- **Acetic Acid, Glacial Ph. Eur. / USP / JP**
- **Acetic Acid, Glacial Ph. Eur. / USP / JP parenteral grade**

- **Acetic Acid 80 %**
- **Acetic Acid 80 % API grade**

HEDINGER
1843
A pure decision.

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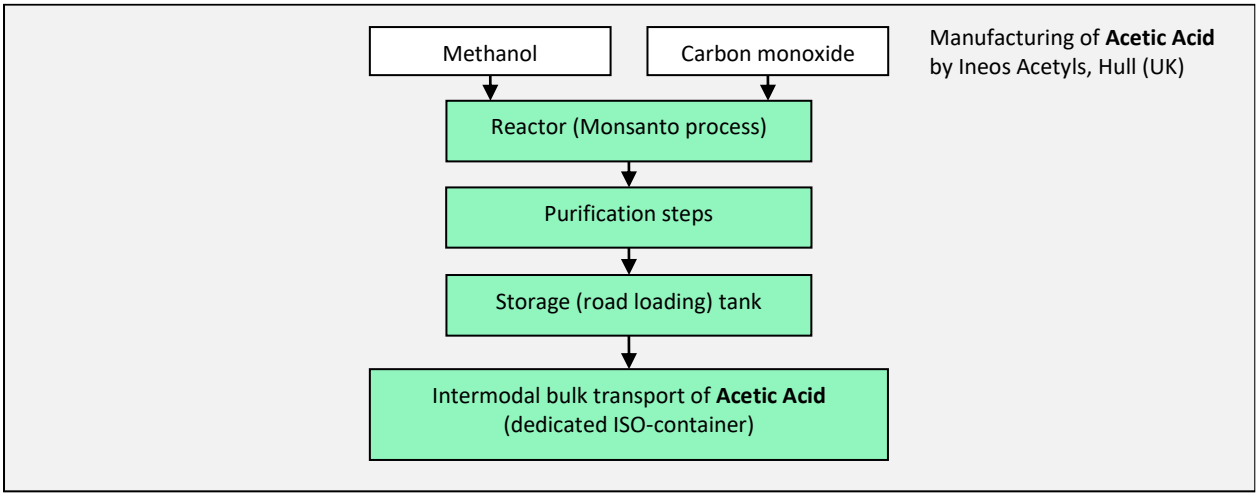
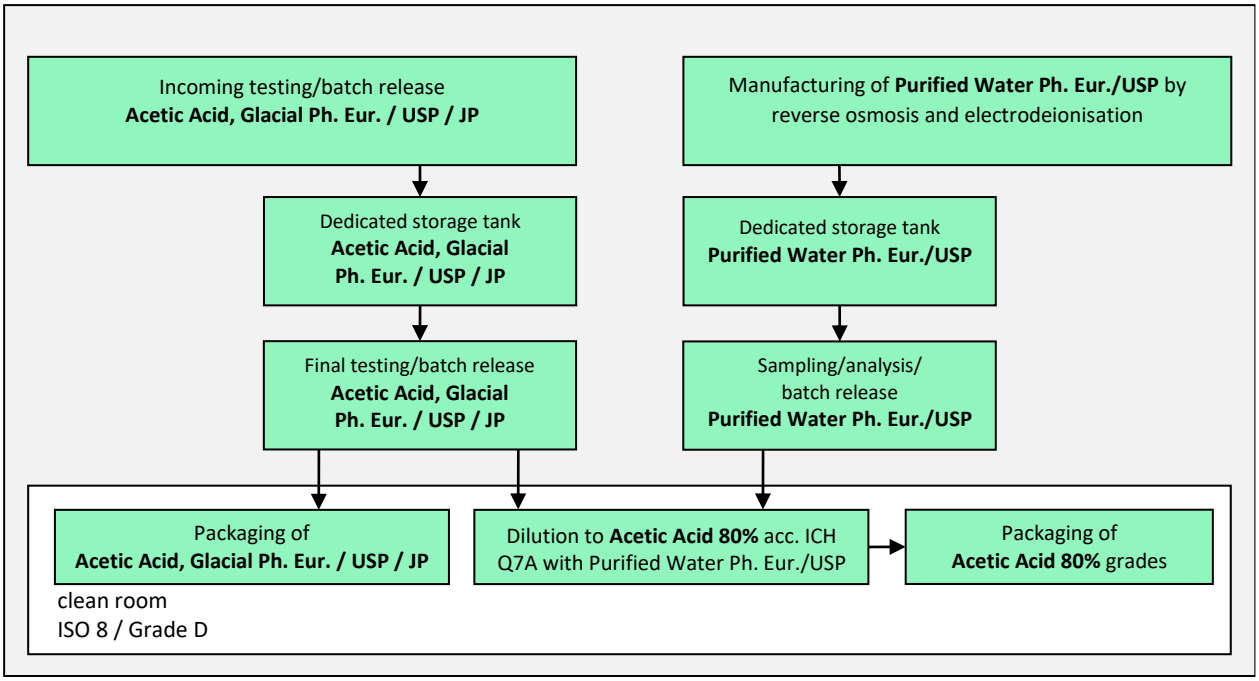
Production of Acetic Acid by INEOS Acetyls UK Ltd., Hull, UK



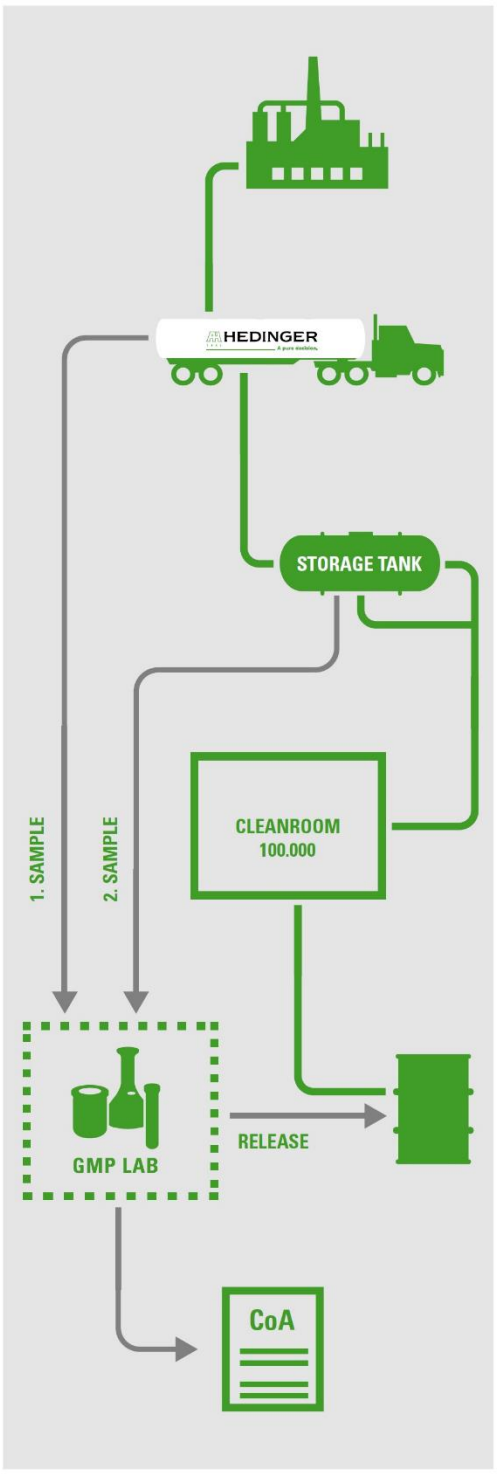
- Dedicated manufacturing unit
- Continuous manufacturing process
- Catalytic carbonylation of methanol
- One storage tank load is defined as one batch of homogenous product
- Intermodal bulk transport in dedicated ISO tank container on behalf of Hedinger

Handling of Acetic Acid by Hedinger



- Sampling by qualified sampling personnel under the responsibility of Quality Control department
- Full analysis according to Ph. Eur., USP and JP in a GMP laboratory in compliance with EU-GMP Part I, Chapter 6
- Release by Qualified Person according to EU-GMP
- Manufacturing and repackaging in classified cleanrooms (classification and operating conditions according to EU-GMP Part I, Annex 1 and ISO 14644)
- Grade D (100,000) / ISO 8
- Qualification of the HVAC (Heating, Ventilation & Air-Conditioning) system
- Regular validation of cleanroom (monitoring)

Hedinger integrated GMP/GDP-System



Excipient Manufacturer
Verifiying of GMP compliance by Hedinger
via GMP audits of the manufacturing plant
"one product – one partner" strategy

Bulk Handling
(loading/transport/unloading)
Only dedicated Equipment
(for example own qualified tank trucks, hoses)
only dedicated storage tanks

Quality of Primary Packaging Material
Supplier qualification
Incoming control and release
Brand new packaging material only

Repackaging Under Controlled Conditions
in Clean Rooms Class D (100.000)
3-step air filtration
Air locks for personnel and packaging material
Repackaging in containers from 250 ml – 1.000 l

Batch-Related Full Analysis in
2 Internal GMP Laboratories
Full analysis according to all pharmacopoeias and GMP
Customised test methods
Batch release from a qualified person (QP)

Reduced Incoming Control at the
Drug Manufacturer
Hedinger's certificate of analysis enables
reduced incoming control (EU-GMP Part 1 Chap. 5)
Significant cost savings possible

Quality Assurance (QA)
Supporting all Levels
of the Supply Chain:

Documentation
According to GMP

–

Full Traceability at
Each Level

–

Training for all
Those Involved

–

Change Control

–

Regulatory Information

–

QA Agreements

Quality / Regulatory Compliance by Hedinger

- Purity of Acetic Acid, Glacial Ph. Eur./USP/JP ≥ 99.9 %
- Bulk transport in dedicated ISO tank container
- Certification according to current pharmacopoeia monographs:
  - European Pharmacopoeia (Ph. Eur.)
  - United States Pharmacopeia (USP)
  - Japanese Pharmacopoeia (JP)
- Questionnaires with regulatory information of the product provided by Hedinger
- No risk of contamination with BSE/TSE risk materials (bovine spongiform encephalopathy /transmissible spongiform encephalopathy)
- No risk of contamination with materials from GMO (genetically modified organism)
- No risk of contamination with aflatoxins
- No risk of contamination with allergens
- Fulfils requirements of ICH Q3C Residual Solvents Guidelines
- Data on elemental impurity profile according to current ICH Q3D guideline available
- EU-approved food additive in accordance with E260 (Commission Regulation (EU) No 231/2012)
- Kosher-certified
- Special grade for parenteral applications available
- Confirmation for nitrosamine risk evaluation is available

GMP

The product is manufactured by INEOS Acetyls UK Ltd. according to ISO 9001.
The manufacturing facility is audited by a Qualified Person of Hedinger approximately every 3 years according to IPEC-PQG GMP principles to ensure an appropriate level of GMP.

Quality Control by Hedinger

The Quality Control department of Hedinger runs a full monograph testing according to current Ph. Eur., USP and JP under EU-GMP Part I conditions. Every batch is released by a Qualified Person according to EU-GMP . A Certificate of Analysis signed by a Qualified Person with all Ph. Eur., USP and JP data will be provided with every delivery.

- Full analysis according to Ph. Eur., USP and JP
- GMP laboratory in compliance with EU-GMP Part I, Chapter 6
  - GMP documentation of analytical results
  - Equipment qualification and maintenance
  - Out-of-specification result investigations
  - Qualification of standards and reference materials
  - Batch documentation and shelf life control of reagents
  - Regular qualification and requalification of personnel
  - Stringent pharmacopoeia revision management
  - Method validation according to ICH Q2
  - Trending and PQR

Certificates of Analysis signed by a Qualified Person

- Manufacturing authorization according to EU drug regulations for laboratories
- Batch release by a Qualified Person according to EU-GMP
- Certificate of Analysis signed by a Qualified Person for each individual shipment
- Format of Certificate of Analysis according to “IPEC Certificate of Analysis Guide”
- Since all pharmaceutical analyses and Certificate of Analysis fully comply with relevant regulations, customers may reduce full incoming testing to save costs (EU-GMP I, chapter 5.35-36.)




Quality Control Laboratory, Stuttgart


Teutschenthal

Repackaging in cleanrooms by Hedinger

The product is repackaged by Hedinger under clean room conditions into customized packaging sizes following EU-GMP Part II and EXCiPACT / IPEC-PQG GMP requirements for excipients:

Repackaging of Acetic Acid in Hedinger cleanroom Grade D

- Manufacturing and repackaging in classified cleanrooms (classification and operating conditions according to EU-GMP Part I, Annex 1 and ISO 14644)
- Grade D (100,000) / ISO 8
- Standard quantities: 5 L - 1000 kg HDPE container or 1 and 2.5 L amber glass bottles
- Qualification of the HVAC (Heating, Ventilation & Air-Conditioning) system according to EU-GMP Part I, Annex 15 and ISO 14644
- Regular validation of cleanroom conditions (monitoring)
  - Airborne particles
  - Microbiology
- State-of-the-art preventive maintenance of HVAC systems
- Hygiene program for staff and premises
  - Regular hygiene training
  - Appropriate gowning and sanitation practices
- Qualified packaging material
  - Audited suppliers
  - Defined specifications
- Exclusively use of brand-new primary packaging materials

Distribution according to GTDP (Good Trade and Distribution Practice) by Hedinger

- Transport in a dedicated ISO tank container provided by an approved haulier
- Compliance with IPEC Good Distribution Practices Guide for Pharmaceutical Excipients and EXCiPACT GMP/GDP
  - Full traceability through documentation of the entire supply chain
  - Prevention of cross-contamination through appropriate GMP handling and use of dedicated equipment
  - Ideal storage conditions
- Transparent and short supply chain

Additional customer-specific services

- Quality assurance agreements including
  - Change control
  - Regulatory information
  - Outsourcing of testing according to EU-GMP Part 1, chapter 5.35 can be discussed
- Customer-specific on-site audit dates at Hedinger possible
- Customer-specific quantities per container
- Customer-specific labelling (customer's data)
- Transfer of analytical raw data (chromatograms etc.)

Parenteral Grade

- Acetic Acid, Glacial Ph. Eur./USP/JP is available as a special grade for parenteral applications
  - Bioburden and Endotoxin specification
  - Bioburden and Endotoxin testing per batch
  - Highest level of controls during filling processes (supervisory personnel permanently present in the clean room during filling)
  - Key point controls during filling processes (sampling from filled containers)
  - Tamper evident closure with void label
  - GDP transport is available for parenteral grade products

API Grade (Active Pharmaceutical Ingredient)

- Acetic Acid 80 % API grade is produced by Hedinger according to EU-GMP Part II (ICH Q7)
  - Raw materials: Acetic Acid, Glacial Ph. Eur./USP/JP and Purified Water Ph. Eur./USP

Customer-specific aqueous solutions

- Customer-specific solutions of Acetic Acid, Glacial Ph. Eur./USP/JP with Purified Water Ph. Eur./USP (1–99 %)
- Qualified water-purification system according to GMP (see last page)
  - Validated manufacturing process
  - Regular monitoring of water quality according to Ph. Eur. and USP
    - Microbiology/Endotoxins
    - TOC (qualified according to Ph. Eur. and USP)
    - Conductivity
    - Pharmacopoeia monographs
- Dilution processes in accordance with GMP
  - Head of manufacturing is responsible for process
  - Validated process
- Full GMP documentation

Water purification in accordance with GMP

Highly Purified Water Ph. Eur. 9.0 / Water for Injection USP*
Purified Water Ph. Eur.*/USP*

Production (Fig.1):
1. Step: Reverse osmosis of potable water
2. Step: Electrodeionisation
3. Step: Ultrafiltration

Quality Control

- Continuous monitoring of production-parameters
- Continuous monitoring of relevant quality parameters for “Highly purified water” according to Ph. Eur. 9.0 and “Water for Injection” according to USP*
- Certificate of analysis according to the “IPEC Certificate of Analysis guide”

GMP

- Purification and storage are carried out in accordance with GMP-guidelines
- Stainless steel materials
- Permanent water circulation with UV-irradiation and cooling
- Monitoring of microbial status according to FDA “Guide to inspections of high purity water systems”
- Periodical sanitisation by heat treatment of all parts of the system
- Complete qualification and documentation to meet the requirements of “Highly purified water” Ph. Eur. 9.0 and “Water for Injection” USP*

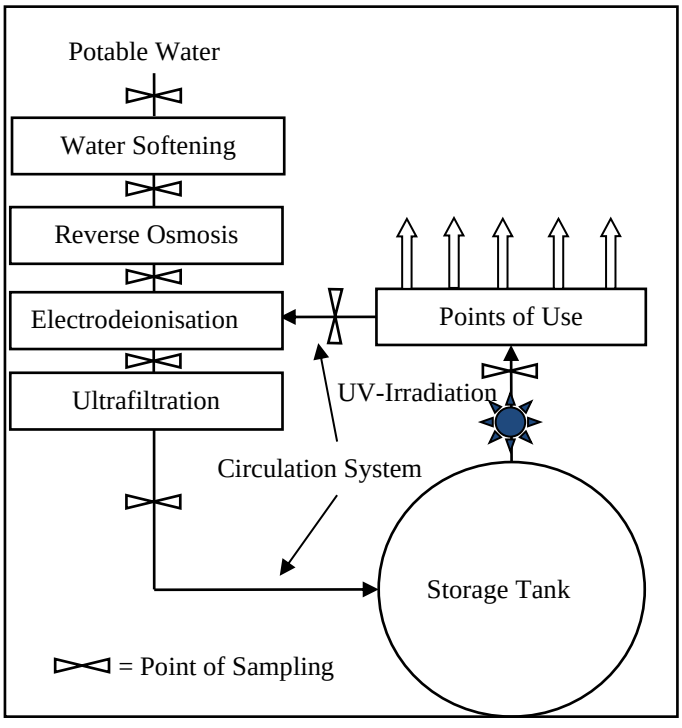
Meeting pharmaceutical requirements:
Highly Purified Water Ph. Eur. 9.0 / WfI USP*

Parameter	Ph. Eur. 9.0	USP*
Characters	clear, colourless	–
Total organic carbon	≤ 0.5 mg / l	≤ 0.50 mg / l
Conductivity	conforms Ph. Eur. 9.0	conforms USP*
Nitrates	≤ 0.2 ppm	–
Microbial contamination	≤ 10 CFU / 100 ml	–
Bacterial endotoxins	< 0.25 EU / ml	< 0.25 EU / ml

Purified Water Ph. Eur.*/USP*

Requirement	Ph. Eur.*	USP*
Description/Characters	clear, colourless, odourless and tasteless liquid	–
Acidity or alkalinity	conforms Ph. Eur.*	–
Oxidizable substances	conforms Ph. Eur.*	conforms USP*
Chloride	conforms Ph. Eur.*	–
Nitrates	≤ 0.2 ppm	–
Sulfate	conforms Ph. Eur.*	–
Ammonium	≤ 0.2 ppm	–
Calcium, Magnesium	conforms Ph. Eur.*	–
Total organic carbon	≤ 0.5 mg / l	≤ 0.50 mg / l
Residue on evaporation	≤ 0.001% (m/V)	–
Conductivity	conforms Ph. Eur.*	conforms USP*
Microbial contamination	≤ 10^2 CFU / ml	–

Figure1:



*Ph. Eur. and USP in their latest issue