SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
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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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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

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1. Background

SAHPRA currently recognises the professional work done by the EDQM as a directorate of the Council of Europe. The EQDM 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.

EQDM 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 24th 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.

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2.3 New applications

All new applications (i.e., supported by a CEP) submitted after the 24th 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.

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Annexure A: Old CEP

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.

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)*:

EXAMPLE

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OLD CEP

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

EXAMPLE

Residual solvents

Dioxane ≤ 380 ppm.

Reference solution: Weigh 300 mg of methanol, 60 mg of dichloromethane, 89 mg of toluene and 59 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 0: Velocity (°C/min) —; Temperature (°C) 35.0; Hold time (min) 5.0 Event 1: Velocity 10.0; Temperature 180.0; Hold time 6.0 Event 2: Velocity 30.0; Temperature 200.0; Hold time 1.67

Head space conditions.

Oven temperature	60 °C
Syringe temperature	80 °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 1.
4. Calculate the content of each solvent in the sample by using the following equations.

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

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

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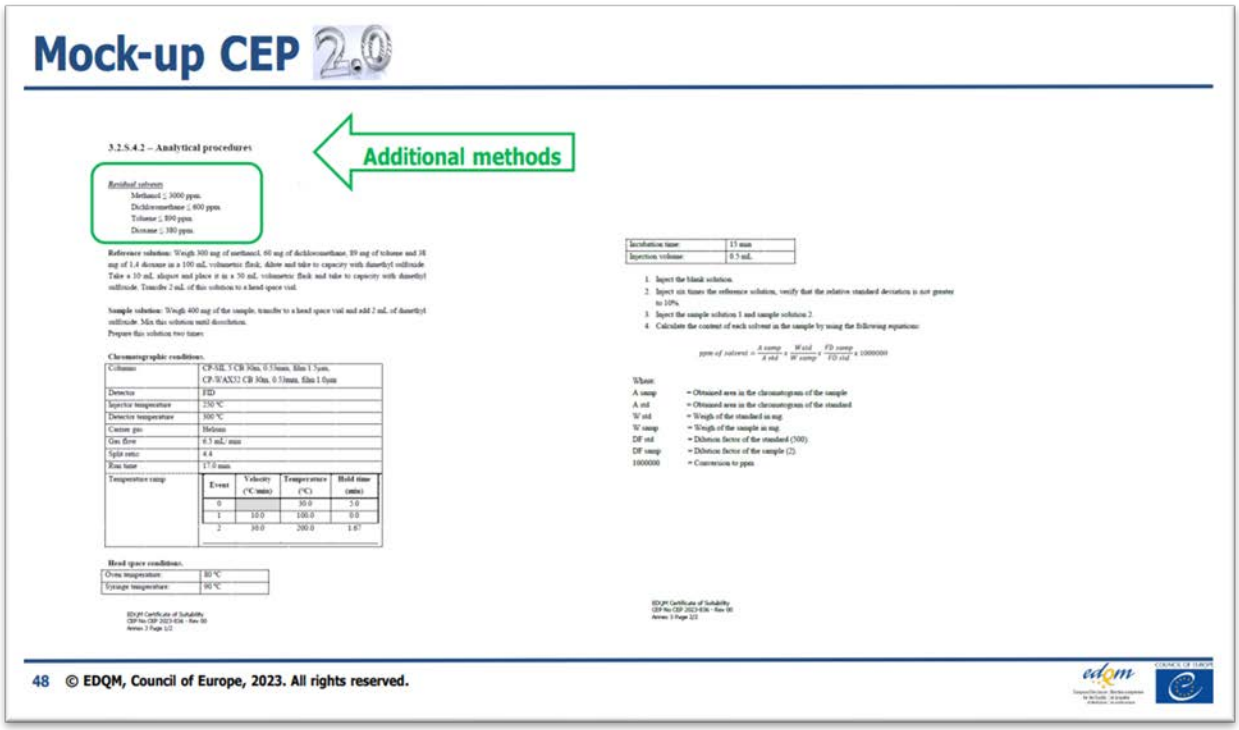
Annexure B: New CEP 2.0 - Mock-up



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Annexure C: CEP letter of access

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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 • Dr Alfred Kgasi • Prof Johanna Meyer • Ms Mandisa Skhosana
• Prof Yahya Choonara • Dr Zinhle Makatini
CEO: Dr Boitumelo Semete-Makokotlela

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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/