

Use of a CEP

Pascale Poukens-Renwart

Certification of Substances Department, EDQM



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



CEP reference
e.g. R0-CEP 2013-001-Rev01

Substance + grade and holder and manufacturers (annex 1 if chemical CEP)

Reference to previous CEP if applicable

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE R0-CEP 2007-001-REV 09

Certificate of suitability No. Reference CEP

Monograph number

Start of validity

Declaration of access

« Statements on CEP » additional tests + limits (methods in annexes)

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

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

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)

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

EDQM is not involved in the use of a CEP!

Company authorised to use the CEP in their MA application

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.





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 is reset to 00 (e.g. R1-CEP 1996-014 Rev 00)

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



Statements on the 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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



Statements on the CEP

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

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



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, 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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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 → 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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

edqm
European Directorate
for the Quality
of Medicines
& HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

CEP and Sterility

Some substances are sterile

If requested by the holder:

- 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)

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

edqm
European Directorate
for the Quality
of Medicines
& HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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)

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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"

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



CEPs & animal derived material

- When a product of animal origin is used for the manufacture of a non-biological substance, the following applies:
 - If there is a TSE risk, this **is** assessed within the Certification procedure and a 'double CEP' (with references to specific & TSE general monograph) is released;
 - If non-ruminant material, viral safety is not considered and the CEP carries a sentence "the holder of the certificate has declared the use of substance of human or animal origin in the manufacture". Viral safety data is not assessed by EDQM even if data is provided.
 - In such situations, each national licensing authority which receives the CEP in a marketing authorization application has to consider if viral safety should be evaluated.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

edqm
European Directorate
for the Quality
of Medicines
& HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

edqm
European Directorate
for the Quality
of Medicines
& HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



CEP in a Marketing Authorisation Application in the 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).

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



CEP in a Marketing Authorisation Application in the EU

- Normally no questions will be raised about the API 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 MAA.
- 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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



CEP in a Marketing Authorisation Application outside the EU

- CEPs may be accepted in countries outside the EU/EEA .
- 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.

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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 (commitment of CEP holder 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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



Is a CEP valid ?

Check the database on www.edqm.eu



You are here: Home > European Pharmacopoeia > Find information on > Knowledge Database

Knowledge Database

Knowledge database: new version released

A new version of the Knowledge Database has been released: please read the "table" immediately underneath the information displayed for the monograph information on work on-going either for a new monograph under elaboration with a view to being more transparent to our users. This will also allow Ph. Eur. European Pharmacopoeia more easily.

["How to read this table"](#)

Search Database online

Search Knowledge

You can search the certification database by:

- Name of the certified substance or
- Monograph number or
- Holder of the certificate or
- Certificate number or
- Issue date of certificate or
- Expiry date of certificate
- Status of the certificate

The substance name is equal to the monograph name and the subtitle for chemical, herbal and double certificates and is the substance name for TSE certificates

If you are interested in all types of certificates, please select the button beside "all". If you are only interested in TSE or herbal certificates, please select the button beside your required choice and only TSE or herbal certificates will be displayed as a result of your choice.

Search a all
 TSE Only
that Herbal Only

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



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

P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.



Thank You and Questions



P. Poukens-Renwart ©2018 EDQM, Council of Europe. All rights reserved.

