

## COMMUNICATION TO STAKEHOLDERS

Issue No.: PEM\_Preg\_01-2024/25

**25 April 2024**

### EDQM CEP 2.0 IMPLEMENTATION

#### INTRODUCTION

This document is intended to provide communication to industry on the changes of EDQM CEP and implementation of CEP 2.0 for all other new applications for orthodox medicines. This will be a “living document” and will be updated in line with changes observed from the EDQM. It is important that Applicants adhere to the regulatory requirements to avoid delays in the evaluation of applications. This document should be used in conjunction with SAHPRA’s BE & Quality guideline and CEP letter of access template available from SAHPRA’s website.

#### Document History

[First publication – Version 0]	24/04/2024
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**Dr Boitumelo Semete-Makokotlela**  
SAHPRA Chief Executive Officer (CEO)

## List of abbreviations and definitions

APIs	Active Pharmaceutical Ingredients
APIMF	Active Pharmaceutical Ingredient Master File
BE	Bioequivalence
CEP	Certificate of Suitability
CPQ	Confirmation of WHO API Prequalification
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
FPPs	Final Pharmaceutical Products
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
RRA	Recognised Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority
USFDA	United States of America Food and Drug Administration
USP	United States Pharmacopeia

## 1. Background

SAHPRA currently recognises the professional work done by the EDQM as a directorate of the Council of Europe. The EDQM performs various activities as part of the effort to protect human and animal health in Europe and one of their major activities include granting of Certificates of Suitability (CEPs) to manufacturers after they have demonstrated that the substance, they produce can be adequately controlled by the quality standards defined in the Ph. Eur. SAHPRA is satisfied with the way EDQM carries out their evaluations and as the result recognizes the CEP in lieu of certain sections in module 3.2.S. The recognition of the CEP by SAHPRA and the manner in which it could be used to support an application is comprehensively described in the SAHPRA's Quality and Bioequivalence guideline.

EDQM in their effort to offer both enhanced user-friendliness and greater transparency of the information conveyed in the CEP, introduced CEP 2.0 effective from the 1 September 2023, and as expected, the CEP 2.0 introduced several great changes. A summary of these changes can be found on the EDQM website, however one major change that has a direct impact on the current SAHPRA's requirements is the completed declaration of access by the APIMF holder to the applicant. The CEP 2.0 will no longer contain a section for the APIMF holder to complete the declaration of access to the applicant. Refer to annexure A & B below for an illustration of the changes on the CEP.

## 2. Plan of Action

### 2.1 Affected applications.

All applications submitted after the 24<sup>th</sup> of April 2024 (excluding herbals/biologicals/complementary medicines).

### 2.2 Applications submitted prior and those already in the evaluation phase.

All applications submitted prior to the release of this letter require no amendments in this regard and the old CEPs with the completed declaration of access will be accepted for evaluation and where necessary, SAHPRA will take the responsibility of sourcing the latest versions (i.e., CEP 2.0) directly from the EDQM database. SAHPRA will only assume this responsibility for the purpose of evaluation of the above-mentioned group of applications. The management of the dossier's 'life circle' will remain the responsibility of the applicant.

### 2.3 New applications

All new applications (i.e., supported by a CEP) submitted after the 24<sup>th</sup> of April 2024 must contain a signed and dated CEP letter of access from the APIMF holder (i.e., annexure C). This letter serves to replace the declaration of access previously included in the CEP.

It must be noted that a written commitment should be included that the applicant will inform SAHPRA in the event of changes, or if the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements (full Module 3.2.S) to support the product dossier.

Annexure A: Old CEP



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

Certification of Substances Department

Address: 1 Main Street, 12 3010  
F400, Sandton (Johannesburg)  
Tel: +27 (0) 11 412 30 00 • e-mail: cep@edqm.eu  
Internet: http://www.edqm.eu

1 Name of the substance:  
2 CHOCOLATE

3 Name of holder:  
4 ABACADABBA LHM  
5 12 Maple Street,  
6 Wonderland 167 434 Sugar town

7 Site(s) of production:  
8 SEE ANNEX 1

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

11 After examination of the information provided in the manufacturing method and subsequent  
12 process (including purification) for this substance in the table(s) of production listed in annex, we  
13 certify that the quality of the substance is suitably controlled by the current version of the  
14 monograph CHOCOLATE (NO. 0000 of the European Pharmacopoeia, current edition including  
15 supplements, only if it is supplemented by the text(s) mentioned below, based on the analytical  
16 procedure(s) given in annex.

17 - Test for residual solvents by gas chromatography (Annex 2)  
18 1,2 Dioxane not more than 300 µg/m

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

20 No elemental impurity specified in ICH Q3D is intentionally introduced in the manufacture of  
21 the substance.

22 The retest period of the substance is 12 months if stored in double polyethylene bags in a  
23 triple laminated bag.

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

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

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

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

31 This certificate is removed from 16 May 2023 according to the provisions of Regulation  
32 (EU) 2017/745, and of Directive 2001/83/EC and Directive 2001/83/EC and any subsequent  
33 amendments, and the related guidelines.

34 This certificate has two annexes, the first of 1 page and the second of 4 pages.

35 This certificate has:  
36 been issued.

On behalf of the  
Director of EDQM

Strasbourg, 16 May 2022

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

**ABACADABBA LHM, as holder of the certificate of suitability**  
**R1-CEP 20XX-XXX-Rev 02 for Chocolate**

I hereby authorize: \_\_\_\_\_ (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): \_\_\_\_\_

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

Certification of Substances Department

Address: 1 Main Street, 12 3010  
F400, Sandton (Johannesburg)  
Tel: +27 (0) 11 412 30 00 • e-mail: cep@edqm.eu  
Internet: http://www.edqm.eu

Production of intermediate:  
CME LTD  
7 Chocolate Street  
Fentonsland 123456 Sugar town

Production of Chocolate:  
ABACADABBA LHM  
12 Maple Street  
Wonderland 167434 Sugar town

EDQM Certificate of Suitability  
R1-CEP 20XX-XXX-Rev 02  
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**Residual solvents**

Dioxane: 100 µg/m

Reference solution: Weigh 100 mg of methanol, 40 mg of dichloromethane, 60 mg of toluene and 10 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 ten times.

**Chromatographic conditions:**

Columns	CP-501 150 mm, 0.5 mm, 5 µm, 1 µm,
Detector	CP-WMS12 CP 30m, 0.5mm, 5µm 1.0µm
Injection temperature	250°C
Detection temperature	300°C
Carrier gas	helium
Flow rate	0.5 mL/min
Split ratio	2:4
Run time	17.0 min

Retention time (min)	Peak	Area	Height	Concentration (µg/mL)
0	1	10.0	100.0	0.0
1	1	10.0	100.0	0.0
2	1	10.0	100.0	1.07

**Head space conditions:**

Oven temperature	60°C
Sample temperature	60°C
Incubation time	15 min
Injection volume	0.5 µL

- Inject the blank solution.
- Inject six times the reference solution, verify that the relative standard deviation is not greater than 20%.
- Inject the sample solution and sample solution 2.
- Calculate the content of each solute in the sample by using the following equation:

$$\text{µg/mL of solvent} = \frac{A_{\text{sample}} \cdot W_{\text{ref}} \cdot F_{\text{Dioxane}}}{A_{\text{ref}} \cdot W_{\text{sample}} \cdot F_{\text{Dioxane}}}$$

Where:  
A<sub>sample</sub> = Observed area in the chromatogram of the sample  
A<sub>ref</sub> = Observed area in the chromatogram of the reference  
W<sub>ref</sub> = Weight of the standard in µg  
W<sub>sample</sub> = Weight of the sample in µg  
F<sub>Dioxane</sub> = Dilution factor of the standard (100)  
F<sub>sample</sub> = Dilution factor of the sample (10)  
D<sub>sample</sub> = Conversion to µg/mL

EDQM Certificate of Suitability  
R1-CEP 20XX-XXX-Rev 02  
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Annexure B: New CEP 2.0 - Mock-up

## Mock-up CEP 2.0

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

**Production of intermediates:**  
CAME Ltd  
7 chocolate street  
Fermilands 12465, Peppercorn  
TOWN: 01 99992310  
LOC\_ID: 246246246

**Production of Pyrimethamine:**  
ABRACADABRA LTD  
13 Magic Street  
Rivonia 21284, Sandton  
TOWN: 011 99997965  
LOC\_ID: 112223666

### 3.2.S.1.1 - Specification

Test	Specification	Method
<b>Appearance</b>	White, odourless, crystalline powder.	In-house
<b>Solubility</b>	Slightly soluble in acetone, in alcohol, and in chloroform, practically insoluble in water.	In-house
<b>Identification</b>		
A) IR	Infrared spectrum obtained with a test preparation exhibits the same profile as that of the same test-amounts as that of a reference preparation.	Ph. Eur. 2.2.24 Method 2
B) CHLORIDE	The solution meets the requirements of the test.	In-house
C) RP LC	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
<b>Assessment of the solution</b>	The solution is clear and just passes turbidity, related to the reference solution 2019.	Ph. Eur. 2.2.2 Method 2
<b>Acidity or alkalinity</b>	The solution is basic.	Ph. Eur. Monograph
<b>Melting range</b>	Between 119 °C and 142 °C	Ph. Eur. 2.2.14 Method 2
<b>Loss on drying</b>	It loses not more than 0.7% of its weight.	Ph. Eur. 2.2.12 Method 2
<b>Reduced ash</b>	≤ 0.10%	In-house
<b>Inpurity</b>	Maximum 02 ppm, determined on solution 1	Ph. Eur. 2.4.13 Method 2
<b>Related substances</b>		
<b>Individual impurities</b>	≤ 0.10%	Ph. Eur. 2.4.29 Method 2
<b>Total impurities</b>	≤ 0.2%	Method 2
<b>Assay (RP LC)</b>	99.0 - 101.0%	In-house
<b>Residual Solvents</b>		
<b>Methanol</b>	≤ 5000 ppm	
<b>Dichloromethane</b>	≤ 400 ppm	In-house
<b>Toluene</b>	≤ 100 ppm	
<b>Diethyl ether</b>	≤ 100 ppm	

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## Mock-up CEP 2.0

### 3.2.S.4.2 - Analytical procedures

**Reference solution**  
Methanol: 1000 ppm  
Dichloromethane: 400 ppm  
Toluene: 100 ppm  
Diethyl ether: 100 ppm

**Reference solution:** Weigh 100 mg of methanol, 40 mg of dichloromethane, 10 mg of toluene and 10 mg of diethyl ether in a 100 mL volumetric flask. Dilute and take to capacity with desalted methanol. Take a 10 mL aliquot and place it in a 50 mL volumetric flask and take to capacity with desalted methanol. 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 desalted methanol. Mix this solution until distribution. Prepare this solution two times.

**Chromatographic conditions:**

Column	CP-301 YCB 30m, 0.33mm, 5m 1.7µm		
Detector	FID		
Detector temperature	250 °C		
Detector gas	Helium		
Carrier gas	Helium		
Gas flow	2.5 mL/min		
Split ratio	4:1		
Flow rate	1.7 L/min		
Temperature ramp			
Event	Velocity (°C/min)	Temperature (°C)	Hold time (min)
0	10.0	50.0	2.0
1	10.0	100.0	0.0
2	10.0	200.0	1.0

**Head space conditions:**

Oven temperature	80 °C
Exhaust temperature	90 °C

**Resolution time:** 15 min  
**Injection volume:** 0.5 µL

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

$$\text{ppm of solvent} = \frac{A_{\text{sample}} \cdot W_{\text{ref}} \cdot DF_{\text{ref}}}{A_{\text{ref}} \cdot W_{\text{sample}} \cdot DF_{\text{sample}}} \cdot 1000000$$

**Where:**  
A<sub>sample</sub> → Observed area in the chromatogram of the sample  
A<sub>ref</sub> → Observed area in the chromatogram of the standard  
W<sub>ref</sub> → Weight of the standard in mg  
W<sub>sample</sub> → Weight of the sample in mg  
DF<sub>ref</sub> → Dilution factor of the standard (ND)  
DF<sub>sample</sub> → Dilution factor of the sample (2)  
1000000 → Conversion to ppm

EDQM Certificate of Authenticity  
CEP No. CEP 2023-836 - Rev. 00  
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**Annexure C: CEP letter of access**

**SAHPRA**  
South African  
Health Products  
Regulatory Authority

SAHPRA Head Office  
Building A  
Loftus Park  
2<sup>nd</sup> Floor  
Kirkness Road  
Arcadia  
0083

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( < FROM CEP HOLDER ON HEADED PAPER > )  
**LETTER OF ACCESS TEMPLATE**

[Date]  
CEP number (including revision number):  
Name of the substance:  
Subtitle (if applicable):  
CEP holder: [name and address]

The CEP holder hereby authorises the marketing authorisation holder/applicant to refer to the abovementioned CEP in support of the following marketing authorisation application(s) or marketing authorisation variation(s):  
[Name of product (if known)]  
[Name of applicant or marketing authorisation holder]

The CEP holder commits to batch-to-batch consistency, to share information in order to enable the abovementioned marketing authorisation holder/applicant to take full responsibility for an evaluation of the suitability of this substance for its intended use, and to inform them of any relevant changes to the CEP dossier.

Signature of the CEP holder  
[Name and function]  
[Signature]

Chairperson: Prof Helen Rees • Vice-Chairperson: Dr Obakeng Khaole • Prof Joyce Tsoka-Gwegweni  
Prof Patrick Demana • Dr Xolani Khayelihle Ngobese • Adv Hasina Cassim • Ms Ditaba Lucy Maraka  
Mr Itani Elias Mashau • Ms Lerato Mothae • Mr Norman Baloyi • Dr Alfred Kgasi • Prof Johanna Meyer  
• Ms Mandisa Skhosana • Prof Yahya Choonara • Dr Zinhle Makatini  
CEO: Dr Boitumelo Semete-Makokotlela

### 3. Reference Links

1. <https://www.edqm.eu/en/what-is-the-cep-2.0>
2. <https://www.sahpra.org.za/general-ectd-human-medicines-communication-to-industry/>
3. <https://www.sahpra.org.za/general-ectd-human-medicines-templates/>