Enhanced Quality Product Documentation

Acetic Acid, Glacial

PharmaGrade, USP/NF, Ph. Eur, JP, Manufactured under appropriate GMP controls for pharma and biopharmaceutical production

Product Number ARK2183

Contents
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- SAFC Arklow Quality Overview
- SAFC Arklow Site and Supply Chain Security Overview
- ISO 14001:2014 Certificate
- OSHAS 18001:2013 Certificate
Product Regulatory Datasheet

1. General Product Information

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Acetic Acid, Glacial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Number</td>
<td>ARK2183</td>
</tr>
<tr>
<td>Qualifier</td>
<td>PharmaGrade, USP/NF, Ph. Eur, JP, Manufactured under appropriate GMP controls for Pharma or Biopharmaceutical production</td>
</tr>
<tr>
<td>Quality Level</td>
<td>GMP-Compendia</td>
</tr>
<tr>
<td>Related documents</td>
<td>SAFC Arklow Quality Overview</td>
</tr>
<tr>
<td></td>
<td>SAFC Arklow Site and Supply Chain Security Overview</td>
</tr>
<tr>
<td></td>
<td>SAFC Arklow ISO 14001:2014 Certificate</td>
</tr>
<tr>
<td></td>
<td>SAFC Arklow OSHAS 18001:2013 Certificate</td>
</tr>
</tbody>
</table>

2. Manufacturing, Packaging, Release Site and Supplier Information

Site of manufacturing, testing, packaging and product release: Sigma Aldrich Ireland Ltd, Vale Rd, Arklow, Co. Wicklow, Ireland.

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

Synonym 1 Acetic Acid
Synonym 2 Glacial Acetic Acid
Synonym 3 Ethanoic Acid

3.2 Linear Formula

CH₃COOH

3.3 Molecular Formula:

C₂H₄O₂

3.4 Molecular Mass

60.05g

3.5 CAS Number

64-19-7

3.6 Origin

The product ARK2183 is manufactured, synthetically. Only raw materials of synthetic origin are used.

3.7 Manufacturing process

Purification by distillation.
3.8 Specification

<table>
<thead>
<tr>
<th>Analytical items</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>The substance to be examined is clear and colourless (Ph. Eur)</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Crystalline mass or clear, colourless, volatile liquid. Miscible with Water,</td>
</tr>
<tr>
<td>Description</td>
<td>with Ethanol and Methylene Chloride (Ph. Eur)</td>
</tr>
<tr>
<td></td>
<td>Clear, colourless, volatile liquid or white, crystalline mass. It has a</td>
</tr>
<tr>
<td></td>
<td>pungent characteristic odour (JP)</td>
</tr>
<tr>
<td>Identification (pH)</td>
<td>A 100g/L solution is strongly acidic and changes Congo Red paper to green/</td>
</tr>
<tr>
<td></td>
<td>blue (Ph. Eur)</td>
</tr>
<tr>
<td></td>
<td>A solution (1 in 3) changes blue litmus paper to red (JP),</td>
</tr>
<tr>
<td>Identification (acetates)</td>
<td>Conforms (Ph. Eur, USP/NF, JP)</td>
</tr>
<tr>
<td>Freezing point</td>
<td>NLT 14.8°C (Ph. Eur)</td>
</tr>
<tr>
<td>Congealing Temperature</td>
<td>NLT 14.5°C (JP), NLT 15.6°C (USP)</td>
</tr>
<tr>
<td>Reducing substances</td>
<td>Passes (Ph. Eur)</td>
</tr>
<tr>
<td>KMnO4 reducing substances</td>
<td>The red colour does not disappear within 30 minutes (JP)</td>
</tr>
<tr>
<td>Readily Oxidizable Substances</td>
<td>The pink colour is not changed to brown within 2 hours (USP/NF)</td>
</tr>
<tr>
<td>Chlorides</td>
<td>NMT 25 mg/L (Ph. Eur), No opalescence is produced (USP, JP)</td>
</tr>
<tr>
<td>Sulphates</td>
<td>NMT 50 mg/L (Ph. Eur), No turbidity is produced (USP/NF, JP)</td>
</tr>
<tr>
<td>Iron</td>
<td>NMT 5 ppm (Ph. Eur)</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>NMT 5 ppm (Ph. Eur), NMT 10 ppm (USP/NF, JP)</td>
</tr>
<tr>
<td>Residue on Evaporation</td>
<td>NMT 0.01% (Ph. Eur), NMT 1.0 mg (USP/NF, JP)</td>
</tr>
<tr>
<td>Assay</td>
<td>99.5-100.5% (USP/NF)</td>
</tr>
<tr>
<td></td>
<td>99.0-100.5% (Ph. Eur)</td>
</tr>
<tr>
<td></td>
<td>99.0% (JP)</td>
</tr>
</tbody>
</table>

3.9 Batch results

Certificates of Analysis are available for each lot produced.

4. Regulatory Information

4.1 Compendial compliance

Acetic Acid, Glacial meets compendia reference, USP/NF, Ph. Eur, and JP.

4.2 Master file

Drug Master File (DMF) is not available for this product.

4.3 BSE/TSE and viral risk statement

This product is not produced using components from animal species (bovine, ovine or caprine) known to harbour BSE/TSE, and is therefore considered negligible risk.

This product is not produced using any bovine, ovine or caprine tissue classified as Category A (per EMEA 410/01 or Specified Risk Material (per USDA 9 CFR 310.22). BSE/TSE risk is negligible.

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 without use of Class 1-3 organic solvents.

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 not recognized as high risk for melamine contamination.
   The 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 800kg.
   Each produced batch is identified by a specific, unique batch number.
   The batch number takes the following general form GLAAXXX-YY
   GLAA is the material abbreviation for Glacial Acetic Acid, XXX is a code number referring to the year of manufacture and finally YY is the actual batch number and is unique for each individual batch.
   Example: GLAA128-1

5.2 Expiration date and/or recommended re-evaluation interval
   A stability programme is currently underway, at present a 2-year retest interval is recommended.

5.3 Handling, Shipping Conditions and Long-term Storage Recommendation
   Store in a cool dry place. Keep container tightly closed in a dry well-ventilated place. Containers which are opened must be carefully resealed and kept upright to prevent leakage. Moisture sensitive. Product classified as Dangerous Goods for transport purposes.

5.4 Packaging
   Consult the Sigma-Aldrich website for pack sizes. Packaged in HDPE containers under inert atmosphere
   With tamper-evident seal. Custom pack sizes for alternative quantities/packs are available on request.

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
Arklow - Quality Overview

The Sigma-Aldrich® / SAFÇ® Arklow facility has Quality and Supply Chains Management Systems to support your Pharmaceutical and Biochemical and Bio-organic supply for industrial use.

Arklow is a multi-product facility that specializes in Active Pharmaceutical Ingredient (API) and Bulk Chemical production. The plant has multiple departments including Supply Chain, Production, Quality Control, Process Technology, QA and Engineering. We also manage a logistics/warehouse facility for distribution of Sigma-Aldrich chemicals/reagents to Irish customers.

1. Facility overview

1.1 Scope
Sigma-Aldrich Ireland Limited, Vale Road, Arklow, County Wicklow, Ireland.

1.2 Corporate ownership
The Arklow facility is a wholly owned subsidiary of Sigma-Aldrich Corporation, St. Louis, Missouri, USA.

1.3 Customer audit policy
Customers who purchase our manufactured products or (or distributed pre-pack or bulk reagents) are welcome to audit the site, depending on the business value.

1.4 Site details
The site has a total area of 64,000m² of which 28,000m² are developed.

- Developed area includes 1656m² of production buildings and 240m² of laboratories
- ~85 employees, including 10 in QC/QA functions, 30 in Production, 4 in Supply Chain/Warehousing, 13 in Sales/Customer Service for Irish pre-pack/bulk reagents, and others in various support groups including Maintenance, Engineering, Environmental Health and Safety, Materials Management and Planning Support.
- Production operates in three shifts, 5.5 days/week.

Site activities conducted:
- Commercial scale manufacture of Generic APIs and Intermediates
- Contract Development, Scale-up, Testing and Validation, through Phase I-III, of APIs/Intermediates and Excipients that are synthesized or can be derived from natural extractive sources.
- Drug Master files preparation and registration (all geographies)

Primary applications of products:
- Pharmaceutical and Biopharmaceutical Secondary manufacturing
- Pre-pack and Bulk products distributed from the site are used for research, industrial and pre-clinical applications.
- The Arklow facility does not permit β-Lactam antibiotics, which includes penicillin derivatives (penams), cephalosporins (cephems), monobactams and carbapenems to enter this facility for processing and/or repackaging purposes.
- The Quality Department (QA/QC) is responsible for releasing and approving all material specifications (raw material, intermediate and final products).
- Sub-contractors may be used in the areas of maintenance, testing, and specialised manufacturing services (e.g. micronisation)

2. Compliance Evidence

2.1 GMP/Quality System Inspections by Competent Authorities (Regulatory Agencies) and Customers:
The Arklow facility operates to cGMP (ICH Q7, US FDA Part 210/211). Numerous Inspections by US FDA over 10 years with approval obtained in all cases.
Numerous inspections by Health Product Regulatory Authority (Ireland Competent Authority) over last 10 years
The Site receives 15-30 customer cGMP audits annually and biannual ISO 9000 inspections of Distribution activities.
3. GMP Compliance Details

The Arklow site operates in compliance with the ICH Q7 and US FDA Part 210/211.

3.1 Quality Management Systems

General
- Sigma-Aldrich SAFC Arklow has established a comprehensive Management System covering all aspects of its business.
- 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 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 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.
- 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.
- 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 Tetra CS3.
- Appropriate processes and documents are in place to ensure compliance with the requirements of ICH Q7.
- Production and service provision are designed to ensure safe and compliant manufacture of materials.
- Control of measuring and monitoring devices
- All measuring and control devices are controlled and calibrated on a regular base.

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 analyze 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. Miscellaneous Site Information
Sigma-Aldrich is committed to serving the communities where we live and work. We are committed to a safe and fair work environment where our employees can grow and enrich themselves in the diversity that this worldwide organization offers.

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. The Arklow Facility participates in Standard, Premium and Elite Quality tier products. For more information about EQP, please visit www.safcsupplysolutions.com/eqp.

- Standard tier products are intended for research use and include: standard change notification and batch-specific Certificate of Analysis.
- Premium tier products are intended for research or raw material use and include: premium change notification, batch-specific Certificate of Analysis, batch-specific Certificate of Origin, expiry or recommended retest dates.
- Elite tier products are intended for raw material use and include: elite change notification, batch-specific Certificate of Analysis, batch-specific Certificate of Origin and expiry or recommended retest dates.

The Arklow facility has the capability to package in a Class 100,000 (ISO 8) environment. The site is registered to OHSAS18001 and ISO14001 Environmental Management Standard and operates under a strict Environmental Licence regime.

5. Contact Information
Please contact your local Sigma-Aldrich representative for more information.
Arklow - Supply Chain Security Overview

1. Scope
   - Sigma-Aldrich Ireland Limited, Vale Road, Arklow, County Wicklow, Ireland.
   - Corporate ownership: The Arklow 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 the Arklow Facility to the end user:
   - The Arklow Facility is an “Authorised Economic Operator” (AEO) - Certificate No. IE AEOF 10001102 issued 27 Jan 2010
   - The Site has been inspected by US Customs under the C-TPAT initiative
   - The Site is a “Known Consignor” – Certificate No. IE/KC/01014
   - All Pharma products are packed in tamper-evident packaging.
   - All shipments are made with approved Logistics partners.
   - Environmental controls can be implemented during transport (e.g. to control cold chain).
   - Shipments are in accordance with INCOTERMS 2010

3. Security Information
   3.1 Scope of Security Plan
      - The Operations Department is responsible for site security.
      - All relevant procedures and policies are part of the management system. The overall system is internally annually reviewed under cGMP, ISO14001 and OHSAS Quality, Environmental and Safety Management Systems.
      - All employees and contractors receive initial Induction, and refresher training on Security, cGMP and EHS requirements
      - Procedures for data and computer system protection are in place and part of the management system.
      - Site access control
        - 24/7 manned security
        - 9 CCTVs with 30 day recording capability. Car registration recording. Security-fenced site.
        - Ingress/egress of employees and contractors is monitored through an electronic access control system or a central gate manned by an external security service and closed circuit television.
        - Sensitive areas are additionally locked with an electronic access control system.
        - Contractors are not permitted access to Pharma Warehouse.

   3.2 Personnel Security
      - Pre-employment background checks are performed on all employees.
      - Background checks are performed on temporary and contract personnel.
      - All employees and contractors receive training on Security, cGMP and EHS requirements.
      - Individual employee badges are collected upon permanent leave of the company to avoid unapproved access to the site.
4. **cGMP, EHS and Security Programs**
   - The site is registered to OHSAS18001, ISO50001 and ISO14001.
   - Quality, EHS and Operations Departments develop and implement Systems to meet cGMP, EHS and Security regulatory and corporate requirements.
   - System elements include Training, Monitoring, Improvement projects, Investigations, Reviews and Internal audits.
   - A documented emergency response plan outlines responsibilities and actions in the event of serious incidents.

5. **Miscellaneous site Information**
   - The Arklow facility has redundancy in manufacturing capability in the event of a critical vessel failure.
   - The initiatives at Sigma-Aldrich Corporation promote greater environmental responsibility and support energy conservation, natural resource conservation, material re-use, 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 Sigma-Aldrich worldwide offices](https://www.sigma-aldrich.com).
Certificate of Registration of Occupational Health and Safety Management System to OHSAS 18001:2007

Sigma Aldrich Ireland Ltd
Vale Road
Arklow
Co. Wicklow

NSAI certifies that the aforementioned company has been assessed and deemed to comply with the provisions of the standard referred to above in respect of:

The manufacture and supply of advanced pharmaceutical intermediates and active pharmaceutical ingredients and the procurement, sales and distribution of reagents and chemicals for research, development, production and analytical purposes.

[Signature]

Registration Number: 18/0267
Original Registration: 20 December 2012
Last amended on: 24 January 2016
Valid from: 26 January 2016
Remains valid to: 19 December 2018

This certificate is subject to conditions that the Approved Occupational Health and Safety Management System is maintained in an adequate and effective manner.

NQA
National Standards Authority of Ireland

IQNet
International Certification Network

CERT-013: 18001:2007 NL A4 (S)
NSAI

Certificate of Registration of Environmental Management System to I.S. EN ISO 14001:2004

Sigma Aldrich Ireland Ltd
Vale Road
Arlow
Co. Wicklow

NSAI certifies that the aforementioned company has been assessed and deemed to comply with the provisions of the standard referred to above in respect of:

The manufacture and supply of advanced pharmaceutical intermediates and active pharmaceutical ingredients and the procurement, sales and distribution of reagents and chemicals for research, development, production and analytical purposes.

Approved by

Registration Number: 14.0125
Original Registration: 08 January 2008
Last amendment: 22 January 2014
Valid from: 22 January 2014
Remains valid to: 07 January 2017

All valid certificates are listed on NSAIs website - www.nsa.ie. The continued validity of this certificate may be verified online.”

Certificate:

SAFC

Arklow Site and Supply Chain Overview
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Sigma Aldrich

Vale Road
Arklow
Co. Wicklow

NSAI certifies that the aforementioned company has been assessed and deemed to comply with the provisions of the standard referred to above in respect of:

The manufacture and supply of advanced pharmaceutical intermediates and active pharmaceutical ingredients and the procurement, sales and distribution of reagents and chemicals for research, development, production and analytical purposes.

Approved by
Minra Ltd.
CEO MD

NSAI Certified

Registration Number: SI 050954
Original Registration: 04 March 2016
Last amended on: 04 March 2018
Valid from: 01 March 2016
Expires valid to: 03 March 2019

This certificate remains valid on condition that the Approved Energy Management System is maintained in an adequate and effective manner.

All valid certifications are listed on NSAI’s website - www. nsai.ie. The continued validity of this certificate may be verified under “Certified Company Search”.

NSAI (National Standards Authority of Ireland), 3 Swift Square, Northwood, Sandyford, Dublin 18, Ireland T: +353 1 807 3000 E: info@nsai.ie www.nsa.ie

CERT-016: ISO 50001 2011 INAB A4 (1)