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

- Use of a CEP -

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2024 EDQM virtual training program:

Module 5: Fundamentals of the CEP Procedure

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Content

1. Aim and scope of EDQM public document PA/PH/CEP (15) 31 "How to read a CEP" (April 2018, currently under revision)

2. How to interpret the information laid down on chemical CEPs - Practical examples

3. Highlight of the most important changes following the implementation of "CEP 2.0"

4. How to use the CEP in marketing authorisation applications

How to read a CEP

EDQM public document **PA/PH/CEP (15) 31 How to read a CEP** describes the information stated on a Certificate of suitability to the monographs of the European Pharmacopoeia (CEP) and clarifies how it should be interpreted by industry and competent authorities.

It does not cover the use of a CEP in the context of a Marketing Authorisation Application (MAA), where a CEP is used to replace the quality part of the CTD dossier related to that given source of the substance, or in any variation. QWP Q&A How to use a CEP in the MAA and MAV: Link

It does not contain new information or new instructions, but it is rather a compilation of information currently spread in other EDQM guidelines/policy documents.

It should be read in conjunction with other applicable EDQM Certification Policy Documents and Guidelines.

Types of CEP

- A chemical or an herbal CEP certifies that the quality of the substance is suitably controlled by the Ph. Eur. monograph and any supplementary tests deemed necessary in line with ICH and EMA guidelines (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

How to interpret the information laid down on each type of CEP

Formats of CEPs (all types of CEP):

In September 2023, major changes were introduced to CEP document, which resulted in 3 different formats: "CEP 2.0", "old CEP" and "hybrid CEP":

	CEP 2.0	Hybrid	Old CEP
Format	Electronic document with electronic signature		Paper document with wet signature
Numbering	2-block code CEP 20XX-XXX-Rev 00		3-block code R0-CEP 20XX-XXX-Rev 00
Information on companies	Name and address of the holder and production sites completed by SPOR OMS LOC &ORG ID		Name and address of holder and production sites
Technical information (Chemical and herbal CEP)	Inclusion of the approved specification and description of additional methods required to control the substance	Limits for additional impurities and inclusion of tests used in addition to the Ph. Eur. monograph tests, required to control the substance	
Expiry date	No reference to a validity date of 5 years (renewal due date, available on public database)		Yes reference to expiry date (before renewal)
Box/Letter of access	Letter of access (template on EDQM website)		Box of access on CEP
Issue date	After 1 September 2023		Until 31 August 2023

CEP declaration of access / LoA (all types of CEP):

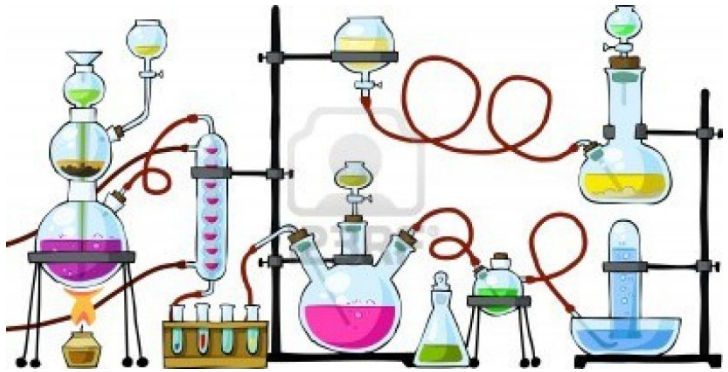
- The CEP holder authorises its customers to use the CEP in support of a MAA for a particular product(s):
  - ➢ by filling in a letter of access (for CEP 2.0 and hybrid CEP, template is available on EDQM website), which is provided together with a copy of CEP received from the EDQM
  - ➢ by filling in a CEP declaration of access or "box of access" (for old CEP) on a copy of CEP in old format received from the EDQM

- CEP is accepted in all Ph. Eur. Convention member states + other countries (e.g. Canada, Australia, Singapore, South Africa, etc.)

Communication CEP holder / MAH

- Communication between CEP holder and drug product manufacturer / MAH is key:
  - MAHs are ultimately responsible for the quality of APIs used in their finished product and are legally obliged to get information they need to take this responsibility.
  - API manufacturers should be supportive to their customers and share information.
- EDQM Policy document PA/PH/CEP (21) 57 "CEP holders' responsibilities towards their customer" (January 2022)
- EDQM continues working with stakeholders to promote better sharing of information

Information on a CHEMICAL CEP



Subtitle (optional)

- A CEP can cover specific physico-chemical characteristics of a substance (e.g. specific polymorphic form or particle size distribution) or its sterility. These are mentioned on a CEP as subtitle.
- A subtitle can also be used to differentiate CEP applications for the same substance from the same holder (e.g. “process B” or “produced in site X”).
- In addition, a subtitle is also used to reflect on the CEP the requirements of the “labelling” section of the monograph, where applicable (e.g. presence of antioxidant for an API-mix)
- A grade (e.g. micronised, polymorphic form) is mentioned on the CEP as subtitle, **only if**:

1. requested* by the CEP holder (application form)
2. accepted* during the CEP evaluation procedure

* in line with EDQM policy document PA/PH/CEP (04) 1 « Content of the Dossier for Chemical Purity and Microbiological Quality »

Subtitle (examples)

- If a subtitle is requested and accepted by the EDQM, the corresponding quality attribute(s) are included in the specification appended to CEP (CEP 2.0) or mentioned on CEP (hybrid and old CEP) + analytical method(s) are annexed to CEP
- A CEP may mention more than one grade provided that they have the same impurity profile; otherwise, separate CEPs will be issued

Examples:

Name of the substance:
ESOMEPRAZOLE MAGNESIUM DIHYDRATE
Micronised, non-micronised

Micronised, non-micronised: data related to determination of particle size (e.g. microscopy, laser diffraction spectroscopy) are assessed by EDQM

Polymorphic form: Data concerning elucidation of the polymorphic form (e.g. XRPD, DSC, IR) are assessed by EDQM

Name of the substance:
ATOVAQUONE
Form A

What does it mean if a CEP has NO subtitle ?

Data relative to a particular grade are not included in the CEP dossier **OR** the CEP holder has not applied for a subtitle.

Manufacturing sites

Sites (name + address) are mentioned according to their roles:

- CEP holder
- Intermediates manufacturer(s)
- Substance manufacturer(s)

4	*Name of holder:*
5	**EDQM, COUNCIL OF EUROPE**
6	7 allée kastner
7	France-67081 Strasbourg
8	*Site(s) of production:*
9	**SEE ANNEX 1**

starting material manufacturers are NOT mentioned on a CEP

Additional sites, when applicable (subtitle), even if already listed as manufacturers (CEP 2.0 change):

- Site(s) of physical treatment
- Site(s) of micronisation
- Site(s) of sterilisation

SPOR/OMS Loc and Org IDs are mandatory for all sites in all CEP applications

Production sites are mentioned in **Annex 1** of the CEP:

Name of the intermediate(s) is not specified on the annex

The CEP does not distinguish which manufacturer produces which intermediate
(if more than one intermediate is involved)

Annex 1 : Site(s) of production for R0-CEP 2007-001-Rev 06

Production of intermediate(s):
LABORATORIES XXX Co. Ltd.
Survey No XX and YY
XX Mandal, XX District
India - 123 456 City C, Telangana

LABORATORIES YYY Co. Ltd.
Survey No XX and YY
YY Mandal, YY District
India – 789 548, City D, Andra Pradesh

Production of Zinc undecylenate:
EDQM, COUNCIL OF EUROPE
7 Allée Kastner
France-67081 Strasbourg

CEP user should communicate with CEP holder to obtain more details on intermediates and manufacturers

Contents of CEPs: Specification (CEP 2.0)

- Specification of the substance is appended to the CEP
- Specification should be based on the corresponding Ph. Eur. monograph, ICH and EMA guidelines. Compliance of these tests is checked and approved during CEP evaluation procedure
- Specification includes limits for related substances as foreseen by Ph. Eur. monograph + additional process-related impurities (not mentioned Ph. Eur.), if needed
- Quality attributes, acceptance criteria and reference to test procedures (e.g. Ph. Eur. or in-house) are included in the specification table
- Specification may include information on skip testing if it is foreseen by the corresponding ICH or EMA guidelines (e.g. elemental impurities in line with ICH Q3D, mutagenic impurities in line with ICH M7, nitrosamine impurities in line with EMA/425645/2020)

Skip testing has to be approved by the relevant authority reviewing marketing application(s) for the medicinal product(s) where a CEP is included.

Contents of CEPs: Test Procedures (CEP 2.0, hybrid and old CEP)

- Alternative test procedures to those described in Ph. Eur. monograph (e.g. developed in-house or taken from another pharmacopoeia) may be used provided that these are at least equivalent to those of Ph. Eur. monograph
  - ➢ The in-house method should be cross-validated against the Ph. Eur. method
  - ➢ This is assessed by EDQM

In the event of doubt or dispute, the texts of the Ph. Eur. are authoritative.

- When Ph. Eur. monograph is demonstrated to be suitable to control the quality attribute, the in-house test procedures are not appended to CEP
- For quality attributes not covered by Ph. Eur. monograph but which are needed to control the quality of the substance, company's in-house test procedures are appended to the CEP (e.g. GC for residual solvents, ICP-MS for elemental impurities)

Impurities statements (old and hybrid CEPs)

For hybrid and old CEPs, full substance specification is not annexed to the CEP.

Tests required in addition to the corresponding Ph. Eur. monograph are reported on the CEP.

Limits for **"additional related substances"** to those already listed in the Ph. Eur. monograph); 2 cases possible:

a) If present in the substance above Identification threshold set by Ph. Eur. general monograph (2034), these impurities are stated on the CEP with specified limits. N.B.: if they can be controlled by Ph. Eur. test for related substances, no test procedure is appended to CEP

The following impurities are detected by the test for related substances of the monograph and their limits are set at:	
Impurity at RRT 1.3	not more than 0.15%
Any unspecified impurity	not more than 0.10%

b) If present in the substance above Reporting threshold set by Ph. Eur. general monograph (2034), and Ph. Eur. monograph method is not suitable to control them, they are controlled by a validated in-house method. The limits for these impurities are stated on the CEP and the in-house method is appended to the CEP

– Test for related substances by liquid chromatography		(Annex 2)
Impurity X	not more than 0.10%	
Any unspecified impurity	not more than 0.10%	

Impurities statements (CEP 2.0, old and hybrid CEPs)

Limits for **"unspecified impurities"**

- When the current Ph. Eur. monograph does not include a limit for **unspecified impurities** (this is still the case in some old monographs; they are progressively revised).
- Such a limit has to be introduced in the specification and included on the CEP (limit to be set in line with Ph. Eur. general monograph (2034).

> Any other impurity than those mentioned in the monograph and detected by the test for related substances of the monograph is individually limited to not more than 0.10%.

- For CEP 2.0, the limit for unspecified impurities is transparent from the specification appended to the CEP.

Impurities statements (old and hybrid CEPs)

What does it mean when the method for related substances is "replaced"?

- If Ph. Eur. monograph describes a **non-quantitative method** (e.g. TLC) for related substances => the manufacturer should replace it by a quantitative validated in-house method, which is appended to CEP

NOTE: a TLC method is nevertheless acceptable for the control of one specified impurity, but not as control method for all related substances.

The statement on the CEP will read as follows :

> The test for related substances by thin-layer chromatography described in the monograph is replaced by:
> – Test for related substances by liquid chromatography (Annex 2)
>
Impurity XXX	not more than 0.30%
Any unspecified impurity	not more than 0.10%
Total impurities	not more than 0.3%

Mutagenic impurities on the CEP

- A mutagenic impurity is limited on the CEP (or in its specification appended to the CEP) when it is present or potentially present in the substance.
- The limit proposed by the applicant is assessed and accepted at EDQM in line with the **ICH M7** requirements.
- If the Ph. Eur. method is not suitable to control this impurity, the in-house method is annexed to the CEP.

Mutagenic impurities on the CEP

What does it mean if no mutagenic impurities are limited on the CEP?

- There are **NO** potential mutagenic impurities formed/introduced in the route of synthesis proposed by the API manufacturer.

OR

- There are potential mutagenic impurities, and the control strategy put in place by the manufacturer enables **NOT** including a limit in the final substance specification (in line with ICH M7).

OR

- They are controlled by the monograph.

Residual solvents (old and hybrid CEPs)

Which solvents are mentioned on a CEP?

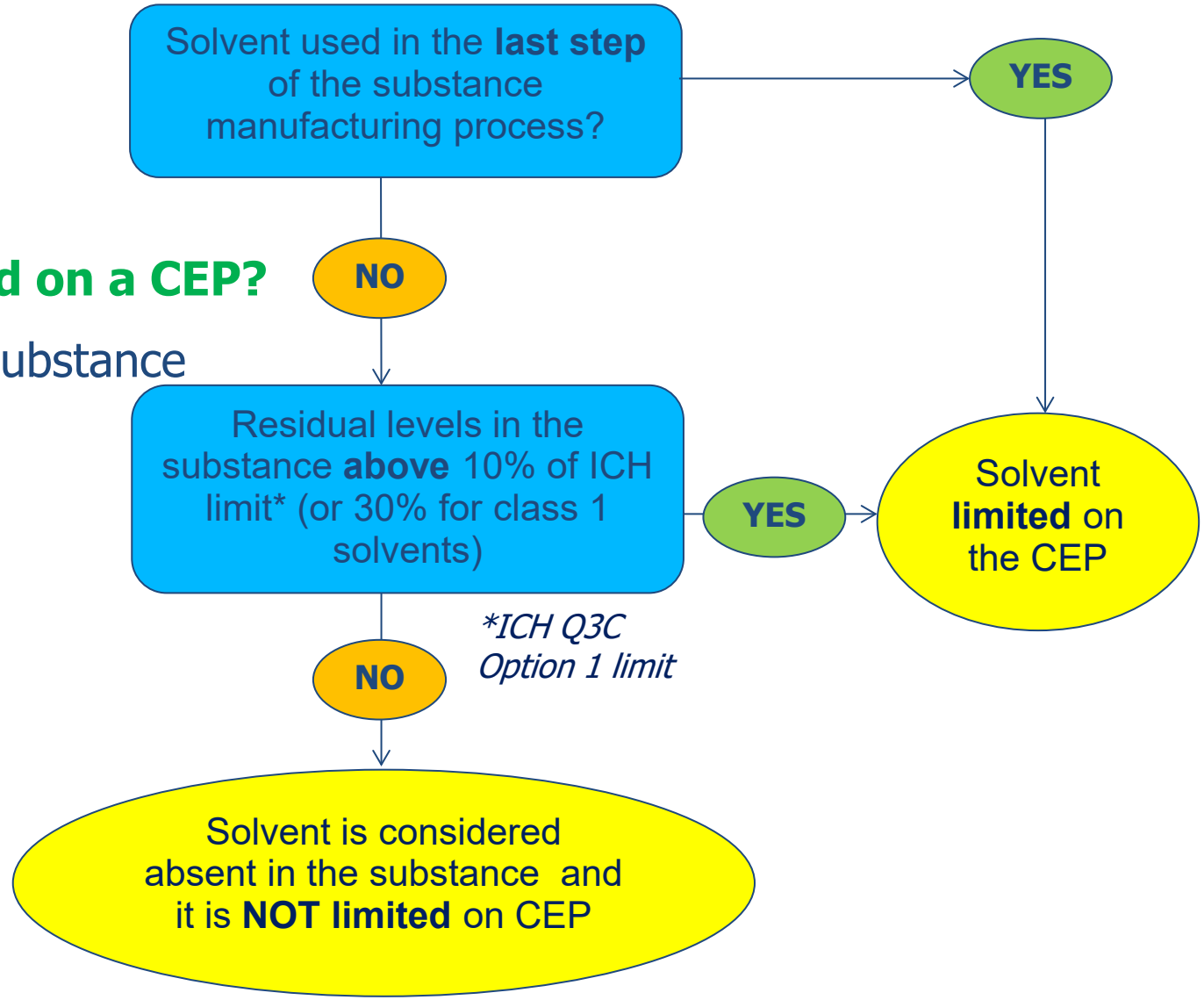
those likely to be present in the substance

AND

those used in the last step

Annexes to:
CPMP/ICH/283/95 Impurities: Guideline for residual solvents &
CVMP/VICH/502/99 Guideline on impurities: residual solvents

Annex I: specifications for class 1 and class 2 residual solvents in active substances



Residual solvents (old and hybrid CEPs)

What are the limits mentioned on the CEP for solvents?

Limits proposed by the manufacturer, as assessed and accepted by the EDQM.

a) Limits on a CEP are mostly those of ICH Q3C Option 1:

– Tests for residual solvents by gas chromatography		
Dichloromethane	not more than 600 ppm	(Annex 2)
Ethyl acetate	not more than 5000 ppm	
Pyridine	not more than 200 ppm	
n-Pentanol	not more than 5000 ppm	(Annex 3)

b) Sometimes limits are tighter than ICH Q3C Option 1:

– Test for residual solvents by gas chromatography		(Annex 1)
Ethanol	not more than 2000 ppm	
Chloroform	not more than 50 ppm	
Toluene	not more than 200 ppm	
Methanol	not more than 1000 ppm	
Benzene	not more than 2 ppm	

c) Exceptionally, higher limits than ICH Q3C Option 1 are acceptable if suitably justified (e.g. Option 2, this is made transparent on CEP).

Residual solvents (old and hybrid CEPs)

When is a Loss on drying test mentioned on the CEP?

a) When LOD test is included in the Ph. Eur. monograph (limit: NMT 0.5%) and class 3 solvents are likely to be present in the substance:

> In the last steps of the synthesis isopropanol is used as solvent. The residual content is limited by the test for loss on drying described in the monograph, with a limit of not more than 0.5%.

b) When LOD test is **NOT** included the Ph. Eur. monograph and manufacturer uses LOD test of Ph. Eur. 2.2.32 (limit: NMT 0.5%) to control water and class 3 solvents:

> In the last steps of the synthesis water and acetone are used as solvents. Their residual content is limited by the test for loss on drying (2.2.32) of the European Pharmacopoeia, with a limit of not more than 0.5%.

Residual solvents (old and hybrid CEPs) - Example:

Applicant's specification:

Loss on drying (at 105°C for 3 hours)	Not more than 0.50% w/w

Residual solvents by GC-HS **Method-1**	
a) Toluene	Not more than 890 ppm
b) *o*-Xylene	Not more than 2170 ppm
c) Dichloromethane	Not more than 600 ppm
d) Ethyl acetate	Not more than 5000 ppm
e) Tetrahydrofuran	Not more than 720 ppm
f) Acetone	Not more than 5000 ppm
g) Methanol	Not more than 3000 ppm
h) Ethanol	Not more than 5000 ppm

However, the CEP mentions only this:

– Test for residual solvents by gas chromatography (Annex 2)
Methanol not more than 3000 ppm

In the last steps of the synthesis acetone is used as solvent. Its residual content is limited by the test for loss on drying described in the monograph, with a limit of not more than 0.5%.

Why? Acetone and methanol are used in the last purification step. All other solvents are used ealier in the process and found < 10% of ICH Q3C Option 1 limit in the substance. In addition Acetone is a class 3 solvent and there is a test for LOD in Ph. Eur. monograph.

Residual solvents (CEP 2.0)

- Limits for residual solvents stated in the specification and the corresponding test procedures appended to the CEP are those proposed by the CEP holder (as accepted by the EDQM)

Note: If all solvents used in the process are limited in the specification, these controls are appended to the CEP as part of the specification

- If class 3 solvents used in the last steps of the process are controlled by LOD test of Ph. Eur. monograph or by Ph. Eur. General chapter 2.2.32 (if LOD test is **NOT** included the Ph. Eur. monograph Ph. Eur.), a corresponding statement is mentioned on CEP

Residual solvents

When is water mentioned on the CEP?

Water is mentioned on the CEP if used in the last process step(s) → likely to be present in the substance.

> In the last steps of the synthesis water is used as solvent.

The quality of water (in line with the EMA "Guideline on the quality of water for pharmaceutical use" EMA/CHMP/CVMP/QWP/496873/2018, i.e. potable water, purified water, water for injections) is specified on the CEP 2.0

> In the last steps of the process, purified water is used as solvent.

Elemental impurities

- **ICH Q3D** on elemental impurities has been applied to medicinal products for human use from September 2016;
- Since January 2021 risk assessment regarding elemental impurities in veterinary medicinal products should also be performed;
- EDQM public document **PA/PH/CEP (16) 23, 2R Implementation of policy on elemental impurities in the Certification Procedure** was published in April 2021;
- EDQM does not make a decision on compliance with ICH Q3D.
- The CEP provides transparency, to be considered by the manufacturer of medicinal product in the context of a MAA.

Elemental impurities

What is the meaning of the following CEP statements?

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

a) A RMS is provided by the CEP holder, and its summary is annexed to the CEP with the necessary information on the level of elemental impurities of the substance

b) RMS reflects the presence/absence of elemental impurities in the final substance

For CEP 2.0:

The section miscellaneous information includes a risk management summary for elemental impurities.

Elemental impurities

- When a RMS is not provided, the CEP is transparent on the introduction of elemental impurities, not on their absence/presence.

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

The following elemental impurities classified in ICH Q3D are intentionally introduced in the production of the substance: Lead and Palladium.

Note: The applicant might have set a **limit** in the specification => in this case, test procedure is annexed.

Intentional introduction

Route of administration

Example of Risk Management Summary to be prepared:

Route of administration considered in the risk assessment:

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	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mo	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

*** Yes / No**

**** The control strategy followed should be clear and mentioned on the RMS:**

- **"Absent"** should be defined (e.g. "less than 30% of ICH Q3D option 1 limit")
- **or "NMT limit in ppm"**calculated based on option 1 (or alternatively and if justified, based on option 2a)
- **or "No risk identified"**

All 24 elemental impurities as mentioned in ICH Q3D

See document **"Implementation of policy on elemental impurities in the Certification Procedure"** (PA/PH/CEP (16) 23, 2R)

Should mention the basis on which "absence" of elemental impurities has been determined

Omission of Ph. Eur. 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 applied route of synthesis or is not used, the absence of control may be accepted (when justified).

Note: Omission is acceptable for specific tests to control one or few impurities; however, it does not apply to the test for related substances.

For CEP 2.0, the omission is transparent from the specification appended to the CEP.

Microbiological quality

Microbiological control generally should not be part of the specification proposed in a CEP dossier

Microbiological quality is covered by Ph. Eur. general monograph 2034 Substances for pharmaceutical use

Microbiological quality is to be addressed considering the final use of the substance in the finished medicinal product, and it is for each national competent authority which receives the CEP in a marketing authorization application to evaluate this aspect.

Container closure system

The full packaging material (immediate and outer) is described on the CEP even when no re-test period is requested by the CEP holder.

Examples:

The substance is packed in a double polyethylene bag in a triple laminated bag (polyethylene terephthalate/aluminium/polyethylene) placed in a polyethylene container.
The substance is packed under nitrogen atmosphere in an epoxy-phenolic resin lined iron drum.
The substance is packed either in a polyethylene bag in a polyester/aluminium/polyamide/polyethylene composite bag or in double polyethylene bags (outer black), placed either in a fibre drum or a paper drum.

Retest period (optional but highly recommended)

The CEP statement reflects the fact that the substance is **stable**

- during XX months mentioned on the CEP
- in the packaging material mentioned on the CEP
- in long term conditions: 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH (short term excursions are covered by additional testing at accelerated test conditions)

> The re-test period of the substance is 36 months if stored in amber glass bottles, with polybutylene terephthalate screw caps, placed in polyethylene bags.

Different re-test periods and storage conditions can be proposed within one CEP application (e.g. different re-test period depending on the container closure system or climatic zone).

Retest period

What does it mean if a CEP does NOT indicate a retest period?

- Not requested by the CEP applicant (thus stability data not assessed).

OR

- Requested by the CEP applicant, however stability data presented did not allow granting a retest period (e.g. insufficient data, invalid data obtained under non-regulatory storage conditions or under unjustified restrictive storage conditions, OOS observed, etc.).

Stability data should be evaluated during the assessment of the MA dossier; alternatively, the finished product manufacturer should demonstrate that the substance complies with the Ph. Eur. monograph (and any additional tests in the specification) immediately before its use.

Storage conditions

- The absence of any specific storage conditions (e.g. temperature) on the CEP means that the substance is stable under climatic conditions for zone I/II (combination of long-term and accelerated conditions)

- **Why some CEPs indicate specific storage conditions?**
  - ➢ either that they are needed to ensure the stability of the substance in the described container closure system.
  - ➢ or that the CEP holder/applicant is applying stricter storage conditions than those recommended by EU/ICH guidelines.

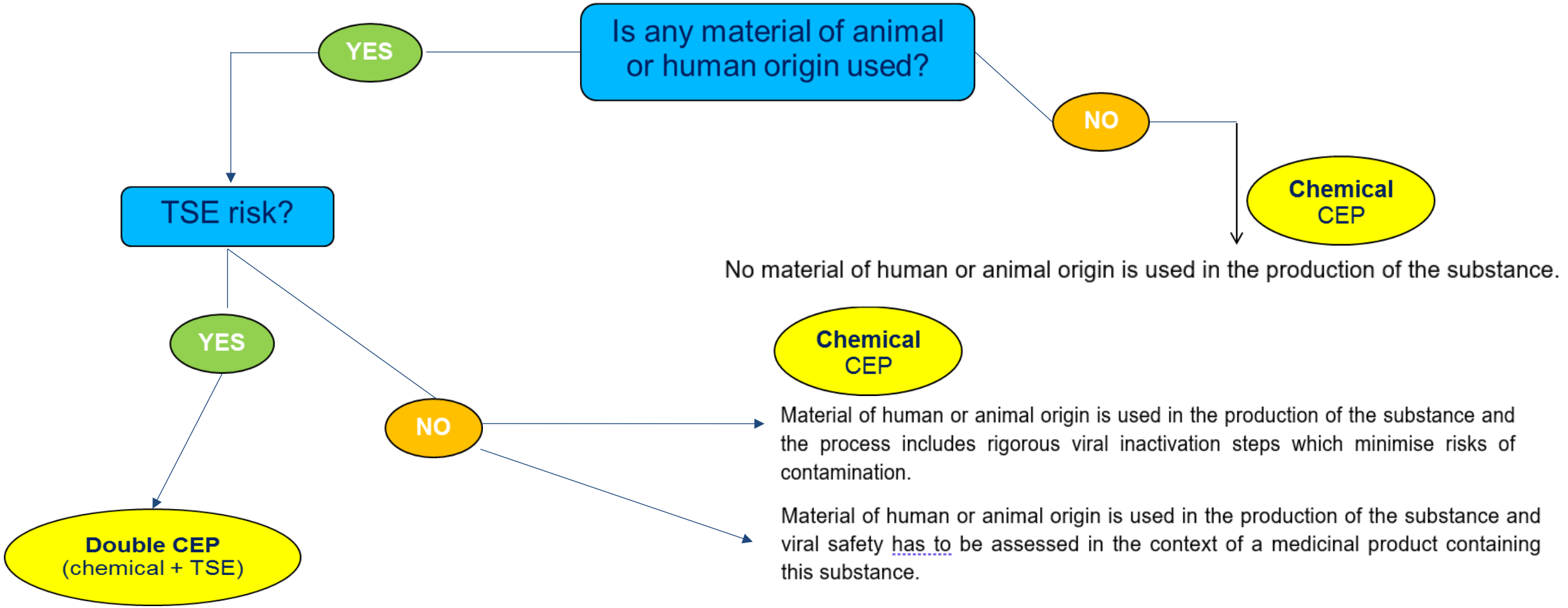
Example:

> The re-test period of the substance is 36 months if stored at a temperature between 2°C and 8°C in double polyethylene bags (outer black) with desiccant bags in between, placed in a polyethylene drum.

In any case, the re-test period is supported by stability data obtained in the appropriate conditions.

Material of human/animal origin

CEP applicants have to declare whether any material of human or animal origin is introduced in the manufacture of the substance



Production section in monographs

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

Not all statements of the Production Section can be verified during the CEP procedure:

- If assessed: nothing mentioned on the CEP → No further action needed during the assessment of the MA dossier
- If not assessed: statement on the CEP →  Information in the Production section is to be addressed during the assessment of the MAA

Statements on CEP for a sterile substance

- A “sterility CEP” does not exist on its own.
- Always combined with a Chemical CEP or with a Double CEP (chemical + TSE).
- The CEP includes the typical statements of each type of CEP (as applicable).

The European system requires that sterilisation data should be included in the MAA even if a CEP for a sterile substance is submitted

Typical sterility related statements

- Subtitle "Sterile"

Name of the substance:
CEFUROXIME SODIUM
Sterile

- Sterilisation method
- Statement regarding compliance with the test for sterility (2.6.1) of the Ph. Eur. (old CEPs)
- Statement that the sterilisation process has been assessed and accepted (old CEPs)

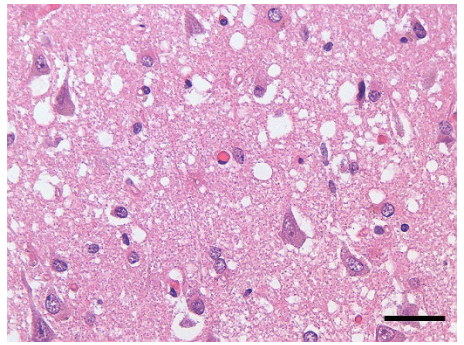
The substance is sterile and shall comply with the test for sterility (2.6.1.) of the European Pharmacopoeia. The method used for sterilisation is a sterile filtration and the sterilisation process has been assessed and approved.

or

The substance is sterile and is produced by sterile filtration.

Statements on a TSE CEP

Additional information, as applicable:



- Subtitle (e.g. manufacturing process for gelatin)
- Country(ies) of origin of source materials
- Nature of animal tissues used in manufacture
- Manufacturing process applied (if relevant for the safety of the product e.g. gelatin)

A TSE CEP does not certify that a particular source of a substance complies with the corresponding Ph. Eur. monograph for that substance.
A TSE CEP certifies that the substance is compliant with Ph. Eur. Monograph 1483 => it is "**TSE safe**"

Statements on a herbal CEP

For extracts:

- Drug extract ratio (DER) calculated on genuine extract (without excipients)
- Residual solvents with acceptance criteria and control methods if used in last steps
- Extraction solvent(s) used
- Information on excipients used: name and percentage (or statement of non-use of excipient)

For all:

- Packaging material
- Re-test period if requested by the applicant
- Use/non-use of material of animal or human origin

CEP in a Marketing Authorisation Application in the EU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 January 2024
EMA/CHMP/CVMP/QWP/5/2024
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)

QWP Questions and Answers (Q&A): how to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV)

CEP in a Marketing Authorisation Application outside the EU

- CEPs are accepted in countries outside Europe
- At the discretion of the authorities of those countries
- These authorities decide on the scope of the acceptance of CEPs and the conditions that 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

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