Metacresol Ph. Eur. / USP parenteral grade

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HEDINGER
1 8 4 3
A pure decision.

Aug. Hedinger GmbH & Co. KG

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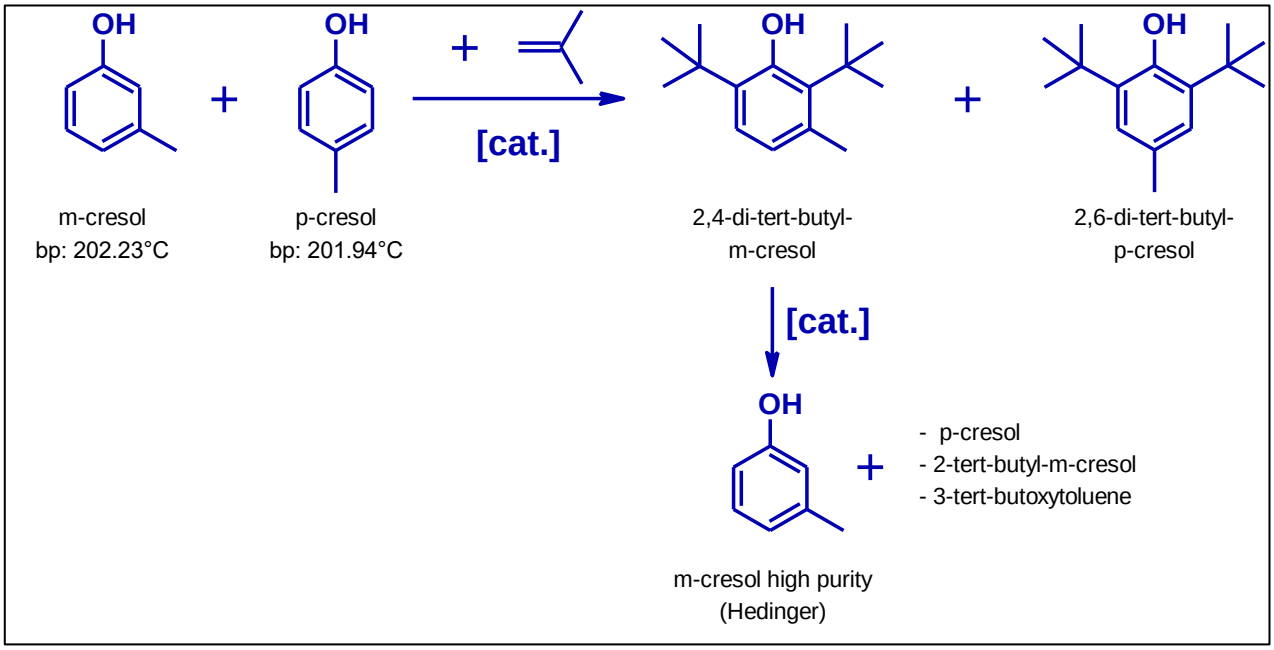
Manufacturing process by LANXESS

M-Cresol high purity (Hedinger) is produced from a mixture of m-/p-cresol.



- Production equipment is closed and dedicated
- Raw materials are supplied online into the production unit
- Specifications define raw materials quality
- M-Cresol high purity (Hedinger) is specifically produced to comply with the purity requirements of the monographs for “Metacresol” in Ph. Eur. and USP
  - o-Cresol ≤ 0.5 %
  - p-Cresol ≤ 0.5 %
  - any other impurity each ≤ 0.1 %
- Process revision has been planned and implemented using a HACCP study

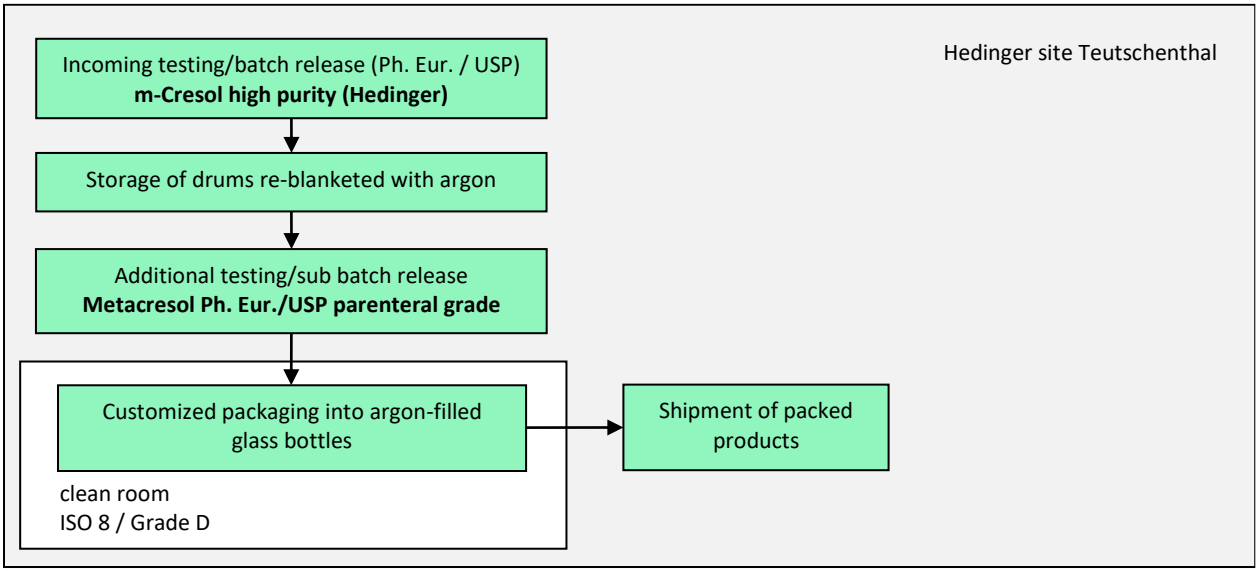
GMP

M-Cresol high purity (Hedinger) is manufactured by LANXESS on the basis of 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 of quality critical processes 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 signing a Confidentiality Agreement.

Processes at Hedinger

Hedinger, Stuttgart (back-up): *testing and release*

Hedinger, Teutschenthal: *testing, release and packaging*



- Testing of O_2-content in gas phase of every drum
- Sampling and optimized blanketing of drums with Argon [max. 0.1% O_2-content in gas phase] performed by qualified sampling personnel
- Batch release by a Qualified Person according to EU-GMP
- Sub-batches (separate testing and release) for every packaging process
- Packaging in classified cleanrooms Grade D / ISO 8 (classification and operating conditions according to EU-GMP Part I, Annex 1 and ISO 14644)
- Filling into argon-filled 100 mL, 1 L and 2.5 L brown glass bottles with subsequent argon blanketing
- Final packaging of the glass bottles in a polystyrene case
- Qualification of the HVAC (Heating, Ventilation & Air-Conditioning) system
- Regular validation of cleanroom (monitoring)
- All processes are designed to comply with EXCiPACT / IPEC-PQG GMP requirements for excipients

Quality / Regulatory Compliance

- Certification of each batch according to current pharmacopoeia monographs by Hedinger:
  - European Pharmacopoeia (Ph. Eur.)
  - United States Pharmacopeia (USP)
  - Chinese Pharmacopoeia (ChP) on request
- Registered in China as excipient for injection (status “A”)
- UV-Absorption specification
- Questionnaire with regulatory information of the product provided by Hedinger
- Fulfils requirements of current ICH Q3C Residual Solvents Guideline
- Data on elemental impurity profile according to current ICH Q3D guideline available
- Kosher- and Halal-certified (by LANXESS)
- Appropriate for parenteral applications (endotoxins specified)
- Confirmation for nitrosamine risk evaluation is available
- Ongoing stability testing programme performed by Hedinger (data available, but confidential)
- Qualification of the LANXESS production site based on IPEC-PQG GMP Guidelines for excipients (regular GMP audits, report available on request)
- Quality agreement between LANXESS and Hedinger including change control is in place

Quality Control by Hedinger

The Quality Control department of Hedinger runs a full monograph testing according to current Ph. Eur. and USP (ChP 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 will be provided with every delivery.

- Full analysis according to Ph. Eur. and USP
- 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

Analytical purity profile of Metacresol – Part I: GC

The gas chromatography (GC) of "Metacresol" according to the Ph. Eur. monograph determines the related substances in metacresol. Related substances therein are the specified impurities B and C. Other detectable impurities mentioned are A, D, E, F, G, H, I, J, K, L, M.

Exemplary, a GC chromatogram of a metacresol sample spiked with all possible detectable impurities (A-M), which are listed below, is shown in figure 1. This spiked sample fully complies with the monograph (total impurities ≤ 1.0 %, any other impurity each ≤ 0.1 %).

Our Metacresol Ph. Eur. / USP parenteral grade shows a very high purity with only three impurities: Impurity C, 2-tert-butyl-m-cresol (with a retention time at 3.5 min) and 3-tert-butoxytoluene (with a retention time at 37.7 min), see figure 2. No other impurities can be found. 2-Tert-butyl-m-cresol and 3-tert-butoxytoluene are unavoidable by-products due to the specific manufacturing process at LANXESS.

Typical values of the manufacturing specific by-products are:

- 2-tert-butyl-m-cresol: mean: 0.04 Area%
- 3-tert-butoxytoluene: mean: 0.06 Area%

A: phenol
B: o-cresol
C: p-cresol
D: 2,6-dimethylphenol
E: 2-ethylphenol
F: 2,4-dimethylphenol
G: 2,5-dimethylphenol
H: 2-(1-methylethyl)phenol
I: 2,3-dimethylphenol
J: 3,5-dimethylphenol
K: 4-ethylphenol
L: 3,4-dimethylphenol
M: 2,3,5-trimethylphenol

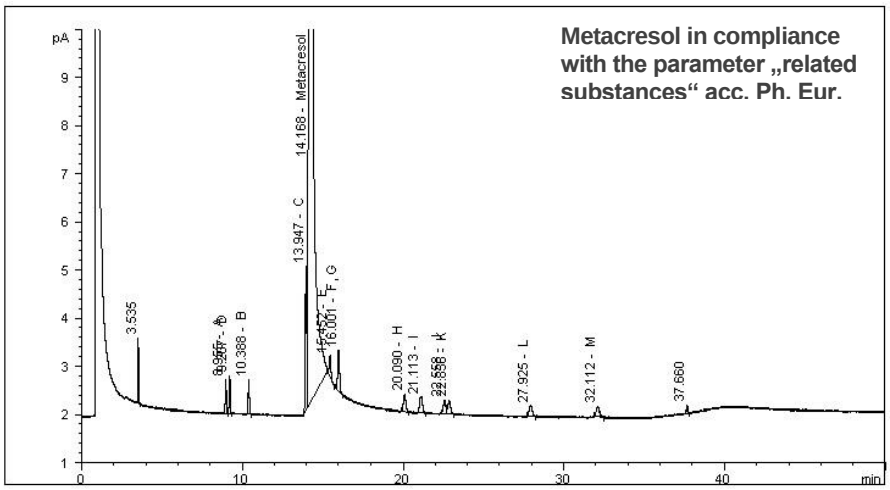


Figure 1. GC chromatogram of metacresol including all detectable impurities according to the Ph. Eur. monograph and in compliance with the applicable requirements.

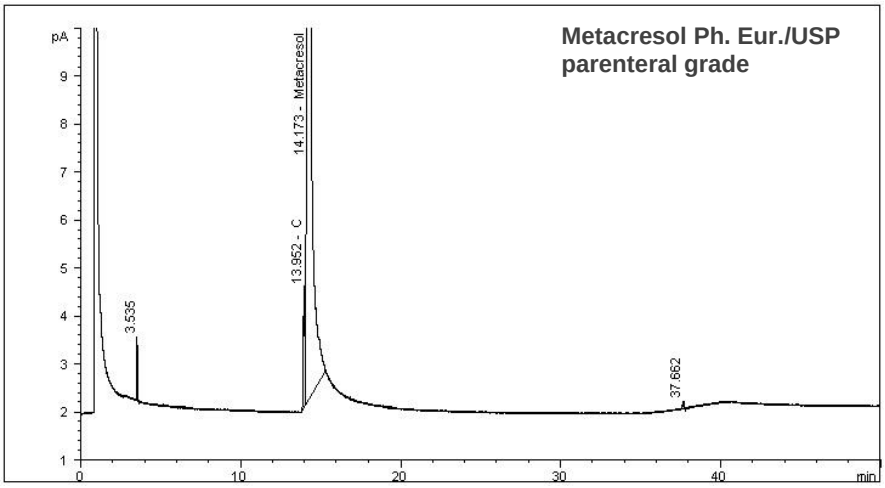
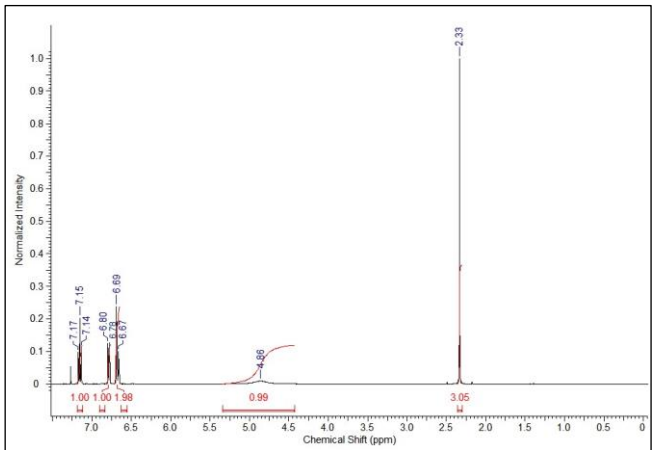


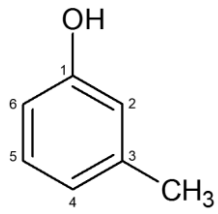
Figure 2. GC chromatogram of Metacresol Ph. Eur./USP parenteral grade according to the Ph. Eur. monograph and in compliance with the applicable requirements.

Analytical purity profile of Metacresol – Part II: ^{1}H NMR

In organic chemistry, NMR analysis is often used to confirm the identity of a substance. In the ^{1}H NMR spectrum of Metacresol Ph. Eur./USP parenteral grade only very small additional peaks were detected, which are even less intense than the ^{13}C satellite peaks and thus can be regarded as negligible. Hence, the high purity of Metacresol Ph. Eur./USP parenteral grade is additionally confirmed by ^{1}H NMR.



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.15 (1H, t, ^{3}J = 7.6 Hz, H_5), 6.79 (1H, d, ^{3}J = 7.6 Hz, H_4), 6.68 (2H, m, $H_{2,6}$), 4,86 (1H, s, OH), 2.33 (3H, s, CH_3)



The ^{1}H NMR spectrum of Metacresol Ph. Eur./USP parenteral grade in deuterated chloroform ($CDCl_3$) was measured using a Bruker 400 MHz spectrometer with dual ^{1}H/^{13}C probe and 32 scans were applied. 30 µl Metacresol Ph. Eur./USP parenteral grade was dissolved in 670 µl $CDCl_3$.

Certificates of Analysis signed by a Qualified Person

- Manufacturing authorization 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 clean rooms by Hedinger

The product is packaged by Hedinger, Teutschenthal under clean room conditions into customized packaging sizes following EXCiPACT / IPEC-PQG GMP requirements for excipients:

- Clean rooms according to EU-GMP Part I, Annex 1 (classification and operating conditions) and ISO 14644
- Grade D (100,000) / ISO 8
- Standard quantities (1 and 2.5 L brown glass bottle)
- 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

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

- 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