SAHPRA
South African Health Products Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
402 Kirkness Road
Arcadia
0083

COMPLEMENTARY MEDICINES
GUIDANCE ON SPECIFIED SUBSTANCES

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Complementary Medicines containing specified substances. In addition to this guideline, SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. The SAHPRA is committed to ensuring that all registered medicines will be of the required quality, safety and efficacy.

Guidelines and application forms are available from the website: www.sahpra.org.za.

Publication for comment_v1 Caffeine and Menthol	April 2017
Due date for comment Caffeine and Menthol	31 May 2017
Publication for comment_v2 Camphor	June 2018
Due date for comment Camphor	31 July 2018
Publication for implementation_v3	May 2020
Publication for comment_v3_1	March 2021
Due date for comment Cannabidiol	30 June 2021

BOITUMELO SEMETE-MAKOKOTLELA

CHIEF EXECUTIVE OFFICER

TABLE OF CONTENTS

In the interest of focus, only the proposed additional Annexure is included to amend version 3 of the guideline published in June 2020 ***(7.06_CMs_Specified_Substances_Jun20_v3)***

Sections 1 - 2 are unchanged as in version 3 published June 2020.

Annexes 1-3 are unchanged as in version 3 published June 2020.

Annex 4 is now published for comment.

ANNEX 4 – Cannabidiol (CBD)

In assessing the safety, efficacy and quality of Cannabidiol (CBD) the attached Annex has been developed to guide the use of the substances listed therein when used in Complementary Medicines.

The maximum dosage of the substance is pre-determined by the inscription in the relevant scheduled to the Medicines and Related Substances Act, 1965 (Act 101 of 1965), and no comment with respect to maximum daily dosage will be considered in this period of comment.

Any comment submitted to the SAHPRA for consideration for amendment should include/consider:

- The recognition of another international regulatory body with a similar regulatory mechanism/standard as a nutritional substance, dietary supplement, nutritional form or health supplement.
- The safety profile of the substance that the new dosage profile represents, including:
  - Therapeutic profile;
  - Minimum effective doses;
  - Maximum safe values (with specific age range values as appropriate);
  - Known side effects;
  - Contraindications; and
  - All known interactions (including interactions with medicines, other complementary medicines, health supplements, disease processes or diagnostics procedures).
- The proposed amendment of any wording of the proposed health claim (indication) of the substance, including any supportive clinical evidence in support of the health claim and levels proposed. Such proposed amendment must continue to be in line with the definition of a health supplement.
- Any other literature or motivation in substantiation of such substance as a health supplement and which refer to the conditions under which it is to be used e.g.: demonstrating evidence for safety at the specified dose or clinical evidence for the particular effect intended. Demonstrating limited clinical efficacy for a disease-based indication is not evidence of health maintenance.

All information submitted should be summarised, contextualised and motivated clearly. If supporting documentation is submitted a concise written case must be made for their consideration clearly identifying the parts of the documentation which support the proposed position.

Comment should be submitted in the attached comment form together with any relevant and appropriately labelled Appendices. These comment documents can be submitted at **www.sahpracm.org.za** – “Guidelines” – “Documents for Comment” by the deadline indicated.

1 UPDATE HISTORY

Date	Reason for update	Version & publication
Feb 2017	New guideline to address caffeine and menthol in CMs published for comment	v1 Apr 2017
31 May 2017	Due date for comment: Caffeine and Menthol	
June 2018	Publication for comment_v2 Camphor	v2 Jul 2018
31 July 2018	Due date for comment: Camphor	
June 2020	Implementation of: Annex 1: Caffeine Annex 2: Menthol Annex 3: Camphor	v3 Jun 2020
March 2021	Publication for comment_v3_1: Annex 4: Cannabidiol (CBD)	v3_1 Mar 2021

Annex 4: CANNABIDIOL (CBD)

GUIDANCE FOR USE AS PART OF A COMPLEMENTARY MEDICINE

Cannabidiol *CBD* *Cannabidiolum* *(−)-cannabidiol* *2-[(1R,6R)-6-isopropenyl-3-metylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (IUPAC)*	
Accepted Sources:	*Cannabis sativa* L.
Use:	Duration of use: No longer than 3 months without advice of a relevant health care provider. Not to be taken: • by children under the age of 18 years; or • during pregnancy or breastfeeding. Health supplements: preparations intended for oral use only. Discipline-specific: preparations for oral or topical use.

Concentration/Maximum Dose:	Health Supplements:
	Schedule 0
	Permitted:
	• As a stand-alone health supplement as a single substance formulation or multiple substance formulation:
	  ○ Maximum Daily Dose: 20 mg cannabidiol; and
	  ○ No more than 600 mg cannabidiol per sales pack; or
	• When CBD is a natural constituent of an existing substance listed in the Health supplement annexures and complies with the corresponding Annexures of Guideline 7.04. (Annexure G - Hemp seed protein; Annexure I - Hemp seed oil) and the total concentration of CBD does not exceed 0,0075 percent. Fortification of such products is not permitted (as per the schedule inscription only the natural amount of cannabinoids is permitted).

	Discipline-specific medicines: Permitted as part of a: • herbal preparation which naturally contains CBD used traditionally for specified indications in any of the stated disciplines where origin and use to be justified with relevant literature as per Guideline 7.01; or • combination product where it is formulated with the herbal substance from which it arises, used traditionally in any of the stated disciplines origin and use to be justified with relevant literature as per Guideline 7.01, and the action of the isolated constituent must be "essentially the same" (not significantly different) (See Guideline 7.01, 1.6.2) as the action of the herbal substance. *Schedule 0* *CBD will be Schedule 0 substance when:* • Low-risk indication(s); • THC content is lower than 0,001 %; • Maximum Daily Dose: 20 mg cannabidiol; and • No more than 600 mg cannabidiol per sales pack. *Schedule 4* *CBD will be Schedule 4 substance when:* • High-risk indication(s); • THC content is lower than 0,001 %; • providing more than 20 mg daily; or • pack size greater than 600 mg total CBD.
Accepted Low-Risk Claim:	Health Supplements: • Contributes to nervous system health • Contributes to healthy sleep • An antioxidant

	Discipline-specific medicines: Claims which can be substantiated by (a) traditional use or (b) traditional use and clinical evidence, related only to: • General health enhancement without any reference to specific diseases; • Health maintenance, or • Relief of minor symptoms (not related to a disease or disorder)
Precautions/Warnings:	Medicine Label: The statements: • *If schedule 0:* Do not exceed maximum daily dose of 20 mg • *For doses greater than 20 mg:* Oral preparations of cannabidiol taken at high doses may worsen symptoms of Parkinson's disease in some patients. • If symptoms persist or get worse, consult a health care provider for advice • Do not take during pregnancy or breastfeeding. • In some cases, taking cannabidiol may cause light-headedness, xerostomia (dry mouth) or somnolence (drowsiness). • Consult your health care provider before starting CBD if you are taking any other medicine. CBD may interact with numerous medicines. 1. Patient Information Leaflet The statements: • *If schedule 0:* Do not exceed maximum daily dose of 20 mg • Oral preparations of cannabidiol taken at doses more than 20 mg per day may worsen symptoms of Parkinson's disease in some patients. • If symptoms persist or get worse, consult a health care provider for advice

	• Do not take during pregnancy or breastfeeding.
	• In some cases taking cannabidiol may cause light-headedness, xerostomia (dry mouth) or somnolence (drowsiness).
	• Consult your health care provider before starting CBD if you are taking any other medicine. CBD may interact with numerous medicines. [1]
	  ○ Taking cannabidiol may (theoretically) cause additive effects when taking sedatives or anaesthetics enhancing the effect of the sedatives beyond what is intended.
	  ○ Cannabidiol inhibits Cytochrome P450 system *in vitro*. Its effect in humans has not been fully established.
	  ○ Co-administration of CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir or clarithromycin) or inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort) may affect medication levels.
	  ○ Avoid use of CBD with clobazam, stiripentol or valproate.
	Notes:
	1. The potential for drug interactions with cannabidiol exist and may become better known based on additional evidence that may emerge. The potential for such interactions at any dose of CBD are nonetheless of concern and require professional oversight if co-administration is intended. The use of CBD together with opioids and caffeine is an emerging area of concern and their concomitant use should be avoided until more evidence is available.