td>
<td>Acetic Acid ≤ 5000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Dichloroacetic Acid: determine</td>
</tr>
<tr>
<td>SOLUBILITY (COLOR)</td>
<td>Colorless to Very Dark Yellow and</td>
</tr>
<tr>
<td></td>
<td>Colorless to Very Dark Greenish Yellow and</td>
</tr>
<tr>
<td></td>
<td>Colorless to Very Dark Brownish Yellow and</td>
</tr>
<tr>
<td></td>
<td>Colorless to Very Dark Orange</td>
</tr>
<tr>
<td>SOLUBILITY (TURBIDITY)</td>
<td>Clear to very faintly turbid (&lt; 12.5 NTU)</td>
</tr>
<tr>
<td>SOLUBILITY (METHOD)</td>
<td>0.25 g in 5mL Ethanol</td>
</tr>
<tr>
<td>INFRARED SPECTRUM</td>
<td>corresponds to reference</td>
</tr>
<tr>
<td>HEAVY METALS</td>
<td>≤ 20 mg/kg</td>
</tr>
<tr>
<td>RESIDUAL SOLVENTS (GLC-HS)</td>
<td>Pentane ≤ 5000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>tert-Butyl methyl ether (MTBE) ≤ 5000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Toluene ≤ 890 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cyclohexane ≤ 3880 mg/kg</td>
</tr>
</tbody>
</table>

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) or EDQM Certificate of Suitability or other master file is not available.
- Please contact Sigma-Aldrich for further regulatory support.

4.3 BSE/TSE and viral risk statement

- The product is manufactured from synthetic, plant, natural-organic and natural-inorganic raw 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 Encephalopathy/ Transmissible Spongiform Encephalopathy).
- The product poses no risk concerning viral contamination.
- Lot specific Certificates of Origin are available on the Sigma-Aldrich web site or from your local Sigma-Aldrich representative.

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 Illa, 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/285/95: None
- Class 2 solvents according to CPMP/ICH/285/95: Cyclohexane, Toluene
- Class 3 solvents according to CPMP/ICH/285/95: Acetic acid, tert-Butyl methyl ether (MTBE), Pentane
- Other solvents: Petroleum ether, Kerosene

4.7 Metal catalyst and metal reagent residues
- The product is produced without the use of metal catalysts or metal reagents.
- Supplier information concerning the use of metal catalysts or metal reagents during manufacture of the starting materials is not available.
- Contact surfaces during production are of glass, PTFE, HDPE and LDPE.

4.8 Kosher/Halal status
- No status.

4.9 Aflatoxin statement
- The Commission Regulation (EC) 1881/2006 and subsequent amendments sets maximum levels of certain contaminants in foodstuffs, including levels of mycotoxins which are a risk for ingredients derived from cereals, peanuts and/or milk.
- None of the materials as itemized in the above regulation has been used as a starting material or reagent during manufacture of this product. Therefore the requirements of this regulation do not apply for our product.

4.10 Melamine statement
- This product is Melamine free.
- This material does not 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 0.6 to 1.3 kg
- Each produced 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 Shelf-life and/or recommended re-evaluation interval:
- 36 months from manufacturing date
- The recommended retest period 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:
  - Storage at 2 – 8°C in a dry storage place
  - Shipping at ambient temperature
  - Hygroscopic, store under inert gas
5.4 Packaging

- Standard pack sizes of 5 g:
  - Filled under Argon
  - 35 mL amber glass bottles with polypropylene cap with tamper evident seal and PTFE disk.

6. Revision History

- Revision 5, July 2018
  - Change of approximate batch size, effective for lots BCBX3920, BCBX3921 and all future lots released after July 2018
- Revision 4, September 2015
  - Change of disclaimer
  - Update of material of contact surfaces
  - Amendment of filling under Argon
- Revision 3, May 2015
  - Change of manufacturing process (replacement of grinding by addition of a new homogenization step)
  - New residual solvent specification
- Revision 2, February 2015
  - Correction of bottle size indication
- Revision 1, February 2013
  - First edition
  - This document is valid for lots released after November 2012.
  - 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/ FOP Site Lead
Sigma-Aldrich Production GmbH, Buchs, Switzerland

Manuel Spettel
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 Merck KGaA, Darmstadt, Germany

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 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 9001:2015, DQS Registration No 005356 QM15
- Please download the ISO certificate on http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma-Aldrich/General_Information/1/iso-9001-certification.pdf.

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 17034
- ISO 14001:2015
- OHSAS 18001:2007
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 9001:2015 and includes all relevant regulatory requirements concerning cGMP production.
  - Responsibilities of Quality Assurance functions are explained in detail.
  - Please download the Buchs Management System Overview on http://www.sigmaaldrich.com/customer-service/quality-systems.html

- 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 7, July 2018
  - Change of local Quality organizational structure.
- Revision 6, December 2017
  - Replacement of ISO Guide 34 by ISO 17034
- Revision 5, April 2017
  - Change of ownership information, change of certification numbers
- Revision 4, December 2015
  - Amendment to header information
- 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
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 subsidiary of Merck KGaA, Darmstadt, Germany

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 5, April 2017
  - Change of ownership information
- Revision 4, December 2015
  - Amendment to header information
- Revision 3, February 2015
  - Update of ISO 14001/ OHSAS 18001
- Revision 2, October 2013
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