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

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Use of a CEP

Alan Hennessy

EDQM, Certification of Substances Department

Module 5: Fundamentals of the CEP Procedure (Live Webinar)

03 July 2023

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 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.

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 drug product 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 substance 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.

CEP in a Marketing Authorisation Application in the EU

- Provided there are no quality or safety concerns only the versions of the CEP (i.e. revised certificates) which were used in the manufacturing process of a batch of finished product / active substance need to be included in the dossier = Multiple versions of a CEP may be valid at the same time

- If with the submission one or more revisions of the CEP are omitted, the MAH should confirm in the variation application form that substance from the omitted CEP version(s) was not used in the manufacture of the FP and/or AS during the validity of this certificate(s).

- Additionally, it should be confirmed that any changes introduced by the omitted CEP revision(s), do not affect the quality of the AS and/or FP.

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure (EMEA-H-19984/03 Rev. 102)

CEP 2.0

CEP 2.0
NEW PAGE IS
ONLINE!

MORE INFORMATION

https://www.edqm.eu/en/what-is-the-cep-2.0

Co-existence of different CEPs

OLD CEP

CEP

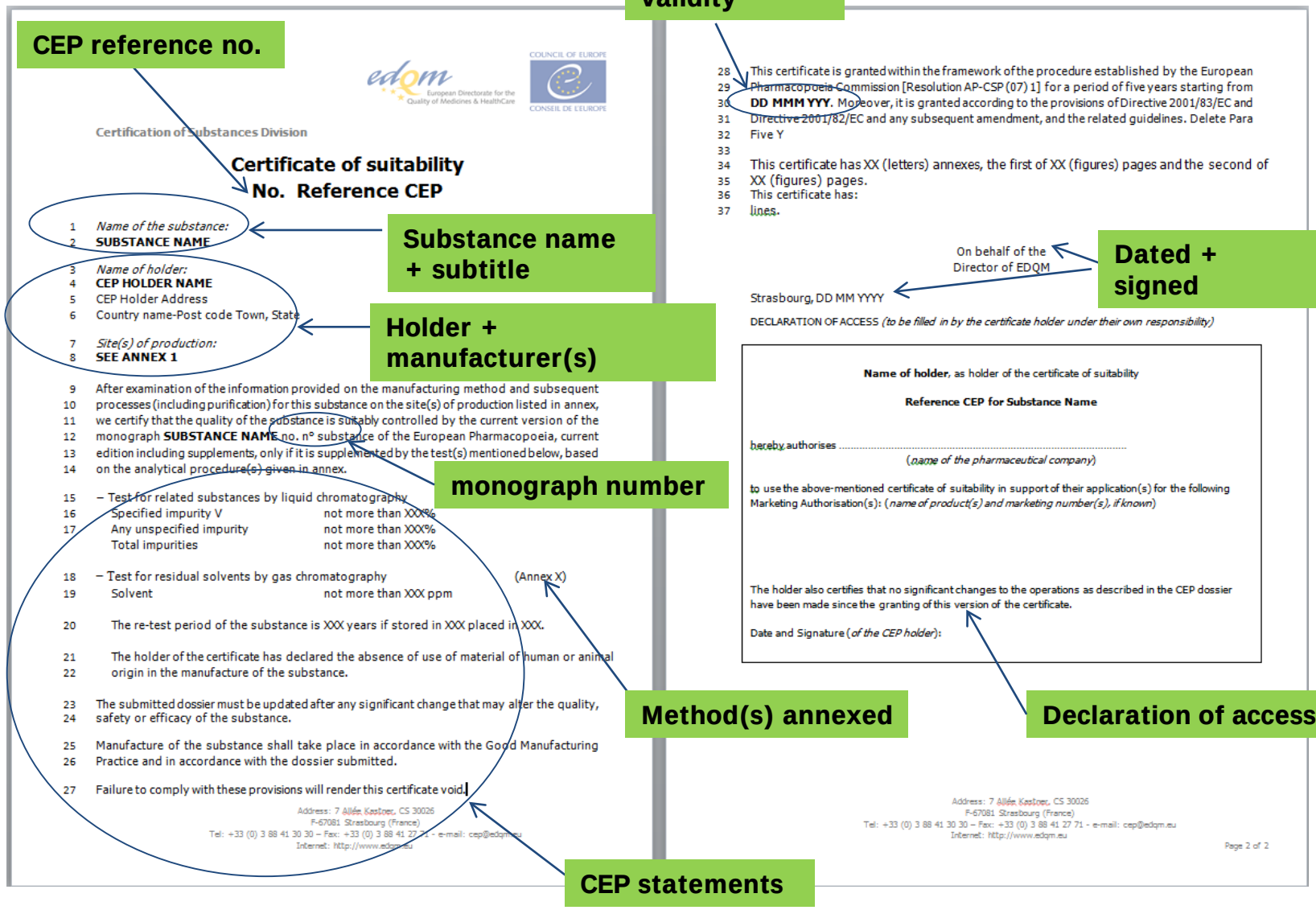
CEP HYBRID

CEP 2.0

How to interpret the information laid down on CEPs

Current and Hybrid

Current “Old” CEP



Certification of Substances Division

Certificate of suitability
No. Reference CEP

Name of the substance:
SUBSTANCE NAME

Name of holder:
CEP HOLDER NAME
CEP Holder Address
Country name-Post code Town, State

Site(s) of production:
SEE ANNEX 1

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph **SUBSTANCE NAME** no. n° substance of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for related substances by liquid chromatography
Specified impurity V not more than XXX%
Any unspecified impurity not more than XXX%
Total impurities not more than XXX%

– Test for residual solvents by gas chromatography (Annex X)
Solvent not more than XXX ppm

The re-test period of the substance is XXX years if stored in XXX placed in XXX.

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

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (07) 1] for a period of five years starting from **DD MMM YYY**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines. Delete Para Five Y

This certificate has XX (letters) annexes, the first of XX (figures) pages and the second of XX (figures) pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, DD MM YYYY

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

Name of holder, as holder of the certificate of suitability

Reference CEP for Substance Name

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*):

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Page 2 of 2

Start of validity

CEP reference no.

Substance name + subtitle

Holder + manufacturer(s)

monograph number

Dated + signed

Method(s) annexed

Declaration of access

CEP statements

CEP

- The “hybrid look” CEP will be granted after approval of revision applications and notifications for existing CEPs, when the content of the CEP is impacted.

- The “hybrid look” CEP will have the new numbering, SPOR/OMS ORG and LOC_ID, the expiry date and declaration of access removed, an e-signature and will be issued as an electronic document.

HYBRID CEP

Certification of Substances Department

Certificate of suitability
No. CEP 202X-XXX-Rev 01

Name of the substance:
CHOCOLATE

Name of holder:
ABRACADABRA Ltd
13 Magic Street
Wonderland-987654
ORG_ID 998877665
LOC_ID 112233456

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 202X-XXX-REV 00

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph **CHOCOLATE** NO. XXXX of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography (Annex 2)
1,2 Dioxane not more than 380 ppm

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

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

The re-test period of the substance is 12 months if stored in double polyethylene bags in a triple laminated bag.

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

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

The holder of this certificate shall share sufficient information in order to enable the authorised user of this certificate to evaluate the suitability of this substance for its intended use and shall inform them of any relevant change in the dossier.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (07) 1] starting from **16 April 2022**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has two annexes, the first of 1 page and the second of 2 pages.
This certificate has:
lines.

Hélène Bruguera

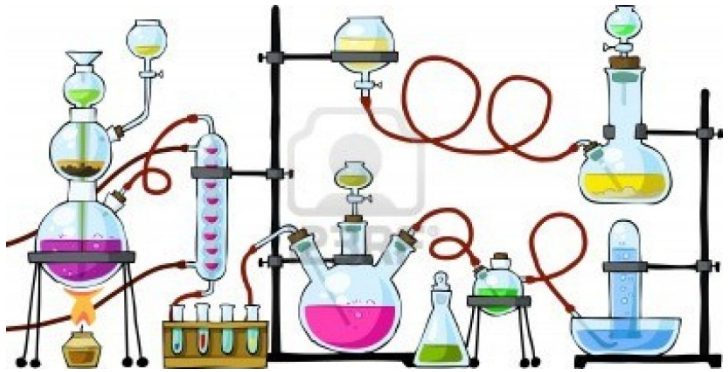
On behalf of the
Director of EDQM

Strasbourg, 16 May 2024

This is a mock up and not the final version
Some legal statements and look may change

Information on a

CHEMICAL CEP



Subtitle (optional)

Sometimes a subtitle is requested by CEP holder when they hold multiple CEPs for the same substance (e.g. Process 1, Process 2)

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 »

Subtitle (optional) – Related to grades

- 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 to those already listed in the Ph. Eur. monograph).
- They are 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%

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 »** developed by the applicant, and which is appended to the CEP.

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

Impurities statements

What about “alternative method”?

- The holder may chose to use alternative “In-house methods” to those of the Ph. Eur. monograph to control related substances.
  - Should be cross-validated against the Ph. Eur. method (should be at least equivalent)
  - Acceptability is determined 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

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.

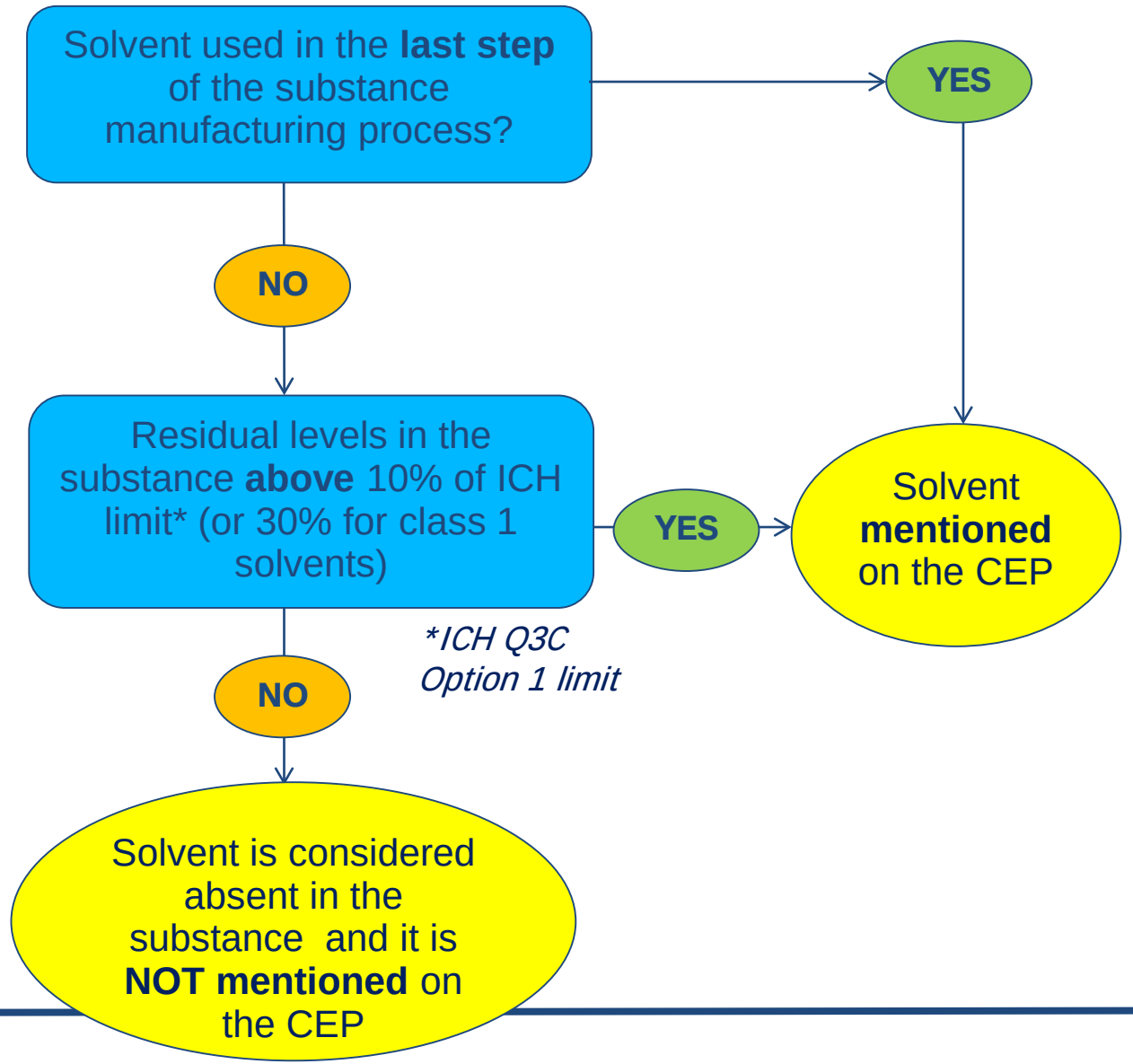
Residual solvents

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 2)
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

- EDQM does not make a decision on compliance with elemental impurities guidance such as ICH Q3D.
- The CEP instead provides transparency on elemental impurities, to be considered by the manufacturer of medicinal product in the context of a MAA.
- CEPs have been providing this transparency since 2016 for human and for human and veterinary substances, and from 2021 for veterinary use only substances (see **PA/PH/CEP (16) 23, 2R** published in April 2021)

Elemental impurities – all scenarios

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.

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, 2R)

All 24 elemental impurities as mentioned in ICH Q3D

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

Elemental impurities – human, human and veterinary use

> 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 <u>not</u> provided
b) The CEP is transparent on the <u>introduction</u> 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.

Elemental impurities – veterinary use only

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

The following elemental impurities are intentionally introduced in the manufacture of the substance: Ni, Mn

a) A RMS is <u>not</u> provided
b) No reference to ICH Q3D is made for substances for veterinary use only
c) The CEP is transparent on the intentional introduction of elemental impurities. This includes those classified by ICHQ3D, intentionally added as catalysts, and those which introduce a concern for toxicity.
d) No limits for elemental impurities in the specification

The following elemental impurity is intentionally introduced in the manufacture of the substance: Ni, Mn	
- Test for elemental impurity by ICP-MS	(Annex 3)
Nickel	not more than 5 ppm

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

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)

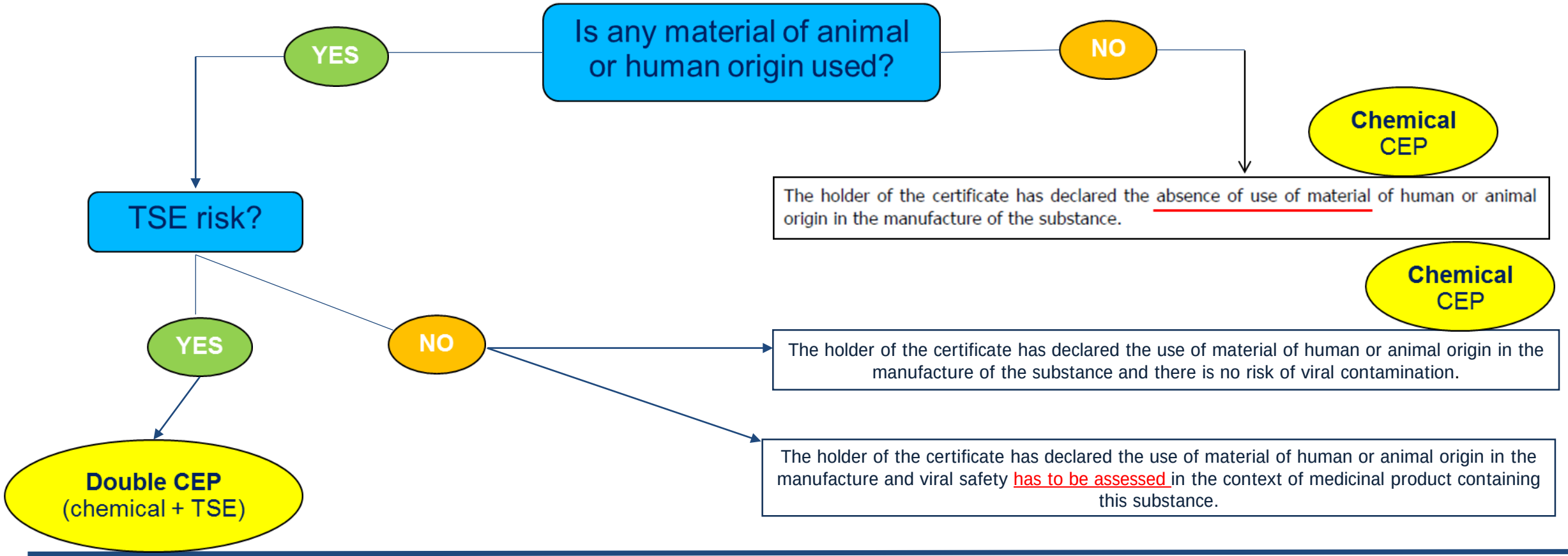
> The re-test period of the substance is 36 months if stored in amber glass bottles, with polybutylene terephthalate screw caps, placed in polyethylene bags.

Why some CEPs indicate specific storage conditions?

- They have been justified by stability data.

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).

- Subtitle “Sterile”
- The CEP includes the typical statements of each type of CEP (as applicable).
- And the following statement

> 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.

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

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

How to interpret the information laid down on CEPs

CEP 2.0

CEPs and information reported

Information which will remain on the CEP as today:

- Subtitle
- List of class 3 solvents used in the last steps of the process and controlled by loss on drying
- Use of water in the last steps of the process
- Information on elemental impurities (Risk management summary (RMS) or statements on use/non-use)
- Container closure system and re-test period.

CEPs and information reported

Information which will remain on the CEP as today:

- Statement regarding Production section of the monograph only when not assessed by EDQM (has to be addressed as part of the MAA)
- Statement on method of sterilisation when applicable
- For herbal CEPs, DER ratio, extraction solvents and excipients
- “Animal or human origin material” sentence kept as today, even if in most of the cases no use of such materials
- Depending on the case, statement regarding viral safety.

CEPs and information reported

Changes to the content

- The full approved specification (section 3.2.S.4.1) applied by the CEP holder

- The additional methods (Part of section 3.2.S.4.2) needed to control the quality of the substance

When : Ph. Eur. method is **not suitable** to control in-house impurities

To supplement monograph method(s)

Unless absence of corresponding impurities is demonstrated, it will be reported on CEP

Validation in line with ICH Q2(R1)

Mock-up CEP 2.0

Certification of Substances Department

Certificate of suitability
No. CEP-2023-836-Rev-00

Name of the substance:
CHOCOLATE

Name of holder:
ABRACADABRA Ltd
13 Magic Street
Wonderland-987654 Sugar town
ORG_ID 998877665
LOC_ID 112233456

We certify that the quality of the substance is suitably controlled by the current version of the monograph **CHOCOLATE** n°XXXX of the European Pharmacopoeia and supplementary tests.
The approved site(s) of production, the specification and any supplementary test procedures are included on the following pages

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

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

The re-test period of the substance is 12 months if stored in double polyethylene bags in a triple laminated bag.

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

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

The holder of this certificate shall share sufficient information in order to enable the authorised user of this certificate to evaluate the suitability of this substance for its intended use and shall inform them of any relevant change in the dossier.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Failure to comply with these provisions will render this certificate void.

This certificate is granted according to the provisions of Resolution AP-CSP (07) 1 of the Council of Europe, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

Hélène Bruguera

On behalf of the
Director of EDQM

Strasbourg, 16 May 2024

This is a mock up and not the final version
Some legal statements and look may change

Mock-up CEP 2.0

Certification of Substances Department

Site(s) of production for CEP-2023-836-Rev-00

Production of intermediate:

CAKE Ltd
7 chocolate street
Fantasyland-123456 Pepper town
ORG_ID 999666333
LOC_ID 246246246

Production of Pyrimethamine:

ABRACADABRA Ltd
13 Magic Street
Wonderland-987654 Sugar town
ORG_ID 998877665
LOC_ID 112233456

3.2.S.4.1 - Specification

Test	Specification	Method
Appearance	White, odorless, crystalline powder.	In-house
Solubility	Slightly soluble in acetone, in alcohol, and in chloroform; practically insoluble in water.	In-house
Identification		
A) IR	Infrared spectrum obtained with a test preparation exhibits the same peaks at the same wavelengths as that of a reference preparation	Ph. Eur. 2.2.24 Method
B) CHLORIDE	The solution meets the requirements of the test.	In-house
C) HPLC	The retention time of the main peak of the sample solution corresponds to that obtained with the reference solution, as obtained in the Assay.	In-house
Appearance of the solution	The solution is clear and not more intensely colored than the reference solution BY6.	Ph. Eur. 2.2.2 Method II
Acidity or alkalinity	The solution is pink	Ph. Eur. Monograph
	The solution is red or orange	
Melting range	Between 239 °C and 242 °C	Ph. Eur. 2.2.14 Method
Loss on drying	It loses not more than 0.5% of its weight	Ph. Eur. 2.2.32 Method
Sulfated ash	≤ 0.10%	In-house
Sulfates	Maximum 80 ppm, determined on solution S	Ph. Eur. 2.4.13 Method
Related Substances		
Individual impurities	≤ 0.10%	Ph. Eur. 2.4.29 Method
Total impurities	≤ 0.3%	
Assay (HPLC)	99.0 – 101.0%	In-house
Residual Solvents		
Methanol	≤ 3000 ppm	In-house
Dichloromethane	≤ 600 ppm	
Toluene	≤ 890 ppm	
Dioxane	≤ 380 ppm	

Mock-up CEP 2.0

3.2.S.4.2 Analytical procedures

Reference solution: Weigh 300 mg of methanol, 60 mg of dichloromethane, 89 mg of toluene and 38 mg of 1,4 dioxane in a 100 mL volumetric flask, dilute and take to capacity with dimethyl sulfoxide. Take a 10 mL aliquot and place it in a 50 mL volumetric flask and take to capacity with dimethyl sulfoxide. Transfer 2 mL of this solution to a head space vial.

Sample solution: Weigh 400 mg of the sample, transfer to a head space vial and add 2 mL of dimethyl sulfoxide. Mix this solution until dissolution.
Prepare this solution two times

Chromatographic conditions.

Columns	CP-SIL 5 CB 30m, 0.53mm, film 1.5µm, CP-WAX52 CB 30m, 0.53mm, film 1.0µm
Detector	FID
Injector temperature	250 ºC
Detector temperature	300 ºC
Carrier gas	Helium
Gas flow	6.5 mL/ min
Split ratio	4.4
Run time	17.0 min
Temperature ramp	

Event	Velocity (°C/min)	Temperature (°C)	Hold time (min)
0		30.0	5.0
1	10.0	100.0	0.0
2	30.0	200.0	1.67

Head space conditions.

Oven temperature:	80 ºC
Syringe temperature:	90 ºC
Incubation time:	15 min
Injection volume:	0.5 mL

1. Inject the blank solution.
2. Inject six times the reference solution, verify that the relative standard deviation is not greater to 10%.
3. Inject the sample solution 1 and sample solution 2.
4. Calculate the content of each solvent in the sample by using the following equations:

Additional methods

$$ppm\ of\ solvent = \frac{A\ samp}{A\ std} x \frac{W std}{W\ samp} x \frac{FD\ samp}{FD\ std} x\ 1000000$$

Where:

A samp = Obtained area in the chromatogram of the sample
A std = Obtained area in the chromatogram of the standard
W std = Weigh of the standard in mg.
W samp = Weigh of the sample in mg.
DF std = Dilution factor of the standard (500).
DF samp = Dilution factor of the sample (2).

CEP 2.0

- Regular information published on dedicated webpage https://www.edqm.eu/en/what-is-the-cep-2.0

The CEP 2.0 (new name of the CEP of the future) is a "new-look" CEP that will better meet the current needs of stakeholders and offer both enhanced user-friendliness and greater transparency of the information conveyed without, however, increasing the regulatory burden related to revisions of CEPs.

Latest updates

EDQM 19/06/2023 STRASBOURG, FRANCE
CEP 2.0: List of authorities and organisations which have access to assessment and/or inspection reports.

EDQM 28/04/2024 STRASBOURG, FRANCE
Requirements for the content of the CEP dossier according to the CEP 2.0 and updated application forms

CEP 2.0: what will change?

In the context of the project of the CEP of the future, the EDQM organised in late 2020 a wide public consultation with its

IMPORTANT INFORMATION

- The CEP 2.0 – Webinar for CEP holders and CEP users
- CEP 2.0 - Public consultation: CEP letter of access
- CEP 2.0: Use of EMA SPOR/OMS ORG_ID and LOC_ID mandatory for CEP applications
- CEP holders responsibilities towards their customers (PA/PH/CEP (21) 57, January 2022)

- Several webinars already held in May.

Thank you for your attention

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