



**Shell Chemicals**

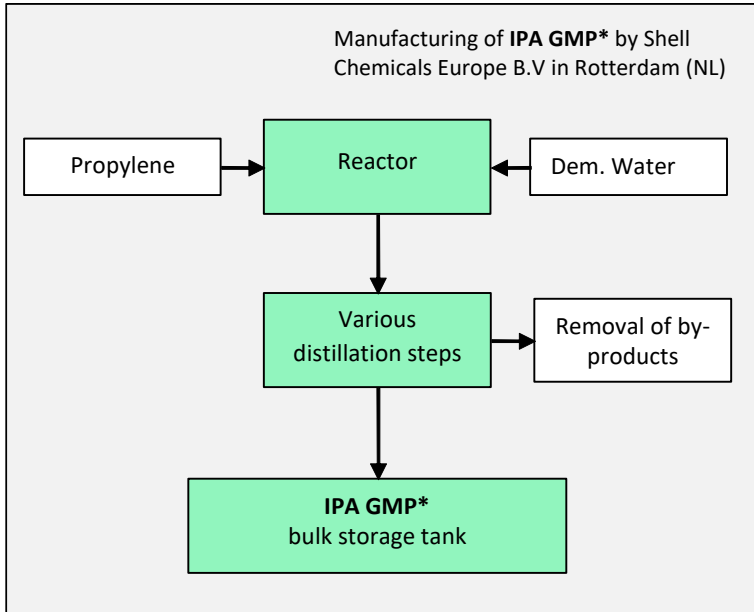
**A HEDINGER**  
1 8 4 3  
A pure decision.

- **Isopropyl Alcohol GMP Ph. Eur. / USP / JP**
- **Isopropyl Alcohol 70 % (V/V) grades  
(incl. biocidal product)**

**Aug. Hedinger GmbH & Co. KG**

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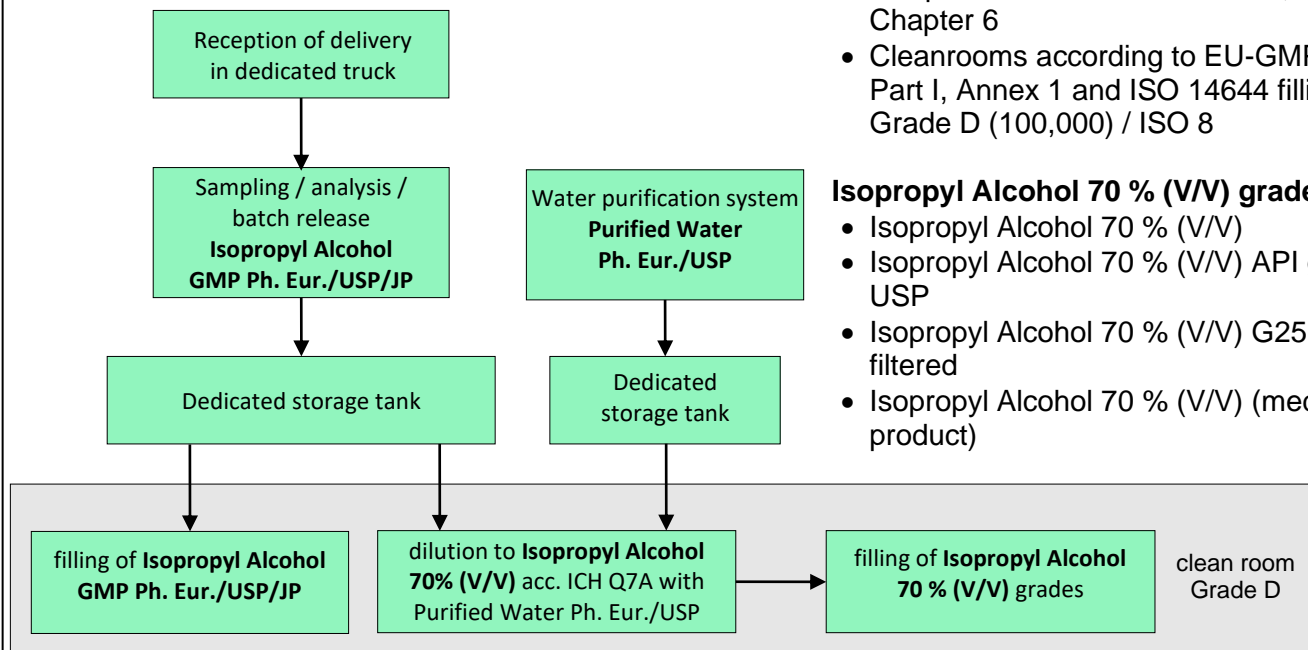
## IPA-GMP\* Production Overview



- Manufactured by Shell Chemicals Europe B.V. at a dedicated facility in Rotterdam (NL)
- Manufacturing fulfils IPEC-PQG GMP Guideline for Pharmaceutical Excipients
- Dedicated process equipment
- Filtration before loading to avoid particles
- Full traceability to raw materials and their analytical data

\*meets excipient level

## Handling of Isopropyl Alcohol by Hedinger



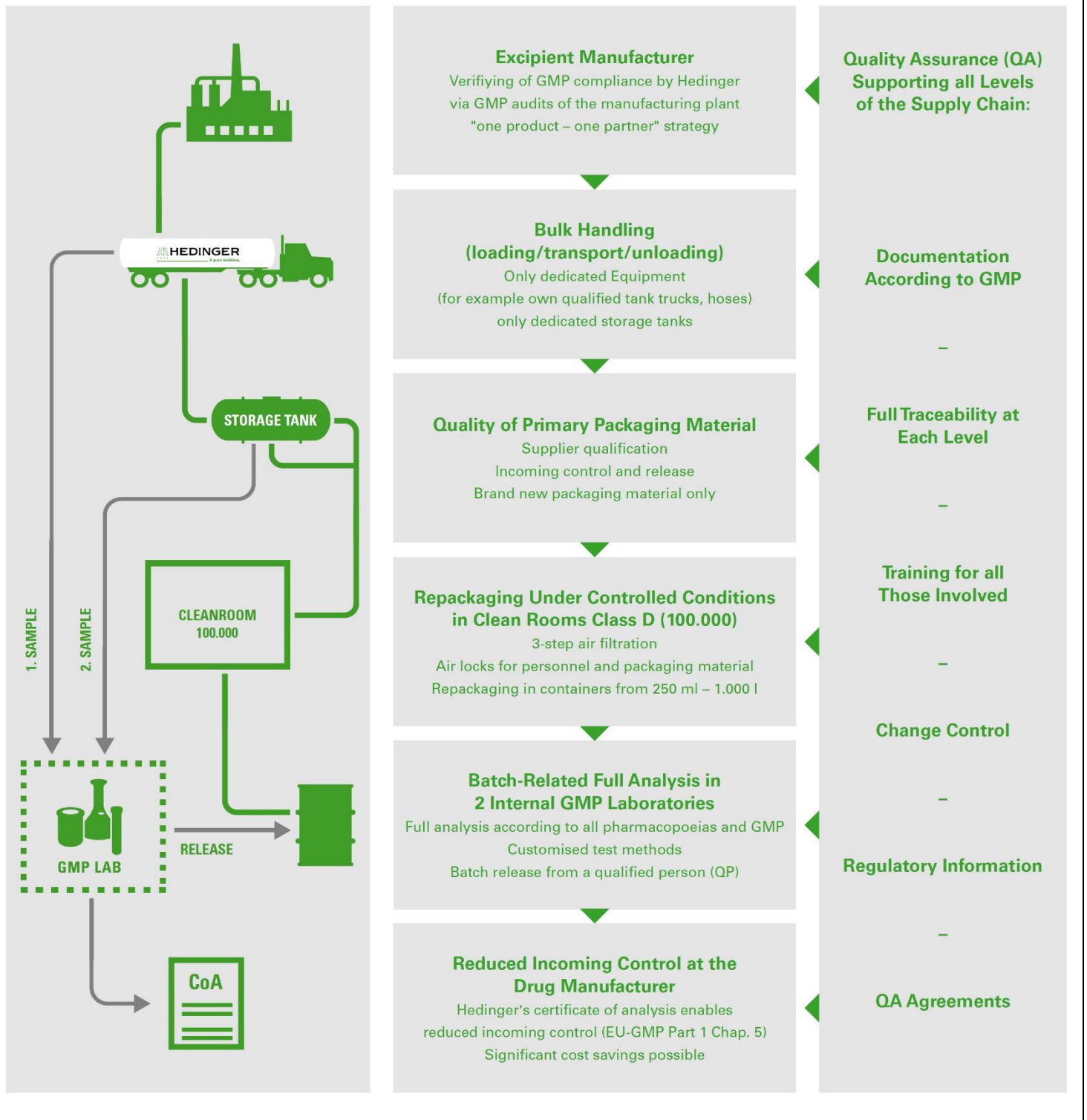
### Isopropyl Alcohol GMP Ph. Eur./USP/JP

- Full analyses according to Ph. Eur., USP and JP in a GMP laboratory in compliance with EU-GMP Part I, Chapter 6
- Cleanrooms according to EU-GMP Part I, Annex 1 and ISO 14644 filling Grade D (100,000) / ISO 8

### Isopropyl Alcohol 70 % (V/V) grades

- Isopropyl Alcohol 70 % (V/V)
- Isopropyl Alcohol 70 % (V/V) API grade/ USP
- Isopropyl Alcohol 70 % (V/V) G25 sterile filtered
- Isopropyl Alcohol 70 % (V/V) (medicinal product)

# Hedinger integrated GMP/GDP-System



## Quality / Regulatory Compliance

- Purity of Isopropyl Alcohol GMP Ph. Eur./USP/JP  $\geq 99.80\%$
- Certification of each batch according to current Ph. Eur. / USP /JP monographs by Hedinger
- Bulk transport in dedicated Hedinger tank trucks
- Questionnaires with regulatory information of the product provided by Hedinger
- No risk of contamination from BSE/TSE (bovine spongiform encephalopathy/transmissible spongiform encephalopathy)
- No risk of contamination from GMO (genetically modified organism)
- Virtually free from aflatoxins
- Virtually free from allergens
- Data on elemental impurity profile according to current ICH Q3D guideline available
- Fulfils requirements of current ICH Q3C Residual Solvents Guideline
- Detailed impurity profile available
- Confirmation for nitrosamine risk evaluation is available

## GMP

The product is manufactured by Shell according to Good Manufacturing Practices principles of the International Pharmaceutical Excipients Council (IPEC). There are special procedures in place at the manufacturing site to achieve GMP compliance and a GMP program is ongoing to improve compliance with these principles permanently. 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. A report is available for customers after signature of a Confidentiality Agreement.

## Isopropyl Alcohol for biocidal use

- Isopropyl Alcohol 70 % (V/V)
- Isopropyl Alcohol 70 % (V/V) G25 sterile filtered

These grades are notified as biocidal product according to national regulations in Germany, Austria and France. The application for authorisation according to the Biocidal Product Regulation (EU) No 528/2012 has been submitted in due time for these countries. In all three countries the product can be used as surface and skin disinfectant.

- Isopropyl Alcohol GMP Ph. Eur. / USP / JP

Produced by Shell according to IPEC-PQG GMP and batchwise fully tested in a GMP laboratory according to the respective pharmacopoeial monographs by Hedinger. For this biocidal active ingredient Hedinger is listed on the Article-95-List (List of active substances and suppliers) of the European Chemical Agency ECHA and an approved supplier. Isopropyl Alcohol GMP Ph. Eur. / USP / JP is packaged in a clean room Grade D, tested and released by a Qualified Person according to EU-GMP by Hedinger. Isopropyl Alcohol GMP Ph. Eur. / USP / JP can be used as an active ingredient for the manufacture of biocidal products.

## 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. and USP data will be provided with every delivery.

- Full analyses 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 packaged by Hedinger under clean room conditions into customized 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
- Grade D (100,000) / ISO 8
- Standard quantities (5 L – 1,000 L)
- 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
  - Monitoring of staff health
  - Appropriate gowning and sanitation practices
- Qualified packaging material
  - Audited suppliers
  - Defined specifications
  - Incoming inspection with verification of key quality parameters and batch release
- Exclusively use of brand-new primary packaging materials (except stainless steel IBCs)



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

- Transport in dedicated tank trucks
- 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
  - Extended liability
- GMP-Audit report by a Qualified Person about the manufacturing site available for customers after signing a Confidentiality Agreement
- Customer-specific on-site audit dates at Hedinger possible
- Customer-specific quantities per container
- Customer-specific labelling (customer's data)

## API Grade (Active Pharmaceutical Ingredient)

- Isopropyl Alcohol 70 % (V/V) API grade/USP is produced by Hedinger according to the following API relevant standards:
  - Raw material compliance (Isopropyl Alcohol GMP Ph. Eur./USP/JP: IPEC-PQG GMP, Purified Water Ph. Eur./USP: EU-GMP Part I)
  - Preparation of the aqueous solution according to EU-GMP Part II (ICH Q7)

## Customer-specific aqueous solutions

- Customer-specific solutions of Isopropyl Alcohol GMP 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

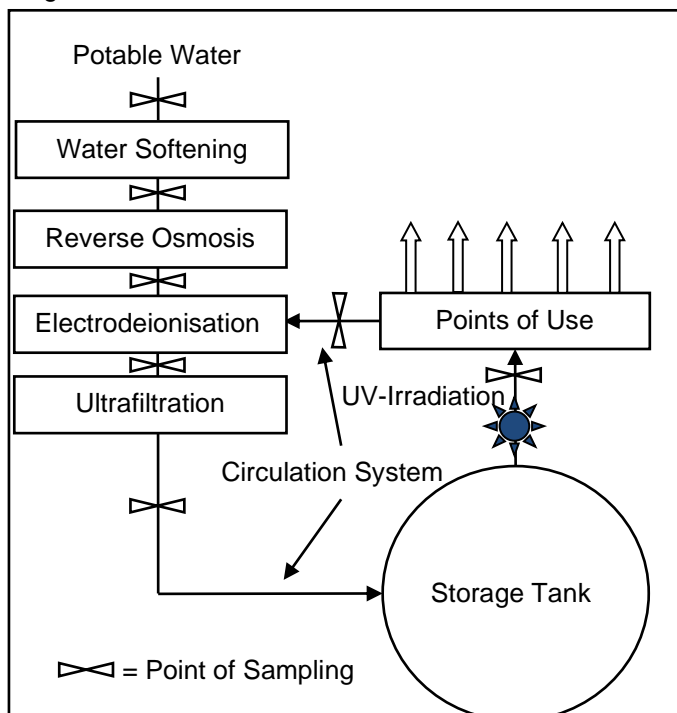
### Quality Control

- 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\*

Figure 1:



### 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 <sup>2</sup> CFU / ml	-



\*Ph. Eur. and USP in their latest issue