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

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The CEP 2.0
Webinar for CEP holders and CEP users

Nataliia MOSTRIANSKA and Andrea MELLONI, Certification of Substances Department, EDQM

Debora MARTINS BRAGA, European Medicines Agency (EMA)

11 and 16 May 2023

Agenda

- The CEP 2.0 – result of the «CEP of the Future» project
- Main changes and developments
  - Requirements to the content and structure of the dossier (module 1 and module 3)
  - Enhanced responsibility for the information-sharing between CEP holders & MAH
  - Reduction of revisions of CEPs
  - On-line databases
  - Information reported on the CEP
  - Implementation timeline
- Questions & Answers

Why CEP 2.0?

- “CEP of the future” launched in 2020 to design a “new-look” CEP

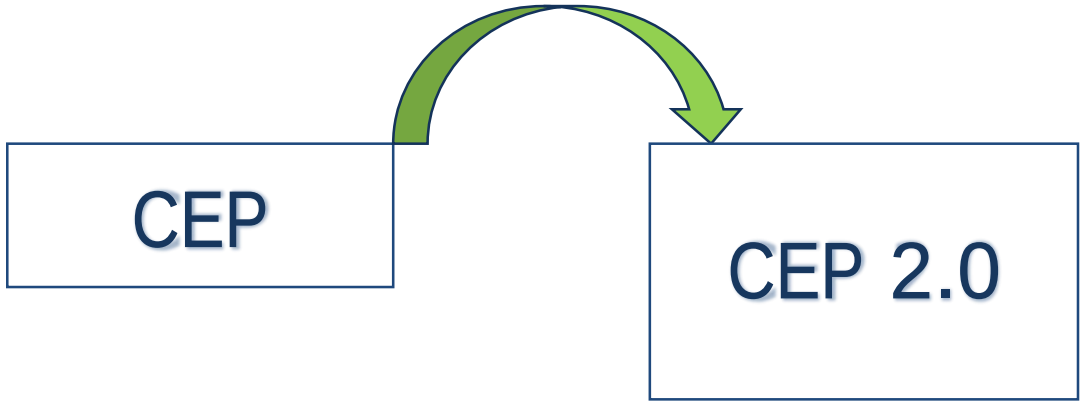
WHY?

- Meet the most recent needs of stakeholders: CEP holders/API manufacturers, drug product manufacturers, regulatory agencies (worldwide)
- Ease the registration activities linked to the use of CEPs
- Increase the acceptance of CEPs

WHO AND HOW?

- EDQM + Survey + public consultations

Why CEP 2.0?



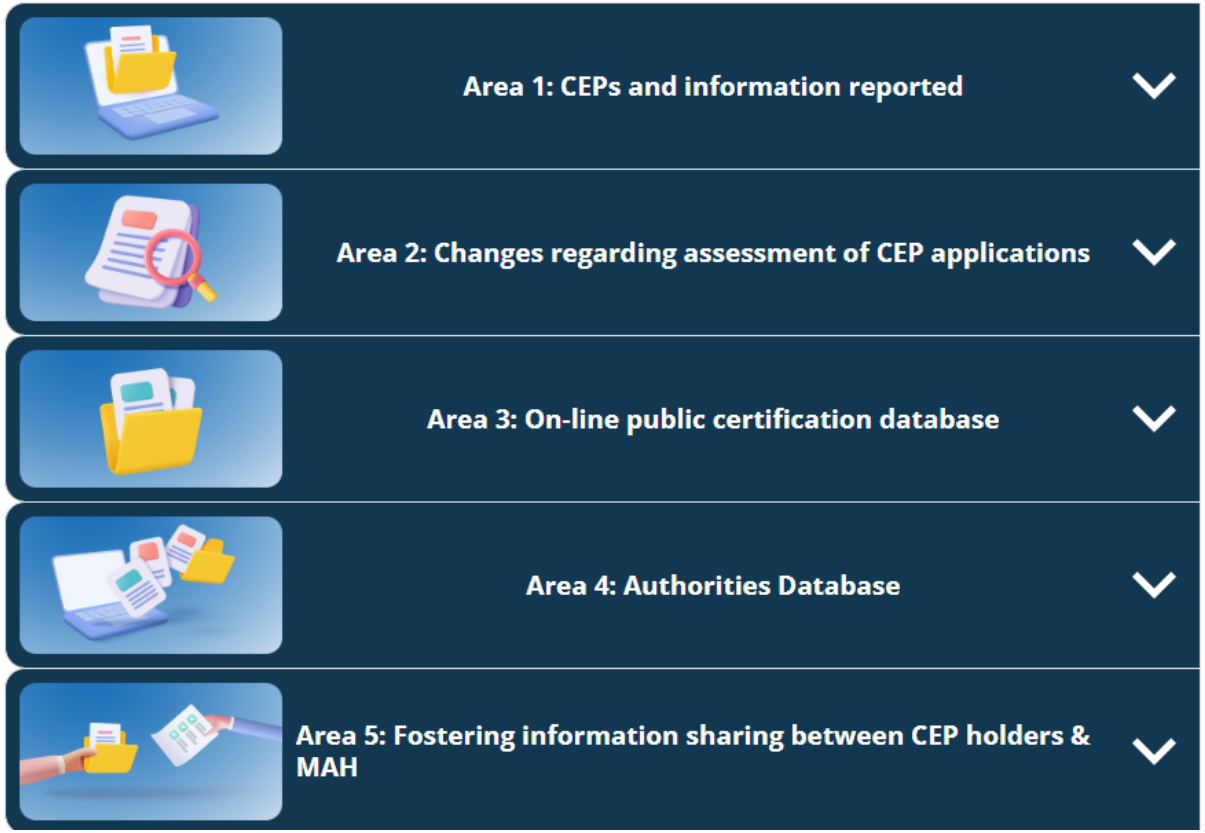
“new-look” CEP:

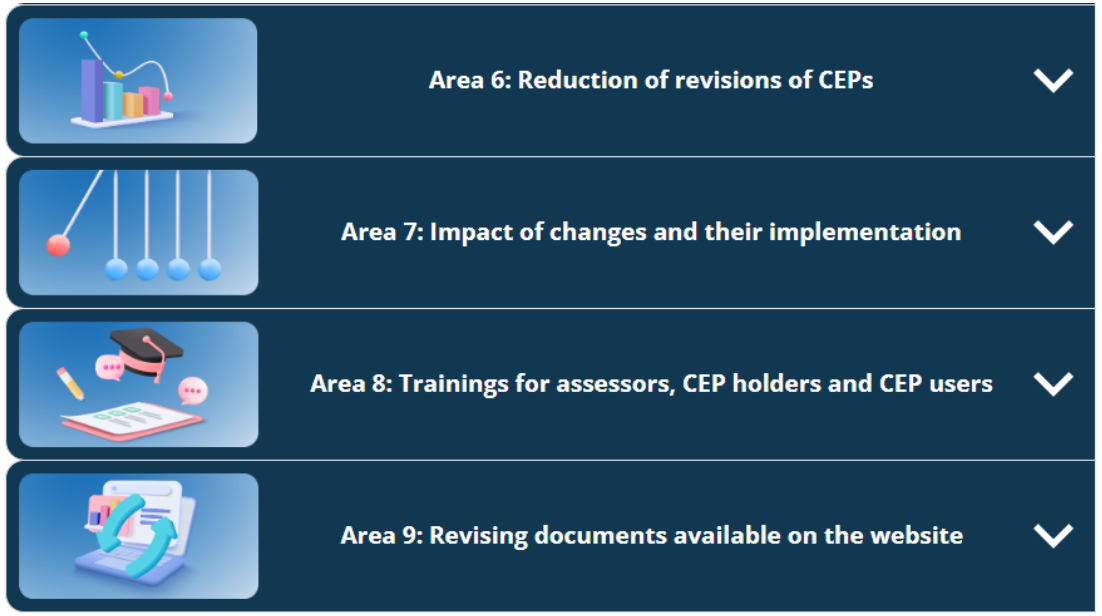
✓ meets the current needs of stakeholders

✓offers greater transparency

✓reduces the regulatory burden

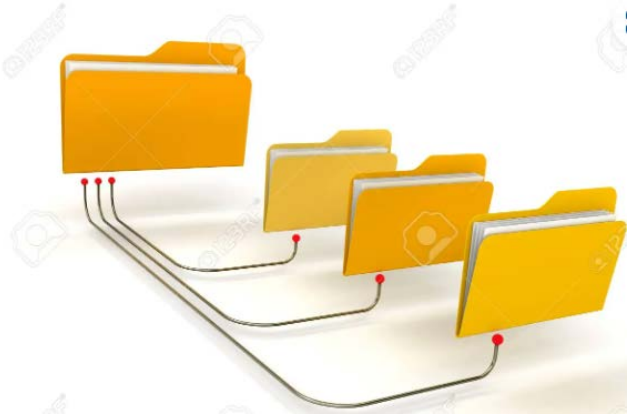
What will change





Download the document explaining the implementation

Requirements to the dossier: content and structure



The CEP 2.0 – requirements to the dossier

Application form and Module 1

- updated application forms in force as of 1 June 2023 (available on the EDQM website link to application forms

- Holder's Commitment updated to reflect the CEP holder's responsibilities towards their customers and to anticipate potential confidential sharing of reports for the dossier with Competent Authorities of those countries with which the EDQM has a Memorandum of Understanding and/or Confidentiality Agreement in place.

The CEP 2.0 – requirements to the dossier

What has changed:

- **use of** the EMA SPOR/OMS Organisation (**Org**) and Location (**Loc**) ID becomes mandatory for all sites listed in the application form. Org and Loc ID will be reflected on the CEP

ACTION: include EMA OMS SPOR Org ID and Loc ID in the application form for all sites

EMA SPOR/OMS Organisation and Location ID

Debora MARTINS BRAGA,
European Medicines Agency (EMA)

The CEP 2.0 – requirements to the dossier

Reminder on the importance of comparative table in applications for revisions

Changes must be individually classified and declared in the comparative table

IF NOT, change(s) considered as: not declared = not assessed = not approved

3. Comparative table

The comparative table should highlight the differences between the approved and proposed text of module 3, together with the correct classification of each change according to the EDQM Guideline for revisions. The justification for the changes should be fully developed in the cover letter.

Annexes	Yes	N/A
7) Comparative table	☒	

link to the refresher on good practices

The CEP 2.0 – requirements to the dossier

CEP dossier (modules 2 and 3) will reflect the assessment performed and the approved specification

The process description and the specification sections of the CEP dossier should contain **only the information** corresponding to the **quality claimed**

Any other data **should not be** included in the dossier if **no corresponding** specific **grade** is requested

ACTION: include only relevant information in the dossier

The CEP 2.0 – requirements to the dossier

Maximum Daily Dose (MDD):

- The CEP holder/applicant is requested to include in their dossier (in 3.2.S.1.3) the Maximum Daily Dose (MDD), route of administration and treatment duration considered for the development of their control strategy and specification presented in their CEP dossier.

- This information is also to be shared between the CEP holder and the drug product manufacturer/MAH.

The CEP 2.0 – requirements to the dossier

GRADES:

it is optional to apply for a grade on the CEP **(no change).**

- In the past situations existed when no grade was mentioned on the CEP in the subtitle, however, numerous specifications could be included and/or reference to optional manufacturing process steps was given (most typical example – optional micronisation).

The CEP 2.0 – requirements to the dossier

GRADES:

In all cases, all sections of the dossier should be consistent within the dossier itself **and** with the CEP when granted

If the applicant **does not apply** for a grade, data on micronisation, particle size, sterilisation, etc. should not be included in the dossier.

Only if a grade is claimed, sites in charge of the concerned physico-chemical treatments such as milling, micronisation and sterilisation should also be listed in 3.2.S.2.1. If a grade is not requested, the information for the related sites should not be included in the CEP dossier and application.

The CEP 2.0 – requirements to the dossier

QUALITY OF WATER:

Section **3.2.S.2.3** should specify the quality of the water used within the manufacturing process.

Choice and definition of the grade should be based on the EMA "Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)" and Ph. Eur.

More information about the quality of water may be required at the level of the marketing authorisation application with regard to the intended final use of the substance.

The CEP 2.0 – requirements to the dossier

Approved specification (as in the section 3.2.S.4.1) will be appended to the CEP;

- the specification sections of the CEP dossier should contain only the information corresponding to the quality claimed
- Specification for micronisation, particle size, microbiological controls, etc. should not be included in the dossier if no corresponding specific grade is requested.

- Any **additional methods** needed to control the quality of the substance included in the specification will be assessed (validation, cross-validation) and appended to the CEP

The CEP 2.0 – requirements to the dossier

Expectations to the specification included in module 3:

- should be free of highlighting, tracked changes, coloured text, and watermarks. The given text should be legible and the use of scanned documents is to be avoided.
- All headers and footers will be removed by EDQM during preparation of the Annexes and CEP holders/applicants are encouraged to avoid their use in sections 3.2.S.4.1 and 3.2.S.4.2 of their submissions.
- The tabular format is requested. Parameters, limits and reference of the method to be reported in the table (e.g. Ph. Eur., in-house).
- In case of in-house impurities controlled in the final substance, an unequivocal chemical name of the compound should be used (in-house code may be added if relevant).

The CEP 2.0 – requirements to the dossier

Example of the specification:

Parameters	Limits	Reference
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.	Ph. Eur. current edition
Identification Test A (IR) Test B (HPLC)	 Complies to reference Positive	Ph. Eur. current edition
Specific optical rotation (o.d.b.)	+158° to + 167°	Ph. Eur. current edition
Loss on drying	≤ 0.5 %	Ph. Eur. current edition
Related substances		Ph. Eur. current edition
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Impurity C	≤ 0.15%	
Impurity D	≤ 0.15%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.5%	
Assay (o.d.b.)	97.0% to 102.0 %	Ph. Eur. current edition
Residual solvents (by GC)		In-house
Ethanol	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house

The CEP 2.0 – requirements to the dossier

Expectations to the layout of the analytical methods:

- separate section 3.2.S.4.2 into **two distinct sections** as follows.

m3

32-body data

32s-drug-sub

32s42-analy-proc

analytical procedures-equiv_ih-subsection 1

analytical procedures-add_ih-subsection 2

The CEP 2.0 – requirements to the dossier

Methods of the Ph. Eur. monograph

Details of the methods of the Ph. Eur. monograph **should not** be reproduced in section 3.2.S.4.2. This applies also in case chromatographic adjustments are made to the Ph. Eur. method within the scope of Ph. Eur. chapter 2.2.46.

The CEP 2.0 – requirements to the dossier

Subsection 1 –Alternative analytical test procedures to those of the Ph. Eur. monograph

- any in house analytical test procedures, which following validation and cross validation with the method of the Ph. Eur. monograph, have been determined to be **equivalent**.
- All analytical test procedures provided in Subsection 1 must be **fully described**.
- As these test procedures are considered equivalent to the method of the Ph. Eur. monograph they **will not be** appended to the CEP document.

The CEP 2.0 – requirements to the dossier

Subsection 2 – Additional in house method(s)

Additional in house methods are those necessary to ensure the quality of the substance when the Ph. Eur. Method(s) is not suitable to control in-house impurities and/or to supplement monograph methods.

The CEP 2.0 – requirements to the dossier

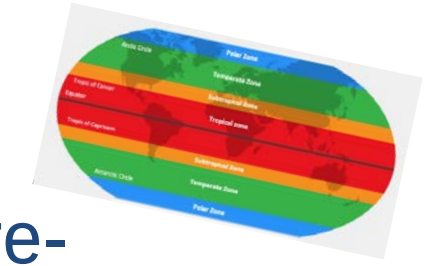
Subsection 2 – Additional in house test procedure(s)

- analytical test procedures in Subsection 2 must be **fully described** and **appropriately validated**.
- they will be appended in full to the CEP.
- **Legible documents** suitable to be appended to the CEP

Stability

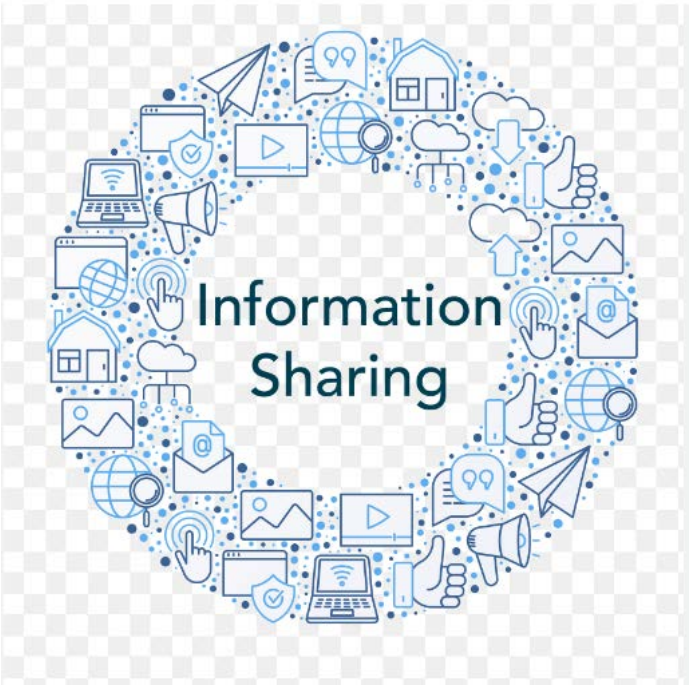
- Encouragement to include stability data in CEP applications and to claim re-test period to benefit from the centralised assessment of these data at the level of the CEP

- More flexibility with regard to storage conditions/temperature
  - Restrictive storage conditions with respect to temperature may be accepted and reflected on the CEP with the re-test period provided they correspond to the conditions in which stability data have been obtained.



- Assessment of stability data with reference to additional climatic zones (III and IV) and inclusion of corresponding re-test period on CEPs if proposed by applicants (optional).

Enhanced responsibility for the information-sharing between CEP holders & MAH



Fostering information sharing CEP holders & MAH

- CEP holder shall provide information to their customers in addition to the CEP. CEP holder and MAH agree on information shared and format.
- In January 2022 the document “CEP holders responsibilities towards their customers” as a reminder to CEP holders (EDQM web-site)
- This aspect is checked during EDQM GMP inspections.
- Reinforcement of this responsibility in 2023
  - A commitment as part of the application form for a CEP
  - A specific sentence on this obligation in the CEP document
  - *Publication of history of procedures in the public certification database, so users are aware of changes and can ask details from the CEP holders.*

Fostering information sharing CEP holders & MAH

- No declaration of access box in the CEP document anymore
  - replaced by a template available on the EDQM website.

ACTION:

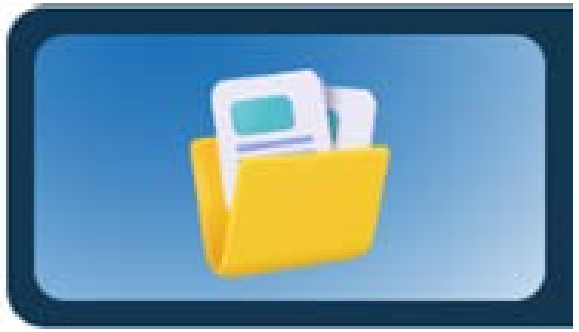
Holders should provide their customers with the letter of access according to the template available on the EDQM website

Reduction of revisions of CEPs

Reduction of revisions of CEPs

- CEPs no longer revised for changes not impacting their content even in case of major revisions.

- Stop releasing a “renewed” CEP following the renewal procedure (the renewal process will be kept), except if the content is impacted ➔ impact on the CEP numbering
  - This will concern CEPs already in the “new look”.



On-line Certification databases

On-line **Public** Certification database

New features in addition to current ones

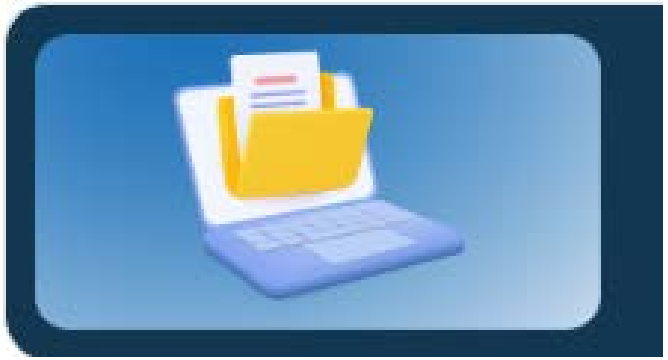
- EMA SPOR OMS ORG_ID and LOC_ID for holder
- Access to short history of finalised procedures with:
  - ✓ type of procedure (e.g. minor revision, notification, major revision, renewal, monograph revision)
  - ✓ end/finalisation date, outcome (i.e. CEP revised, CEP remains valid etc)
  - ✓ corresponding CEP number if any.

Full history information may not be available due to change of IT technology and tool

Authorities database (restricted)

- Restricted access already granted to Ph. Eur. regulatory authorities

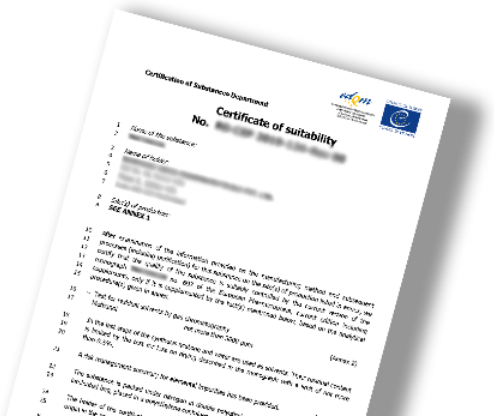
- Extension of access to some regulatory authorities beyond Ph. Eur. as part of worldwide acceptance of CEPs under suitable confidentiality agreements and MoU
  - Display on the EDQM website of a public list of authorities which will have access to the Authorities database
  - Updated holder's declarations as part of the CEP application form to cover this aspect.



CEPs and information reported

The CEP 2.0 – information reported

- CEP remains a « document », with a layout similar to the current one.
- Electronic document with a digital signature.
- Downloadable as a pdf or printed by CEP holders to share with their customers, for inclusion in MAA.
- **No paper copy** will be delivered by EDQM



The CEP 2.0 – information reported

Information which remains on the CEP 2.0 (unchanged):

- 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

The CEP 2.0 – information reported

Information which remains on the CEP 2.0 (unchanged):

- 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, extraction solvents and excipients.

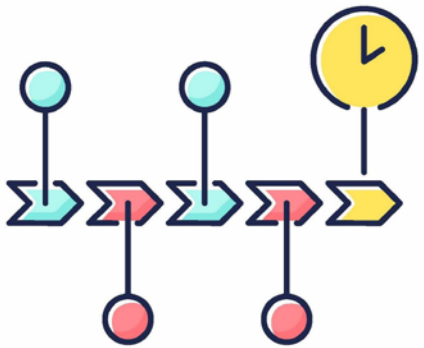
The CEP 2.0 – information reported

What will change:

- **numbering system**: the increment due to renewal is no longer part of the number

Before:	After:
No. R1-CEP YEAR-123-Rev 05	No. CEP-YEAR-123-Rev-05

Stepwise Implementation



The CEP 2.0 – implementation timeline

Coexistence of “old look”, “hybrid look” and “new look” CEPs for some time

Q3 2023:

- « **New look CEPs** » for any new CEP and at renewal
- « **Hybrid look** » after revision of existing dossiers when there is no impact on the information reported on the CEP
- Valid « **Old look** » CEPs (= current layout) will remain
- Possibility for CEP holders to submit a special type of revision to move to « New look » CEP for existing ones – optional (at later stage).

CEP

- The “old look” corresponds to CEPs as granted till the implementation of CEP 2.0
- This means that no CEP will be granted with the “old look” after the implementation of the CEP 2.0
- CEPs granted before this date will still be valid until they get revised.

OLD CEP

Certification of Substances Department

Certificate of suitability
No. R1-CEP 20XX-XXX-Rev 02

Name of the substance:
CHOCOLATE

Name of holder:
ABRACADABRA Ltd
13 Magic Street
Wonderland-987 654 Sugar town

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 20XX-XXX-REV 01

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

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy 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: https://www.edqm.eu

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 renewed from **16 May 2021** according to the provisions of Resolution AP-CSP (07) 1, and 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 4 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 16 May 2022

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

ABRACADABRA Ltd, as holder of the certificate of suitability

R1-CEP 20XX-XXX-Rev 02 for Chocolate

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*):

Certification of Substances Department

Annex 1: Site(s) of production for R1-CEP 20XX-XXX-Rev 02

Production of intermediate:

CAKE LTD
7 chocolate street
Fantasyland-123456 Pepper town

Production of Chocolate:

ABRACADABRA Ltd
13 Magic Street
Wonderland-987654 Sugar town

Residual solvents

Dioxane ≤ 380 ppm.

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:

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

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).
1000000 = Conversion to ppm

Mock-up 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

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

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

The CEP holder should provide the Marketing Authorisation Holders with any necessary information that is needed to guarantee the quality, safety and efficacy of the medicines.

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

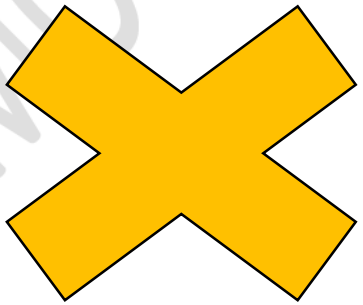
This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (07) 1] starting from **16 April 2022**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment,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

Page 2 of 2

Mock-up CEP

Certification of Substances Department

Annex 1: Site(s) of production for CEP-202X-XXX-Rev-01

Production of intermediate:

CAKE LTD
7 chocolate street
Fantasyland-123 456 Pepper town
ORG_ID 999666333
LOC_ID 246246246

Production of Chocolate:

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

Residual solvents

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.

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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)
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1	10.0	100.0	0.0
2	30.0	200.0	1.67

Head space conditions.

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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%.
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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).

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

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 **CHOCOLATE** NO. XXXX of the European Pharmacopoeia, current edition including supplements, and any additional test(s) and analytical procedure(s) in line with the approved specification given in **ANNEX 2**.

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.

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

The CEP holder should provide the Marketing Authorisation Holders with any necessary information that is needed to guarantee the quality, safety and efficacy of the medicines.

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 May 2024**. 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 three annexes, the first and the second of 1 page each and the third 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

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

Additional methods

3.2.S.4.2 – Analytical procedures

Residual solvents

Methanol ≤ 3000 ppm.
Dichloromethane ≤ 600 ppm.
Toluene ≤ 890 ppm.
Dioxane ≤ 380 ppm.

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 °C
Detector temperature	300 °C
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 °C
Syringe temperature:	90 °C

Incubation time:	15 min
Injection volume:	0.5 mL

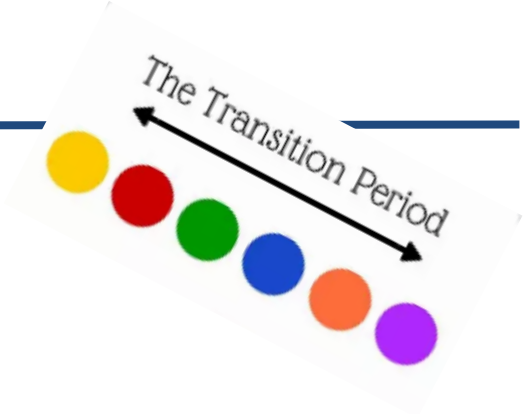
1. Inject the blank solution.
2. Inject six times the reference solution, verify that the relative standard deviation is not greater to 10%.
3. Inject the sample solution 1 and sample solution 2.
4. Calculate the content of each solvent in the sample by using the following equations:

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

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).
1000000	= Conversion to ppm

Stepwise & smooth implementation



Smooth transition for CEP holders, EDQM and users

- EDQM will provide guidance and support to identify and understand the different layouts.

- Dedicated webpage for the project here

MORE INFORMATION

CEP 2.0

Any question, need of clarification or suggestions?

- Consult the EDQM website for supportive guidance documents
- The Certification Department provides support through the EDQM helpdesk.

Thank you for your attention

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