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

edqm

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

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

Use of a CEP

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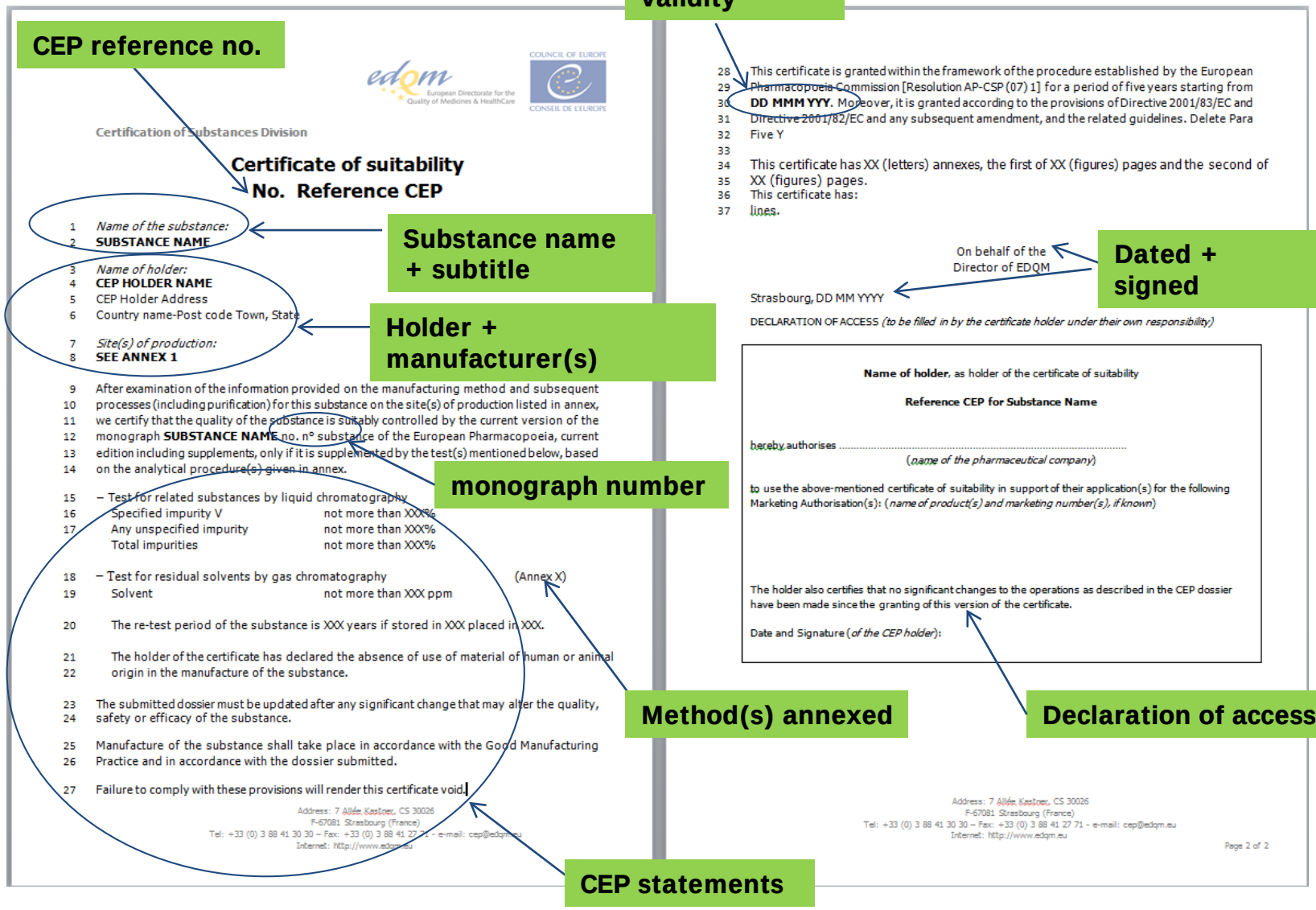
Types of CEP

- 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.

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

Practical examples



CEP reference (all types of CEP):

Unique alphanumerical reference.

Composed of 22 characters (including spaces and dashes).

- **R1:** this CEP has been renewed once (5 years after issue)
- **2011:** original CEP application was submitted to EDQM in 2011
- **398:** chronological number assigned at reception
- **Rev 03:** this CEP has been revised 3 times since its renewal

CEP declaration of access (all types of CEP):

The CEP holder (not the EDQM) makes a copy of the original CEP, completes the “Declaration of access” box and signs.

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)*

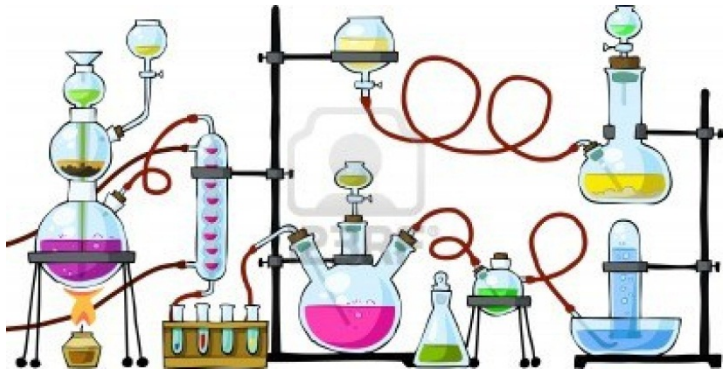
The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

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

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

Information on a

CHEMICAL CEP



Subtitle (optional)

Sometimes a subtitle is requested when a CEP holder has multiple CEPs for the same substance (e.g. Process 1, Process 2) to further distinguish these CEPs from each other

However, the subtitle may also be related to a **Grade**

A grade (e.g. micronised, polymorphic form) is mentioned on the CEP as subtitle, **only if**:

1. requested by the CEP applicant (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 »

- A CEP may mention more than one grade provided that they have the same impurity profile; otherwise separate CEPs will be required.

- Any grade requested should be defined by appropriate limit(s) and associated test(s) which are then mentioned on the CEP + analytical method(s) are annexed.

What does it mean if a CEP has NO grade ?

Data relative to a particular grade are not included in the CEP dossier **OR** the applicant has not asked for a grade (even if the data are provided in the dossier).

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), if not already listed as manufacturer:

- Site(s) performing sterilisation steps
- Site(s) performing physical treatments (e.g. micronisation)

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

Name of the intermediate(s) is <u>not</u> specified on the annex

The CEP does <u>not</u> 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

Impurities statements

What does it mean if there are limits for related substances on the CEP?

- These related substances are process-specific impurities (additional related substances to those already listed in the Ph. Eur. monograph).

AND

- These impurities have been found above the identification threshold in the substance and need to be specified.

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%

Impurities statements

What does it mean if there are methods for related substances annexed to the CEP?

- The Ph. Eur. monograph method is NOT suitable to control the process-specific impurities in the substance.
- The monograph should be supplemented with an **« additional method »**.
- The applicant has developed and validated an in-house method.
- In-house method annexed to CEP to control these impurities.

– Test for related substances by liquid chromatography		(Annex 2)
Impurity X	not more than 0.15%	
Any unspecified impurity	not more than 0.10%	

Impurities statements

What about “alternative method”?

- In-house method used by the manufacturer instead of the Ph. Eur. monograph method (can be a method developed in-house or taken from another pharmacopoeia).
  - ➢ The in-house method should be cross-validated against the Ph. Eur. method (they should be at least equivalent)
  - ➢ This is assessed by EDQM

Will it be annexed to the CEP to control impurities? **NO**

- The reason is because the Ph. Eur. monograph method is suitable to control the impurities in the substance.

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

Impurities statements

What does it mean if the method for related substances is “replaced”?

- Ph. Eur. monograph describes a **non-quantitative method** (e.g. TLC) => the manufacturer should replace it by a quantitative validated in-house method.

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%	

Impurities statements

Why the following statement is sometimes mentioned on CEPs?

> 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%.

- 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).

- The manufacturer has introduced such a limit in the specification (limit to be set in line with Ph. Eur. monograph 2034 - Substances for pharmaceutical use).

Mutagenic impurities on the CEP

- A mutagenic impurity is limited on 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 (Option 1 control).
- If the Ph. Eur. method is not suitable to control this impurity, the in-house method is annexed to the CEP.

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

a) There are **NO** known mutagenic impurities formed/introduced in the route of synthesis proposed by the API manufacturer. **Or**

b) Any mutagenic impurities present are controlled in accordance with an acceptable ICHM7 option 2, 3 or 4 control. **Or**

c) They are controlled by the monograph.

Nitrosamines

The EDQM reviews risk assessments for nitrosamines provided by CEP holders with new applications and renewals and with requests for revision where a risk of nitrosamine formation may be introduced (i.e. changes to the manufacturing process, change of suppliers of starting materials or intermediates, etc.).

Please note that other than if it is concluded that a test in the final substance is required - no statement will be reported on the certificate to indicate that a risk assessment has been submitted.

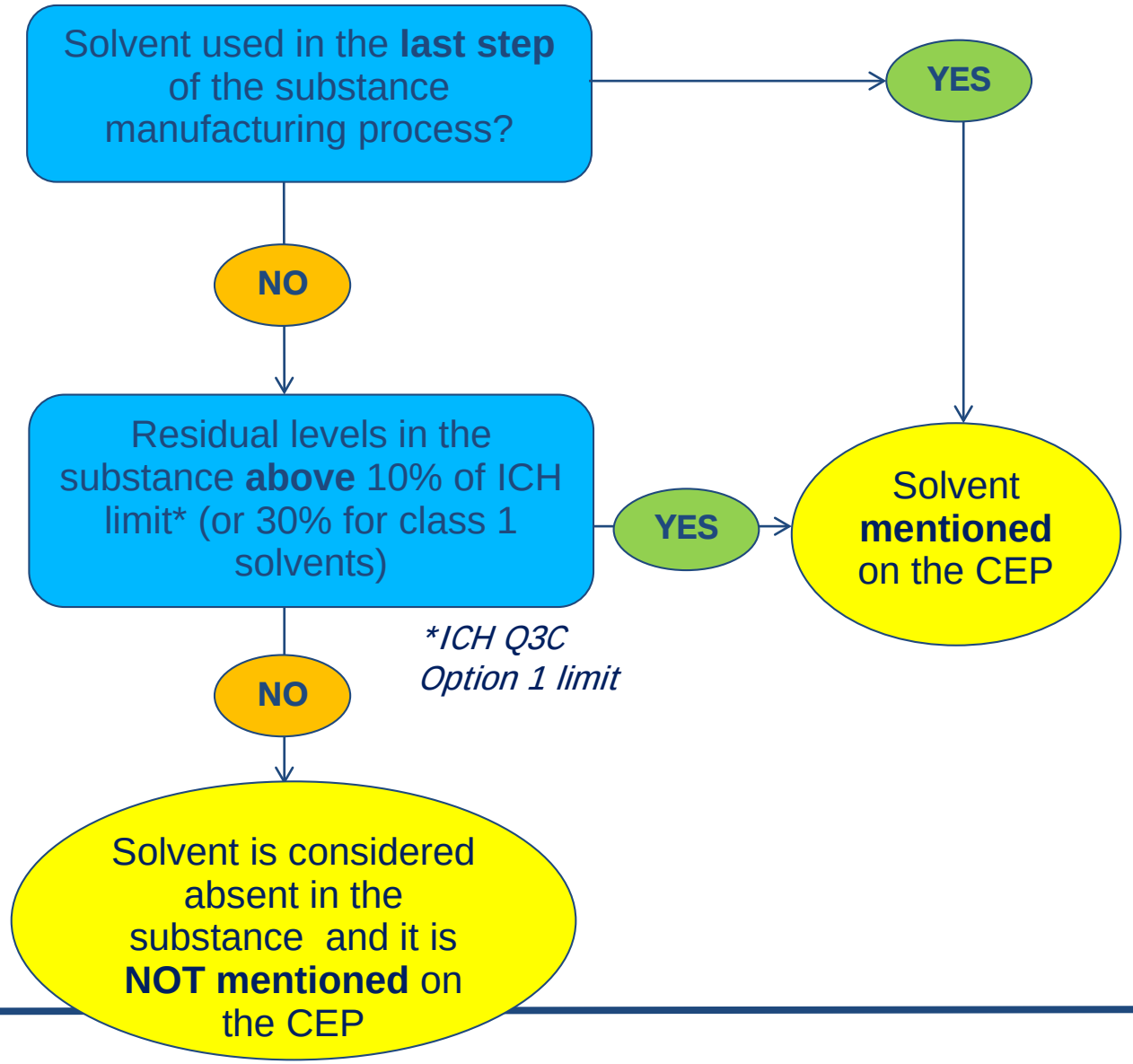
Residual solvents

Which solvents are mentioned on a CEP?

those likely to be present in the substance

AND

those used in the last step



Residual solvents

What are the limits mentioned on the CEP for solvents?

Limits proposed by the manufacturer, as 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 Option 1 are acceptable if duly justified (e.g. Option 2, this is made transparent on CEP).

Residual solvents

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

a) When LOD test 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 no LOD test 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%.

When is water mentioned on the CEP?

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

> In the last steps of the synthesis 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 now be performed.
- **PA/PH/CEP (16) 23, 2R** 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 and it is annexed to the CEP
b) RMS reflects the presence/absence of elemental impurities in the API
c) The applicant has **not** set limits in the specification

A risk management summary for elemental impurities has been provided.		(Annex 2)
– Tests for elemental impurities by ICP-MS		
Palladium	not more than 3 ppm	(Annex 3)
Nickel	not more than 6 ppm	(Annex 4)

a) and b) as above
c) The applicant has set **limits** for elemental impurities => limits on the CEP and methods annexed.

Elemental impurities

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

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

a) A RMS is not provided
b) The CEP is transparent on the introduction of elemental impurities, not on their absence/presence.
c) No limits for elemental impurities in the specification

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

– Test for elemental impurities by atomic absorption spectrometry		(Annex 3)
Palladium	not more than 10 ppm	

a) and b) as above

b) The applicant has set a **limit** in the specification => limit on the CEP and method annexed.

Intentional introduction

route of administration

Example of Risk Management Summary to be prepared:

Intended route of administration / Use of the substance: .....

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**

See document **"Implementation of ICH Q3D in the Certification Procedure"** (PA/PH/CEP (16) 23, 1R)

All 24 elemental impurities as mentioned in ICH Q3D

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

Other

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.

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

Container closure

Systematically assessed and mentioned on the CEP (immediate + outer packaging), even if no retest period is requested.

Retest period (optional but highly recommended)

Requested by the applicant, otherwise absent. CEP statement reflects the fact that the substance is **stable**

- during the 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.

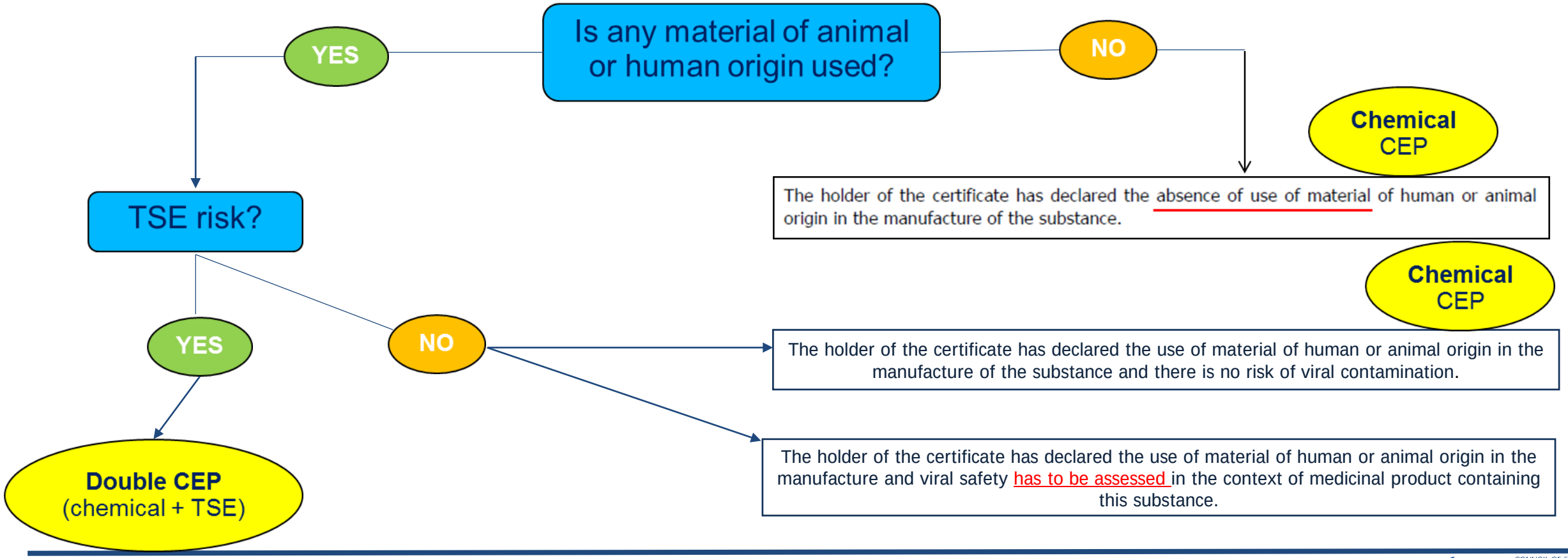
The applicant may wish to define stricter conditions (e.g. for transportation) however this is not specified on the CEP.

Why some CEPs indicate specific storage conditions?

- They have been justified by stability data. Precautionary storage conditions are not accepted

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



Information on a

TSE CEP

Information 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**".

Information on a

CEP for a sterile substance

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

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

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.

Information on a CEP for herbal drugs or herbal drug preparations

Typical Herbal CEP statements:

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

CEP (chemical purity) is intended to be included in Part 3.2.S of the Marketing Application- *often via type 1A variation*

- A complete copy of the CEP, with its annexes
- Specification of the active substance as implemented by the FP manufacturer (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 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 (if absent on CEP), etc. Hence additional data might be needed.

Thank you for your attention

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