Glycerol (vegetable)

- **Glycerol Ph. Eur./USP (vegetable)**
- **Glycerol Ph. Eur./USP/JP parenteral grade (vegetable)**

- **Glycerol 85% Ph. Eur. (vegetable)**

Aug. Hedinger GmbH & Co. KG

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Glycerol Ph. Eur./USP (vegetable)
Glycerol Ph. Eur./USP/JP parenteral grade (vegetable)

Manufactured from crude glycerol from biodiesel production (mainly from rapeseed oil)

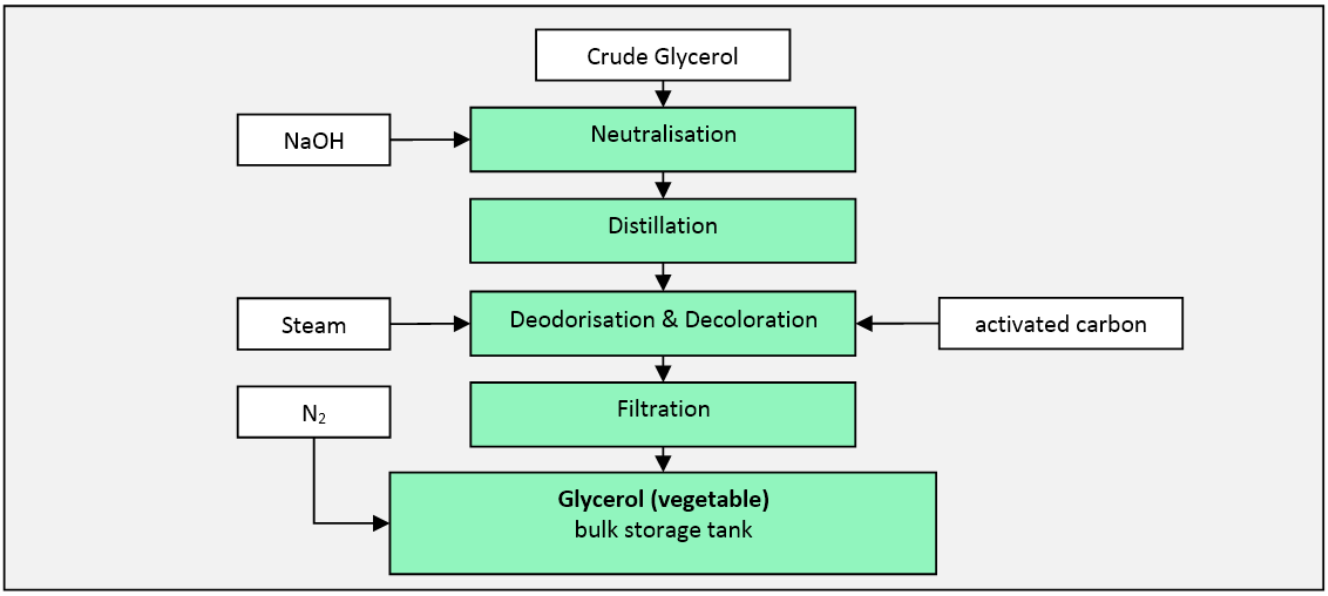
Glycerol 85% Ph. Eur. (vegetable)

Manufactured from Glycerol Ph. Eur./USP (vegetable) and Purified Water Ph. Eur./USP

Fast facts

- Manufacturing, testing and packaging processes in compliance with **EU-GMP Part II**
- **Outsourcing of testing** according to EU-GMP Part I (chapter 5.35/5.36) is possible
- Final packaging in **classified cleanrooms** (grade D / ISO 8) (1 L - 1000 kg)
- **CEP** available for Glycerol Ph. Eur. / USP (vegetable)
- **EU-GMP Part II Certificate** of ANSM available for the **manufacturing site** of Glycerol
- **EU-GMP Part II Certificate** of German authorities available for **Hedinger**
- **EXCiPACT GMP/GDP** Certificates and audit reports (on the basis of an NDA) available for **Hedinger** sites
- Products are **kosher certified**
- Glycerol Ph. Eur./USP/JP parenteral grade (vegetable) is available for microbiologically sensitive applications with **TAMC, TYMC** and **endotoxin specification**
- **Shelf life: 24 months** from manufacturing date for Glycerol Ph. Eur. / USP (vegetable) and Glycerol Ph. Eur./USP/JP parenteral grade (vegetable)

Manufacturing process at Oleon SAS, Venette, France



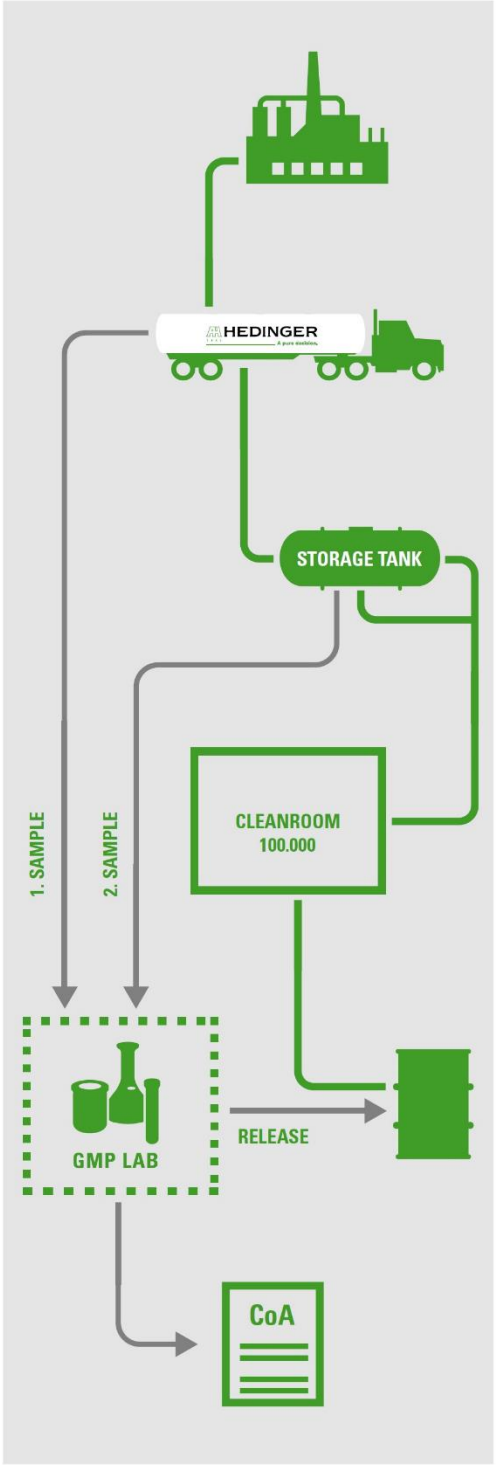
- Manufacturing process complies with EU-GMP Part II Guidelines and IPEC-PQG GMP Guidelines for Pharmaceutical Excipients
- Dedicated manufacturing facility

GMP compliance of the manufacturing process (EU-GMP Part II) is certified by French competent authorities (ANSM). The manufacturing facility is audited by a Qualified Person of Hedinger. An audit report is available for customers after signing a Confidentiality Agreement.

Regulatory Compliance

- Certification of each batch according to current pharmacopoeia monographs by Hedinger:
  - Ph. Eur., USP, JP (on request)
- Quality assurance agreements between customers and Hedinger upon request
- Customer-specific (on-site) audits at Hedinger
- Classified by FDA as Generally Recognized As Safe (GRAS)
- Compliance with FDA guidance “Testing of Glycerine for Diethylene Glycol”
- Questionnaires with regulatory / GMP information of the product provided by Hedinger
- Fulfills requirements of current ICH Q3C Residual Solvents Guideline
- Data on elemental impurity profile according to current ICH Q3D guideline are available
- EU-approved food additive in accordance with E422 [(EC) No 1333/2008, (EU) No 231/2012)
- Produced from non-GMO sustainable vegetable oils. No labelling is required according to EU Regulation (EC) No 1829/2003 and (EC) No 1830/2003
- Kosher certified
- Special grades for microbiologically sensitive formulations available (TAMC, TYMC, endotoxins specified)
- Confirmation for nitrosamine risk evaluation is available

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

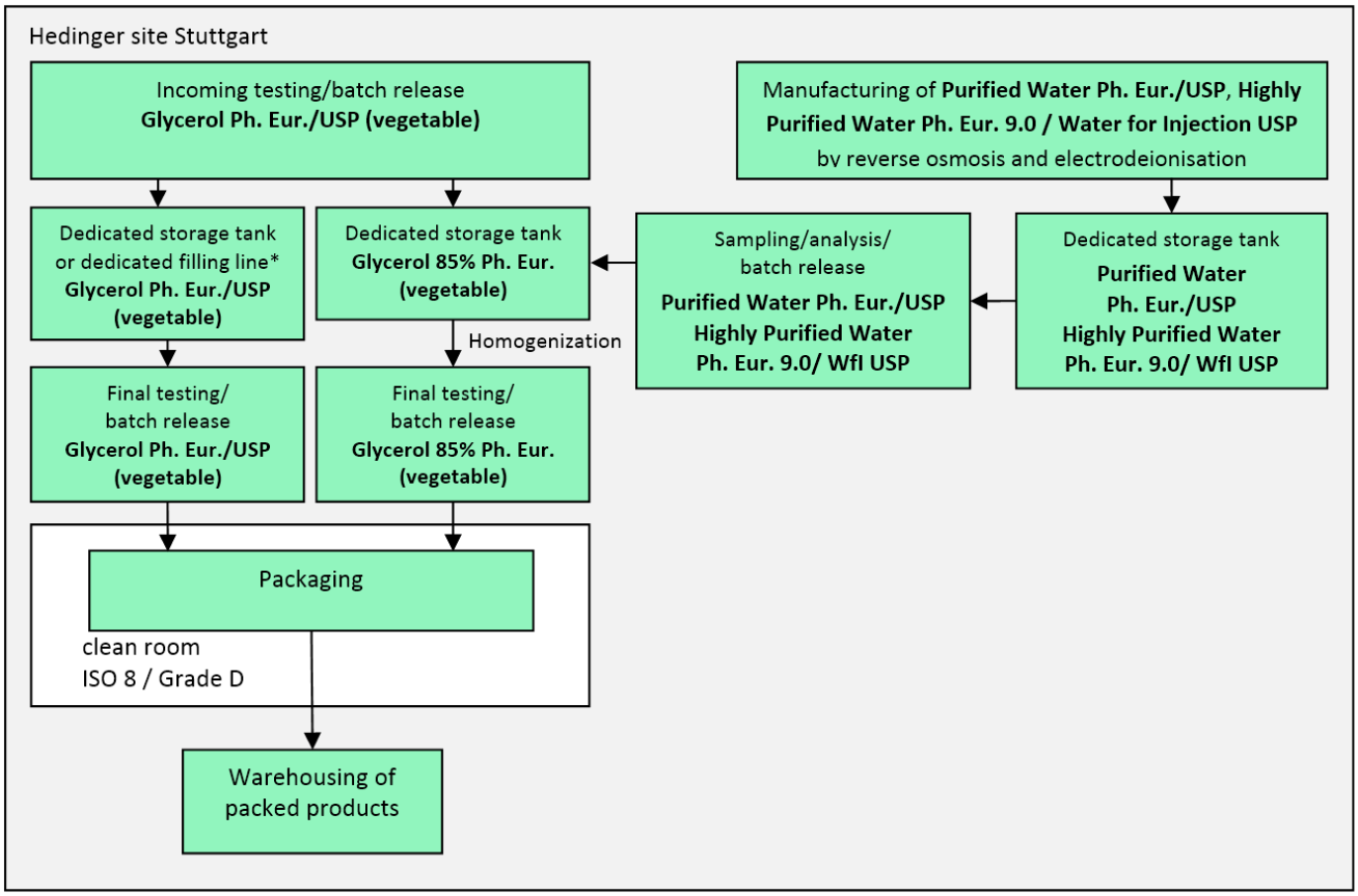
–

Regulatory Information

–

QA Agreements

Handling of Glycerol / Manufacture of Glycerol 85% by Hedinger



- Sampling by qualified sampling personnel under the responsibility of Quality Control department
- Water purification (see last page) by Hedinger in accordance with GMP
- Manufacturing and repackaging in classified cleanrooms EU-GMP Grade D / ISO 8
- Qualified HVAC (Heating, Ventilation & Air-Conditioning) system
- Regular validation of cleanroom (monitoring)

* In case of direct packaging through a dedicated filling line, there is only one complete specification testing.

Quality Control by Hedinger

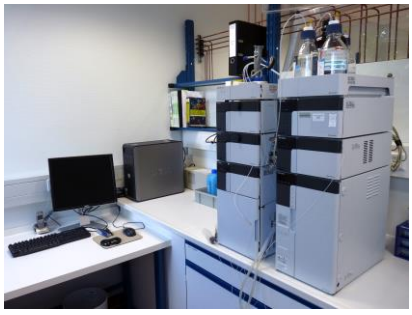
The Quality Control department of Hedinger runs a full monograph testing according to current Ph. Eur. and USP (JP on request) under EU-GMP Part I conditions. Every batch is released by a Qualified Person according to EU-GMP. A Certificate of Analysis signed by a Qualified Person with all Ph. Eur. and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

- Full analysis according to Ph. Eur. and USP (JP, ChP and others on request)
  - Provision of analytical raw data (chromatograms etc.)
- 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 authorisation according to EU drug regulations
- Batch release by a Qualified Person according to EU-GMP
- Certificate of Analysis signed by a Qualified Person for each individual delivery
- 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

Packaging in cleanrooms by Hedinger

Hedinger packages the product under cleanroom conditions into customised packaging sizes following EU-GMP Part II and EXCiPACT / IPEC-PQG GMP requirements for excipients:

- Cleanrooms according to EU-GMP Part I, Annex 1 (classification and operating conditions) and ISO 14644 (Back-Up cleanroom at Hedinger site in Teutschenthal for packaging of Glycerol in case of shut-down of the Stuttgart site)
- Grade D (100,000) / ISO 8
- Standard quantities (5 L - 1000 kg HDPE containers, 200 L drums or 1 and 2.5 L brown 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 programme for staff and premises
  - Regular hygiene training
  - Appropriate gowning and sanitation practices
- Qualified packaging material
  - Audited suppliers
  - Defined specifications
  - Incoming inspection with verification of key quality parameters and batch release
- Exclusive use of brand-new primary packaging materials

Repackaging of Glycerol in Hedinger cleanroom Grade D

Final packaging according to GMP, distribution according to GDP (Good Distribution Practice)

- Compliance with IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, EXCiPACT GMP/GDP, EU-GMP Part II and ICH Q7
  - 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

- Customer-specific packaging sizes
- Customer-specific labelling (customer's data)

Customer-specific aqueous solutions

- Customer-specific solutions (1–99%) of Glycerol Ph. Eur./USP (vegetable) with Purified Water Ph. Eur./USP
- 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
- Manufacturing processes in accordance with EU-GMP Part II (ICH Q7)
  - Head of manufacturing is responsible for process
  - Validated process
- Full GMP documentation

Parenteral Grades

Glycerol Ph. Eur./USP/JP parenteral grade (vegetable) as special grade for parenteral applications:

- Bioburden and Endotoxin specification
- Bioburden and Endotoxin testing of every batch
- Highest level of controls during filling processes (especially qualified supervisors)
- Key point controls during filling processes (sampling from filled containers)
- Temperature controlled transport is available for parenteral grade products

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*

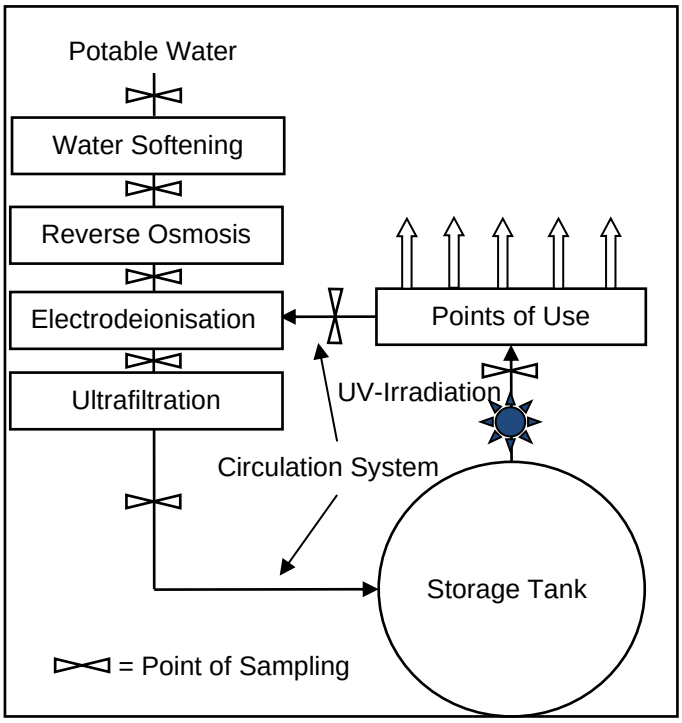
Meeting pharmaceutical requirements:
Highly Purified Water Ph. Eur. 9.0 / WfI USP*

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