Enhanced Quality Product Documentation

Sodium pyruvate
PharmaGrade, Manufactured under appropriate GMP controls for pharma or biopharmaceutical production
Product Number 80443

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

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

Revision 4, September 2018
Product Regulatory Datasheet

1. General Product Information

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Sodium Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Number</td>
<td>80443</td>
</tr>
<tr>
<td>Quality Level</td>
<td>GMP</td>
</tr>
<tr>
<td>Disclaimer</td>
<td>Not suitable for use as Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>Related documents</td>
<td>Buchs Quality Overview, Buchs Site and Supply Chain Security Overview</td>
</tr>
</tbody>
</table>

PharmaGrade, manufactured under appropriate GMP controls for pharma or biopharmaceutical production.

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
- This product is manufactured under appropriate cGMP to be used as an excipient.
- This product is manufactured in multi-purpose equipment.

3. Physico-chemical Information

3.1 Synonyms
- α-Ketopropionic acid sodium salt
- 2-Oxopropanoic acid sodium salt
- Pyruvic acid sodium salt

3.2 Structural Formula

\[
\text{H}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\equiv \\
\text{O} \\
\text{Na}
\end{array}
\]

3.3 Molecular Formula: \( \text{C}_3\text{H}_3\text{NaO}_3 \)

3.4 Molecular Mass
- 110.04

3.5 CAS Number
- 113-24-6

3.6 Origin
- The product is manufactured by chemical synthesis.
- Only raw materials of synthetic and 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
- Purification of Pyruvic acid
- Formation and subsequent crystallization of Sodium salt
- Drying
3.8 Specification

<table>
<thead>
<tr>
<th>Analytical items</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White to almost white solid</td>
</tr>
<tr>
<td>Identity</td>
<td>Corresponds to reference spectrum</td>
</tr>
<tr>
<td>Infrared spectrum (ATR) Sodium</td>
<td>Corresponds</td>
</tr>
<tr>
<td>Assay (non-aqueous titration HClO₄ 0.1M)</td>
<td>≥ 98.0% w/w</td>
</tr>
<tr>
<td>Purity (HPLC Area %)</td>
<td>≥ 99.5%</td>
</tr>
<tr>
<td>Every single impurity (HPLC Area %)</td>
<td>≤ 0.2%</td>
</tr>
<tr>
<td>Solubility (1.5 g in 25 ml H₂O)</td>
<td>Colorless, clear solution (&lt; 3.5 NTU)</td>
</tr>
<tr>
<td>Water (Karl-Fischer-Titration)</td>
<td>≤ 0.5 %</td>
</tr>
<tr>
<td>Residual solvents (GC-HS, EP 2.4.24)</td>
<td>Ethanol ≤ 5000 ppm</td>
</tr>
</tbody>
</table>

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated (*).

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 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 fermentation origin 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.

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 IIIa, 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
- Other solvents: none

4.7 Metal catalyst and metal reagent residues
- No elements listed in classes 1, 2 and 3 according to ICH Q3D were intentionally added during the manufacturing process for Sodium pyruvate. Any potential sources of elemental impurities have been evaluated in a risk assessment.
- 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 glass, steel, Hastelloy®, PTFE and PE.

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 20 to 40 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
  - 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:
- Recommended retest period: 60 months from manufacturing date.
- The retest period is based on the current results of our stability study according to “The IPEC Excipient Stability Program Guide, 2010” and our SOP “Stability Studies and Definition of Retest Periods and Expiry Dates”.
- The above stability study of the GMP grade material is ongoing to further confirm and support this period.

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 room temperature in a dry storage place.
  - Keep containers tightly closed.
  - Shipping at ambient temperature.
5.4 Packaging

- Standard pack size of 250 g
  - 500 mL wide-mouth amber glass bottles
  - Polypropylene cap with tamper evident seal and PTFE coated LDPE foam gasket
- Standard pack size of 1 kg:
  - 2.5 L wide-mouth amber glass bottles
  - Polypropylene cap with tamper evident seal and PTFE coated LDPE foam gasket

6. Revision History

- Revision 4, September 2018
  - Change of specification. Addition of elemental impurity information to specification.
- Revision 3, October 2016
  - Change of recommended retest period
- Revision 2, December 2014
  - Change of product qualifier text
  - Correction of ICH residual solvents guideline number
  - Amendment to materials in contact with product
  - Amendment to batch number explanation
  - Change of recommended retest period
  - Deletion of custom pack sizes
  - Adoptions to new template
- Revision 1, August 2011
  - This document is valid for lots released after May 2011.
  - 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

Mag. Edeltraud Schwärzler
Manager Quality
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 subsidiary of Merck KGaA, Darmstadt, Germany

1.3 Customer audit policy

- Customers who purchase our excipients and/or APIs are welcome to audit our Buchs site.
- Depending on the business value, an audit fee may be charged.
- The Buchs site is regularly audited by Rx-360. On request a Rx-360 questionnaire is available.

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 excipients or APIs are manufactured.
- Responsible for product release (APIs and excipients) is the head of QA (qualified person) and his deputy. Please inquire about our organizational chart.
- Sub-contractors are used in the areas of preventive maintenance, qualification and validation, microbiological testing, storage of stability samples.

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 GMP inspections by competent authorities (Regulatory Agencies):

- Manufacturing authorization by Swissmedic as API production site and approved GMP testing laboratory.
  - Registration No. 506042
  - Last inspection date: March 2017
- Please download the gMP certificate on http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/SAFC/General_Information/1/gmp_compliance_certificate_english.pdf.

2.3 General GMP statements

- The site operates to cGMP standards as applicable for the intended use.
2.4 API production
- Manufacturing, including packaging and quality control, is in full compliance with the GMP requirements of the local regulatory authority.
- The batch processing, packaging and analysis records are reviewed by QA for compliance with GMP requirements prior to release.
- Final release according to marketing authorization is of customer’s competence.

2.5 Excipient production
- Procedures are in place to ensure that manufacturing, including packaging and quality control, is performed under appropriate GMP for excipients as laid down in the IPEC-PQG GMP Guide 2006 “GMP for excipients”.
- The batch processing, packaging and analysis records are reviewed by QA for compliance with the GMP requirements prior to release.
- Final release according to marketing authorization is of customer’s competence.

2.6 Other certifications
- ISO 13485:2016
- ISO 17025:2005/ ISO 17034
- ISO 14001:2015
- OHSAS 18001:2007

3. IPEC-PQG GMP Compliance Details
The Buchs site operates in compliance with the IPEC-PQG GMP Guide 2006.

3.1 Quality Management Systems - Excipient Quality 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 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 GMP Guidelines and archived for at least ten years after production date.
- Change Control
  - A 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 excipients and to provide adequate resources. This is laid down in the Merck Quality Policy, in the Mission Statement 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 excipient batches is the responsibility of the head of quality assurance, who is registered with Swissmedic as qualified person. 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

- Resource management is compliant to ICH Guidelines for API production respective EU GMP guideline part II and the IPEC-PQG GMP Guide 2006.

- All facilities and equipment complies with current GMP 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 excipients.

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 IPEC.

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

- Production and service provision are designed to ensure safe and compliant manufacture of excipients. 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 16, September 2018
- Revision 15, December 2017
- Revision 14, October 2017
  - Added Rx-360 Audit information
  - Amendment to Management Responsibility
- Revision 13, September 2017
  - Replacement of ISO Guide 34 by ISO 17034
  - Update of last GMP inspection date
- Revision 12, March 2017
  - Change of ownership information, change of certification numbers
- Revision 11, December 2015
  - Amendment to header information
- Revision 10, August 2015
  - Update of last GMP inspection date
- Revision 9, September 2014
  - Amendment of ISO 14001/ OHSAS 18001 certification
- Revision 8, March 2014
  - Change of GMP registration number
- Revision 7, December 2013
  - Update of internet addresses, last GMP inspection date and process numbers
- Revision 6, January 2013
  - Update of ISO 13485 version
- Revision 5, July 2011
  - Change of last GMP inspection date
- Revision 4, July 2011
  - Change of Manager Quality Assurance
- Revision 3, May 2011
  - Layout changed
  - Review of information and related documents

5. Contact Information

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

Mag. Edeltraud Schwärzler
Manager Quality
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 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 or outsourced only to qualified contract suppliers.
   - All excipients 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 8B, September 2017
  - Precision of ownership information
- Revision 8A, March 2017
  - Change of ownership information
- Revision 7, December 2015
  - Amendment of header information
- Revision 6, February 2015
  - Update of ISO 14001/OHSAS 18001 certification
- Revision 5, December 2013
  - Update of supply chain security information
- Revision 4, July 2011
  - Change of Manager Quality Assurance

6. Contact Information

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

SAFC worldwide offices

Mag. Edeltraud Schwärzler
Manager Quality
Sigma-Aldrich Production GmbH, Buchs, Switzerland