Enhanced Quality Product Documentation

Fumaric Acid

PharmaGrade, USP / NF, Manufactured under appropriate GMP controls for pharma or biopharmaceutical production

Product Number ARK2164

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

2. General Product Information

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Fumaric Acid</th>
</tr>
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<tbody>
<tr>
<td>Product Number</td>
<td>ARK2164</td>
</tr>
<tr>
<td>Qualifier</td>
<td>Fumaric Acid PharmaGrade, USP / NF, Manufactured under appropriate GMP controls for pharma or biopharmaceutical production</td>
</tr>
<tr>
<td>Quality Level</td>
<td>GMP- Compendia</td>
</tr>
</tbody>
</table>

3. Manufacturing, Packaging, Release Site and Supplier Information

Site of manufacturing, testing, packaging and product release:
Sigma Aldrich Ireland Limited
Vale Road, Arklow, County 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.

4. Physico-chemical Information

4.1 Synonyms
- (E)-Butenedioic acid
- trans-1,2-Ethylenedicarboxylic acid
- 2-Butenedioic acid

4.2 Linear Formula
HOOCCH=CHCOOH

4.3 Molecular Formula:
C₄H₄O₄

4.4 Molecular Mass
116.07

4.5 CAS Number
110-17-8

4.6 Origin
- The product is manufactured, synthetically. Only raw materials of synthetic origin are used.

4.7 Manufacturing process
- Synthesis from Maleic Acid.
4.8 Specification

<table>
<thead>
<tr>
<th>Analytical Items</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identification:</td>
<td>Infra-Red Spectrum conforms to Reference Spectrum</td>
</tr>
<tr>
<td>2. Residue on Ignition</td>
<td>Limit: NMT 0.1%</td>
</tr>
<tr>
<td>3. Heavy Metals</td>
<td>Limit: NMT 10 ppm</td>
</tr>
<tr>
<td>4. Organic Impurities by HPLC</td>
<td>Limit: Maleic Acid NMT 0.1%</td>
</tr>
<tr>
<td>5. Assay (Titrimetric):</td>
<td>Limit: 99.5 – 100.5%</td>
</tr>
<tr>
<td>6. Water Content:</td>
<td>Limit: 0.5%</td>
</tr>
</tbody>
</table>

4.9 Batch results
Certificates of Analysis are available for each lot produced.

5. Regulatory Information

5.1 Compendial compliance
*Fumaric Acid* meets compendia reference USP NF.

5.2 Master file
Drug Master File (DMF) is not available for this product.
EDQM Certificate of Suitability is not currently available for this product.

5.3 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 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.

5.4 Allergen information
This product is not produced with any known major food allergens (as defined by the FDA and WHO).

5.5 GMO information
The product is not produced using GMOs and is considered GMO free.

5.6 Residual solvents information
The product is produced without use of Class 1-3 organic solvents.

5.7 Metal catalyst and metal reagent residues
The product is produced without use of metal catalyst or metal reagent.

5.8 Kosher/Halal status
No status.

5.9 Melamine statement
This product is not recognized as high risk for melamine contamination.
This material is not assayed by a test that detects nitrogen. This product is considered negligible risk for melamine contamination.
The measured nitrogen content of this material is less than 2.5%. This product is considered negligible risk for melamine contamination.

6. Miscellaneous Product Information

6.1 Explanation of the lot/batch numbering system
The product is manufactured in a batch process.
Batch size is approximately 500 to 750 kg.
Each produced batch is identified by a specific, unique batch number.
The batch number takes the following general form B-FMAC-XXX-YYY
B- refers to batch, FMAC- is the material abbreviation for Fumaric Acid, XXX- is a code number referring to the year of manufacture and finally YYY- is the actual batch number and is unique for each individual batch.
Example: B-FMAC-127-1

6.2 Expiration date and/or recommended re-evaluation interval
A stability programme is currently underway at present a 1 year retest interval is recommended.

6.3 Handling, Shipping Conditions and Long-term Storage Recommendation
If stored in the original unopened containers under ambient conditions, no significant change of the material can be observed.
No special storage conditions are required.

6.4 Packaging
SAFC Arklow can accommodate various pack sizes:
- Primary packaging material: double Polyethylene Liner sealed with Tamper proof tag
- Secondary packaging material: HDPE or Fibreboard drum, sealed with a numbered Sigma-Aldrich tamper evident seal

7. Revision History
Please note that updates are communicated to customers with Change Notification Agreements only.

8. Contact Information
Please contact your local Sigma-Aldrich representative for more information:
Arklow - Quality Overview

The Sigma-Aldrich® / SAFC® 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 Irish Medicines Board (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 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/01014/1112
   - 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 under cGMP and ISO14001 Quality and Environmental 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, EMS and Security Programs
   - 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 worldwide offices](#).
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.

Registration Number: 18.0267
Original Registration: 20 December 2012
Last amended to: 20 December 2012
Valid from: 20 December 2012
Remains valid to: 19 December 2015

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

NSAI (National Standards Authority of Ireland), 1 Swift Square, Northwood, Santry, Dublin 9, Ireland T: +353 1 819 3800 F: info@nsai.ie www.nsa.ie
NSAI Inc. 463 Airmont Street, Nashua, New Hampshire, NH 03063, USA T: 603 883 1411 F: info@nsai.com www.nsaiinc.com

CERT-015: 18001: 2007 NL A4 (5)
NSAI Certificate of Registration of Environmental Management System to I.S. EN ISO 14001:2004

Sigma Aldrich Ireland Ltd
Vale Road
Arkwlow
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:
Mairead Buckley
CEO NSAI

Registration Number: 1440425
Original Registration: 08 January 2008
Last renewed on: 24 January 2012
Valid from: 22 November 2010
Valid to: 07 January 2014

All valid certificates are listed on NSAI's website - www.n sai.ie. The continued validity of this certificate may be verified under 'Certified Company Search'.

Sigma-Aldrich Ireland Ltd.
Registered in Ireland No. 259923 Registered Office: Vale Road, Arklow, Co. Wicklow, Ireland
Directors: James Ennis, Mike Harris (UK), Eric Green (USA), Graham Lucas (UK)