THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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Use of a CEP

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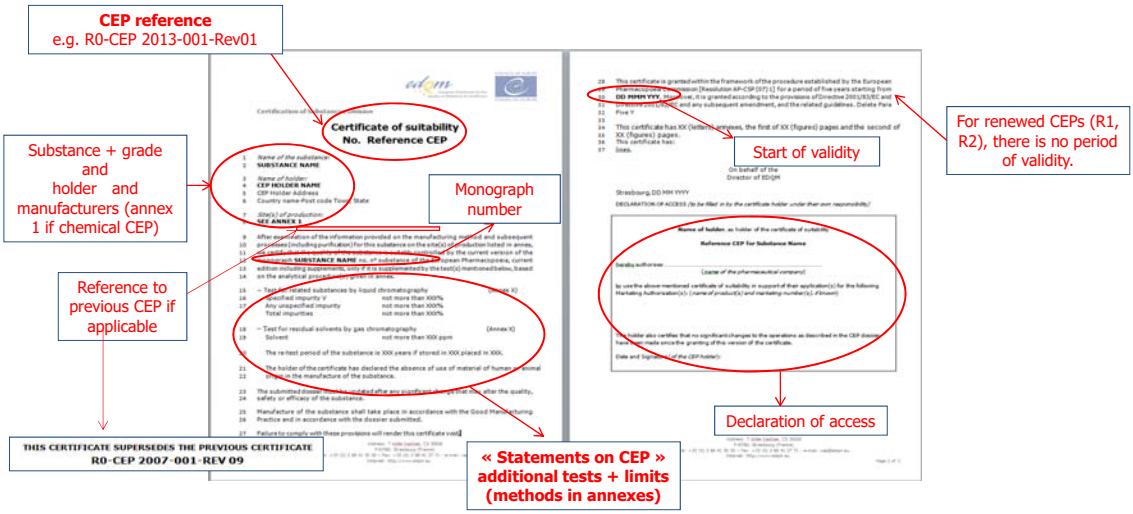
CEP: What does it mean?

- A chemical or a herbal CEP **certifies** that the quality of the substance is suitably controlled by the Ph. Eur. monograph with addition of tests if necessary (mentioned on the CEP).
- A TSE CEP **certifies** that the substance complies with the Ph. Eur. General Chapter 5.2.8 on minimising the TSE risk. It **does not** certify that the quality of the substance is suitably controlled by a specific Ph. Eur. Monograph.
- A CEP **does not** replace a certificate of analysis.
- A CEP **does not** replace the QP declaration.
- A CEP **is not** a GMP certificate.

All CEPs specify:

- Unique reference number (e.g. R0-CEP 2013-001-Rev01)
- Title: clear definition of the substance and grade when requested by the applicant (e.g. micronised, sterile,…) or necessary to distinguish from linked application
- Holder and manufacturing site(s)
- Monograph(s) concerned
- Starting validity date
- Line numbering and annex details if appropriate

CEP



Declaration of Access

- The CEP holder receives the original CEP (blue paper, hologram) and can use this box to make controlled ("true") CEP copies for its customers

EDQM is not involved in the use of a CEP!

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

EDQM, as holder of the certificate of suitability

R0-CEP 2007-001-Rev 00 for ZINC UNDECYLENATE

hereby authorises ..... *(name of the pharmaceutical company)*

Company authorised to use the CEP in their MA application

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

Detail of the MA(s) involved

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

Signed by the CEP holder

CEP numbering

- When an application is received from a Company, a dossier number is assigned. This number is made of the year of submission followed by a chronological sequential number (e.g. **CEP 1996-014**)
- When the CEP is revised the revision indicator increments by one (e.g. **R0-CEP 1996-014 Rev 01**)
- When the CEP is renewed the quinquennial indicator increments by one and the revision indicator resets to 00 (e.g. **R1-CEP 1996-014 Rev 00**)

Statements on the CEP

Additional impurities

- Limits on the CEP + method(s) annexed if applicable (in-house methods)

Residual solvents

- Solvents mentioned on the CEP → when levels in API >10% of ICH limit and all solvents used in the last steps of synthesis.
- Limits on CEP + method(s) annexed (except if only class 3 solvents present, which can be controlled by LOD at NMT 0.5%)
- If Option 2 applied → indicated on the CEP

Statements on the CEP

Use of water in last step

- Use of water in final step of the synthesis is stated on the CEP.
- Quality of water used is not mentioned on CEP

Elemental impurities (depends from the option chosen by applicant)

- Risk Management Summary (RMS) provided by the applicant, the summary containing the necessary information about the level of contamination of the substance, in order to implement the ICH Q3D component approach in the finished medicinal product is appended to the CEP.

Statements on the CEP

A risk management summary for elemental impurities has been provided. (Annex 2)

Intended route of administration / Use of the substance: parenteral

Does not restrict the use of the CEP!

Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	*	Yes	* *
Pb	1	*	Yes	* *
As	1	*	Yes	* *
Hg	1	*	Yes	* *
Co	2A	*	Yes	* *
V	2A	*	Yes	* *
Ni	2A	*	Yes	* *
Tl	2B	*	*	* *
Au	2B	*	*	* *
Pd	2B	*	*	* *
Ir	2B	*	*	* *

"Maximum level:<x ppm"

"Yes" for all which have been discussed

Statements on the CEP

- No risk assessment performed by the applicant, elemental impurities classified in ICH Q3D which are intentionally used in the process are mentioned on the CEP, regardless of the levels found in the final substance. Alternatively if no elemental impurities are intentionally added in the process, this is mentioned on the CEP.

> No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

or

> The following elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance: Palladium

- Whenever necessary, Limits applied by the company on CEP + method(s) annexed.

> – Test for elemental impurities by ICP-MS (Annex 3)
> Palladium not more than 10 ppm

CEPs and manufacturing sites

- In 2013 it was confirmed in the EU that details on manufacturers of intermediates should be in the open part of the ASMF (point clarified in the EU ASMF guideline in June 2013).

- Since July 2013 all CEPs carry:
  - Holder details
  - All sites involved in the manufacture of the substance after the introduction of the starting materials: Annex 1 to the CEP lists these sites. It is for users to clarify the exact role of sites.

- For CEPs granted before July 2013, there is a need for CEP holder to communicate info to customers

For a Chemical Certificate

- Additional impurities/solvents/elemental impurities with acceptance criteria and methods
- Information on Elemental impurities and if applicable presence of RMS
- Packaging material
- Re-test period if requested by the applicant (including storage temperature conditions and container)
- Tests of the monograph which can be omitted
- Production section of the monograph
- Use/non use of animal or human derived material

CEP and grades

Grades (e.g. micronised, polymorphic form) are optional.

•If requested and approved:

- ➢ mentioned as subtitle
- ➢ specification and methods appended to the CEP

•If NOT mentioned on the CEP → not assessed by EDQM!

•Data can be submitted directly in the MA application

CEP and grades, physico-chemical characteristics

Polymorphism:

If the substance shows polymorphism,

- It is possible to request a grade ➔ subtitle on CEP → data concerning elucidation of the polymorphic form (e.g. XRPD, DSC, IR) and consistency of the process are assessed by EDQM
- If grade not requested ➔ no subtitle for polymorphism → data not assessed → to be considered during the assessment of the MA dossier

Particle size:

- if grade is not requested → data related to determination of particle size (e.g. microscopy, laser diffraction spectroscopy) are not assessed by EDQM → to be considered during the assessment of the MA dossier

CEP and Sterility

Some substances are sterile, if requested by the holder, sterility aspects can be included on the CEP:

- The validation of the sterilisation process has to be submitted for assessment by EDQM, and this is mentioned on the CEP
- Mentioned in a subtitle on the CEP when granted
- The site is under a systematic inspection programme

European policy is that sterilisation data should be included in the MAA (part 3.2.P) even if the CEP has the subtitle Sterile

For a TSE Certificate

- Country(ies) of origin of animals
- Animal and nature of tissue(s) used
- Manufacturing process applied (when relevant, e.g. gelatins)

- The scope of the evaluation is to show compliance to Ph. Eur. General Chapter 5.2.8. The overall assessment of the risk of transmitting TSE should take into account also the final use of the substance and this is amongst the responsibilities of National Competent Authorities.

For a Herbal Certificate

In case of extracts:

- Drug extract ratio (DER) for extracts
- Calculated on genuine extract (without excipients)
- Extraction solvents with acceptance criteria and control methods if used in last steps
- Information on excipients used (or statement of non use)

For all:

- Packaging material
- Re-test period if requested by the applicant (storage temperature conditions and container)

Omission of tests

- When it is demonstrated that a **test** specified in the Ph. Eur. monograph is not necessary for a named compound because the impurity/solvent/compound cannot be present with the route of synthesis or is not used, the mention of the omission of the test for the routine control of the named compound may be put on the certificate provided suitably explained and demonstrated in the dossier.

01/2017:0577

AMOXICILLIN SODIUM

***N,N*-Dimethylaniline** (*2.4.26, Method A or B*): maximum 20 ppm.

On the CEP: "The test for *N,N*-dimethylaniline described in the monograph is not necessary since this compound is not used in the synthesis"

CEPs & animal derived material

- When no product of animal origin is used for the manufacture of a non-biological substance, this will be mentioned on the CEP:

  The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

- When a product of animal origin is used for the manufacture of a non-biological substance, this will be mentioned on the CEP:
  - If there is a TSE risk, this **must be** assessed within the Certification procedure and a 'double CEP' (with references to specific & TSE general monograph) is granted.

CEPs & animal derived material

- When a product of animal origin is used for the manufacture of a non-biological substance, viral safety is considered. One of the following statements will be made on the CEP:

  The holder of the certificate has declared the use of material of human or animal origin in the manufacture of the substance and there is no risk of viral contamination.

  or

  The holder of the certificate has declared the use of material of human or animal origin in the manufacture of the substance and viral safety has to be assessed in the context of a medicinal product containing this substance.

- There are older CEPs which were granted before the viral safety risk was considered during the assessment and these will state:

  The holder of the certificate has declared the use of material of human or animal origin in the manufacture of the substance.

Users of CEPs have to consider if viral safety data should be submitted in the marketing application with reference to the statement on the CEP.

Stability data

Re-test period on CEP is optional but highly recommended

- If re-test period requested by the applicant, stability data are assessed → re-test period, once approved, mentioned on the CEP
- If re-test period not requested → stability data are not assessed and this information **is to be considered during the assessment of the MA dossier**

Production Section of a Ph.Eur. Monograph

Instructions to manufacturers about particular aspects of the manufacturing process (e.g. source materials, manufacturing process, in-process testing or testing to be carried out by the manufacturer on the final product prior to release).

- During the CEP procedure, not all statements of the Production Section can be verified:
  - If assessed → not mentioned on the CEP → no further action needed
  - If not assessed → stated on the CEP that this should **be considered during the assessment of the MA dossier. On the CEP:**

> Compliance with the statements of the Production Section of the monograph is to be considered in the context of a medicinal product containing this substance.

Production Section of a Ph.Eur. Monograph

07/2017:2736

IMATINIB MESILATE

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in imatinib mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

07/2010:1140

POTASSIUM CLAVULANATE

PRODUCTION

The methods of production, extraction and purification are such that clavam-2-carboxylate is eliminated or present at a level not exceeding 0.01 per cent.

CEP in a Marketing Authorisation Application in EU

CEP (chemical purity) is intended to be included in Part 3.2.S of the Marketing Application

- A complete copy of the CEP, with its annexes
- Specification of the active substance (may include other tests than those of the monograph + the CEP)
- Batch data in 3.2.S.4 demonstrating compliance to Ph. Eur. monograph and any additional tests on CEP
- If needed stability data in 3.2.S.7

CEP (TSE risk) is intended to be included in the Regional part of the CTD (EU, module 1).

CEP in a Marketing Authorisation Application in EU

- Normally no questions will be raised about the quality of the substance covered by the CEP during evaluation of MA dossier, except for items not covered by CEP.
- EDQM assessment is performed taking into account the 'general'/common use of the substance. Specific uses should be addressed at the level of the MA dossier.
- A CEP may **not** address all parameters relevant for the specific use in the finished product e.g. physico-chemical characteristics, Production section, stability data for a re-test period (only if absent on CEP), etc. Hence additional data might be needed.

CEP in a Marketing Authorisation Application outside EU

- CEPs may be accepted in countries outside the EU/EEA .
- Acceptance is at the discretion of the authorities of those countries.
- These authorities decide on the scope of the acceptance of CEPs and the conditions they may apply, e.g. in addition to the CEP there may be a requirement for provision of a DMF (open part or full content) or other documents.
- Applicants to verify the acceptability and conditions associated with the use of a CEP in such countries prior to submission.

Transparency of CEPs

If authorities need information about assessment of the CEP application:

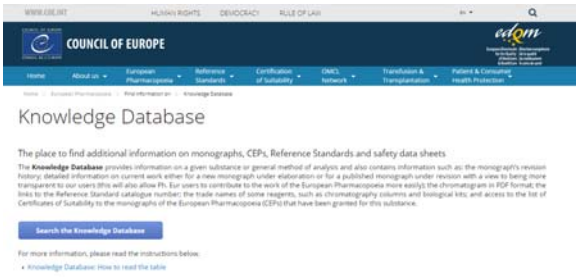
- EDQM can answer specific questions about CEPs
- CEP evaluation reports may be shared with Licensing Authorities in Ph. Eur. Member states (commitment of CEP holder present in Application form)

> We are informed of and accept that the Certification of Substances Department of the European Directorate for the Quality of Medicines & Healthcare may share the assessment reports for this application with the National Competent Authorities of the Ph. Eur. member states, and with the EMA including EMA committees and working parties/groups and the members and experts thereof.

- For authorities outside Ph. Eur. member states, CEP holder's consent is requested prior to sharing the report

Is a CEP valid ?

Check the databases on www.edqm.eu



Is a CEP valid ?

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
49	Paracetamol	Rhodia Organique SAS FR 69006 Lyon	R1-CEP 1996-004-Rev 02	14/02/2005	WITHDRAWN BY HOLDER	21/06/2006	Chemistry
49	Paracetamol	Bristol Laboratories Ltd GB HA1 2EN Harrow	R0-CEP 2001-092-Rev 02	13/10/2004	WITHDRAWN BY HOLDER	25/10/2005	Chemistry
49	Paracetamol	LIAOYUAN CITY BAIKANG PHARMACEUTICAL CO. LTD CN 136 200 Liaoyuan	R1-CEP 2007-054-Rev 00	24/09/2013	VALID		Chemistry
49	Paracetamol	Mallinckrodt Inc US 63042 St Louis	R1-CEP 1996-039-Rev 03	02/05/2008	VALID		Chemistry
49	Paracetamol	Hebei Jiheng (Group) Pharmaceutical Co., Ltd. CN 053 000 Hengshui City	R1-CEP 2005-032-Rev 02	05/10/2017	VALID		Chemistry
49	Paracetamol	Weistar Industry Limited CN 313 000 Huzhou	R0-CEP 2006-156-Rev 00	17/04/2008	WITHDRAWN BY EDQM	16/04/2013	Chemistry
49	Paracetamol	NOVACYL FR 69130 Ecully	R1-CEP 2002-214-Rev 02	09/10/2017	VALID		Chemistry
49	Paracetamol	Rhodia Opérations S.A.S. FR 93306 Aubervilliers	R2-CEP 1992-010-Rev 02	31/08/2006	WITHDRAWN BY HOLDER	09/11/2011	Chemistry
49	Paracetamol	Zhejiang Kangle Pharmaceutical Co., Ltd. CN 325 011 Wenzhou	R1-CEP 2004-309-Rev 01	06/12/2013	VALID		Chemistry

Is a CEP valid ?

Status	In use
Monograph Number	00049
English Name	Paracetamol
French Name	Paracétamol
Latin Name	Paracetamolum
Pinyin Name	
Chinese Name	
Pharmeuropa	32.1
Published in English Supplement	9.4
Published in French Supplement	9.4
On-going	Revision
State of work	2 - Pharmeuropa
Pharmeuropa	32.1
Description	Revision of the test for related substances: optimisation of the LC method.
Chromatogram	Available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
Pharmacopoeial harmonisation	NO

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
	Y0001944	Paracetamol impurity J CRS	1	15 mg	79 EUR	2016006E5
	Y0001955	Paracetamol impurity K CRS	1	15 mg	79 EUR	2016011I5

Practical Information

Test(s)	Brand Name/Information
Related substances	From 9.4: Precolumn: Halo C18 is suitable; Column: Halo C18 is suitable; Dwell volume used for the development of the method = 1.07mL. Before 9.4: Lichrospher 100 RP8 and Zorbax Rx C8 are suitable.

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
49	Paracetamol	Rhodia Organique Fine 69634 Lyon	R1-CEP 1996-004-Rev 02	14/02/2005	WITHDRAWN BY HOLDER	21/06/2006	Chemistry
49	Paracetamol	LIAOYUAN CITY BAIKANG PHARMACEUTICAL CO. LTD CN 136 200 Liaoyuan	R1-CEP 2007-054-Rev 03	06/11/2019	VALID		Chemistry
49	Paracetamol	Bristol Laboratories Ltd GB HA1 2EN Harrow	R0-CEP 2001-092-Rev 02	13/10/2004	WITHDRAWN BY HOLDER	25/10/2005	Chemistry
49	Paracetamol	NOVACYL FR 69130 Ecully	R1-CEP 2002-214-Rev 03	19/07/2018	VALID		Chemistry
49	Paracetamol	SRI KRISHNA PHARMACEUTICALS [illegible] IN 500	R1-CEP 2000-144-	04/07/2018	VALID		Chemistry

Any Questions?



Thank you for your attention

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