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# 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.

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| Publication for comment_v1<br>Caffeine and Menthol | April 2017 |
| Due date for comment: Caffeine and Menthol | 31 May 2017 |
| Publication for comment_v2<br>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 |
| Publication for implementation_v3_2 | January 2022 |
| Deadline for comment: Annex 4 - Cannabidiol: Table 4.1 | 30 April 2022 |

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## 1 INTRODUCTION

The South African Health Products Regulatory Authority (SAHPRA) is responsible for regulating all medicines and medical devices in South Africa by ensuring that they meet standards of safety, efficacy and quality. The SAHPRA operates in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) (the Medicines Act), the Regulations issued in terms of that Act, and associated guidelines.

The SAHPRA has noted that several Complementary Medicines (CMs) contain amounts of certain substances for which specific guidance is needed. Some of these may by default exist as an integral part of any formulation (e.g.: Caffeine in *Camellia sinensis* (L.) Kuntze and *Paullinia cupana* Mart, or Menthol in *Mentha arvensis* L*., Juniperus communis* L.) while other products may be inappropriately loaded with these ingredients or contain insufficient amounts thereof relevant to the intended use.

This not only presents particular challenges related to patient safety but also yields significant questions as to the intended efficacy of the medicine. As a number of herbs used within the Discipline-Specific (DS) sub-category of Complementary Medicines may contain these ingredients, and considering the addition of these ingredients to Health Supplements and their close association to DS medicines, it is considered imperative to provide guidance on the use of either substance which may inform the development of CM products suitable for registration.

After comparisons of international policies and monographs and South Africa's existing policy, the attached guidance documents have been developed to guide the use of specified substances in Complementary Medicines (CMs). Any guidance stipulated should be viewed as being in addition to any existing requirement(s) of the Medicines Act or its associated regulations.

Where applicable, the maximum dosage of the substance is pre-determined by the inscription in the relevant schedules to the Medicines Act

## 2 SCOPE

This guideline applies to all applications for registration of complementary medicines containing any of the substances stipulated herein:

Annex 1 – Caffeine
Annex 2 – Menthol
Annex 3 – Camphor
Annex 4 – Cannabidiol (CBD)

## 3 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 | |

| Date | Reason for update | Version & publication |
|---|---|---|
| June 2020 | Implementation of:<br>Annex 1: Caffeine<br>Annex 2: Menthol<br>Annex 3: Camphor | v3 Jun 2020 |
| March 2021 | Publication for comment_v3_1:<br>Annex 4: Cannabidiol (CBD) | v3_1 Mar 2021 |
| Jan 2022 | Amendment of:<br>Annex 1: Caffeine: Accepted sources<br>Implementation of:<br>Annex 4: Cannabidiol (CBD)<br>Minor grammatical amendments. | v3_2 Jan 2022 |

## Annex 1: CAFFEINE

### GUIDANCE FOR USE AS PART OF A COMPLEMENTARY MEDICINE

| **Caffeine** | |
|---|---|
| *1,3,7-Trimethylxanthine*<br>*3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione*<br>*guaranine*<br>*methyltheobromine* | With respect to Complementary Medicines, caffeine is not permitted as an isolated single substance formulation. When used as an active ingredient as part of a multiple substance formulation or as a constituent of a single herb, it is permitted only in products where the action of the caffeine modifies or contributes to the effect of other ingredient(s) and is not the main ingredient responsible for the primary action of a product.<br>Total caffeine content should be calculated from all ingredients within a product so as not to exceed the maximum daily dose prescribed herein.<br>May only be indicated for adults. |
| **Accepted Sources:** | The following ingredients should be considered in relation to guidance on caffeine:<br>Caffeine; *Camellia sinensis* (L.) Kuntze; *Coffea arabica* L.<br>*Coffea canephora* Pierre ex A.Froehner; Coffee; *Cola acuminata* (P.Beauv.) Schott & Endl.<br>*Cola nitida* (Vent.) Schott & Endl.; *Ilex guayusa* Loes.; *Ilex paraguariensis* A.St.-Hil.<br>*Paullinia cupana* Mart.; *Paullinia cupana* Mart.; *Theobroma cacao* L.<br>Caffeine-containing members of the genera *Coffea, Cola or Ilex* |
| **Cautions and Warnings:** | **<u>Medicine label</u>**<br>The statements:<br>• CONTAINS CAFFEINE.<br>• Identifying and contextualising the quantity of caffeine contained in the product per dosage unit:<br>"Contains <*state quantity per dosage unit or ml or gram of product*> caffeine per <*dosage unit or ml or gram*>.<br>A cup of instant coffee contains approximately 80 mg of caffeine."<br>• "Adults only" or similar statement.<br>• "Consult a relevant health care provider if you are taking any other medicine or have been diagnosed with a chronic condition."<br>• "Use of caffeine may result in sleep deprivation." |

| **Caffeine** | |
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| | • "Limit the use of caffeine-containing products (including tea and coffee) when taking this product."<br>• When the maximum recommended daily dose provides more than 10 mg of total caffeine:<br>"Total caffeine intake more than 200 mg per day is not recommended during pregnancy or breastfeeding."<br>**<u>Patient Information Leaflet</u>**<br>The statements:<br>• "CONTAINS CAFFEINE."<br>• Identifying and contextualising the quantity of caffeine contained in the product per dosage unit:<br>"Contains <*state quantity per dosage unit or ml or gram of product*> caffeine per <*dosage unit or ml or gram*>.<br>A cup of instant coffee contains approximately 80 mg of caffeine."<br>• "Not suitable for children under the age of 18 years."<br>• "Consult a registered healthcare professional if you-<br>o are taking any other medicine (such as lithium) including chronic, complementary, or traditional medicines; or<br>o have high blood pressure, glaucoma, and/or detrusor instability (overactive bladder syndrome)."<br>• "Consumption with other medicines *(e.g. bitter orange extract, synephrine, octopamine, ephedra, ephedrine)* which increase blood pressure is not recommended."<br>• "Use of caffeine may result in sleep deprivation."<br>• "Consumption with other caffeine-containing products or foods *(e.g. medications, coffee, tea, colas, cocoa, guarana, maté)* is not recommended."<br>• "Discontinue use two weeks prior to surgery".<br>• "If you are of childbearing age, pregnant or breastfeeding and have concerns that your daily intake of caffeine from all sources may exceed 200 mg per day, please consult a relevant health care provider prior to use." |
| **Contra-indications:** | • "Hypersensitivity/allergy, in which case, discontinue use." |
| **Concentration/Maximum dose:** | Undivided preparations (e.g. bulk powders) must not contain a concentration of total caffeine greater than 1 %.<br>Divided preparations (e.g. tablets) must not contain a concentration of total caffeine greater than 33 %.<br>Maximum Daily Dose: 300 mg |

| **Caffeine** | |
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| | Discipline-specific products containing a daily dose of more than 300 mg will only be considered in the context of a high-risk application requiring associated clinical and safety evidence of its use and benefit.<br>**Dose(s):** up to 200 mg per single dose within a 6-hour period, not to exceed 300 mg per day. |
| **Health Claim:** | Temporarily promotes alertness and wakefulness.<br>Temporarily assists to relieve fatigue.<br>Temporarily assists to increase mental activity. |
| **Known symptoms of overdosage:** | At doses of more than 600 mg per day, caffeine may cause anxiety, tachycardia (rapid heart rate), palpitations, insomnia, restlessness, nervousness, tremor, and headache. |

## Annex 2: MENTHOL

## GUIDANCE FOR USE AS PART OF A COMPLEMENTARY MEDICINE

| **Menthol** | |
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| *L-menthol, Levomenthol*<br>*(-)-menthol*<br>*(1R,2S,5R) (-)5-Methyl-2-(1-methyethyl) cyclohexanol*<br>*(1R,2S,5R)-5-methyl-2-(propan-2-yl) cyclohexan-1-ol*<br>*Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R,2S,5R)-* | The synthetic form (Dl-menthol) is not permitted for use in Complementary Medicines.<br>Synthetic forms when used in discipline-specific medicines should be suitably motivated. |
| **Accepted Sources:** | May be sourced from, but not limited to, the following natural sources:<br>*Juniperus communis* L. (Fruit) — *Mentha arvensis* L. (Herb top, Herb top flowering, Leaf)<br>*Mentha canadensis* L. (Herb top) — *Mentha pulegium* L. (Whole plant)<br>*Mentha spicata* L. (Leaf) — *Mentha x piperita* L. (Herb top flowering, Leaf)<br>*Ocimum basilicum* L. (Whole plant) — *Zea mays* L. (Leaf, Stigma and style) |
| **Cautions and Warnings:** | **Medicine label**<br>The statements:<br>• Avoid contact with eyes and mucous membranes.<br>• Do not use with other products containing camphor, menthol, eucalyptol and/or eucalyptus essential oil.<br>• If you experience pain, swelling or blistering, stop use and get medical help right away.<br>• Keep out of reach of children.<br>**Topical products:**<br>• Do not expose the area where applied, to sunlight. |

| **Menthol** | |
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| | **Where applicable:**<br>• External use only.<br>• Do not use on the face or near the nose or mouth<br>**For children (2 to 12 years):**<br>• The product should be handled/applied by adults only.<br>**Products in liquid or semi-solid form (i.e. chest rubs):**<br>• Apply thinly and evenly to the <*state body area*>, up to three (3) times per day.<br>**Products in patch forms or vaporizers:**<br>• Do not use (on skin) for more than eight (8) hours.<br>*Note: Patches for children must contain a bittering agent and must not include any flavouring agent.*<br>**Patient Information Leaflet**<br>The following statements in addition to those listed for the medicine label:<br>• If accidental ingestion occurs, seek urgent medical attention, or contact a Poison Control Centre.<br>• If symptoms persist or worsen, reoccur, or are accompanied by a fever, rash, or persistent headache, discontinue use, and consult a relevant health care provider. |
| **Contraindications:** | If you are pregnant or breastfeeding, do not use this product.<br>If you have epilepsy, asthma, persistent or chronic cough, or other chronic lung conditions, do not use this product.<br>Do not apply this product to broken, irritated, or sensitive skin. |
| **Known Adverse Reactions:** | Rashes, burning discomfort, nausea, dizziness and/or headache, have been known to occur; in which case, discontinue use.<br>Hypersensitivity has been known to occur; in which case, discontinue use. |
| **Use:** | When used as an active ingredient, it is permitted only in topical applications, medicated space sprays or medicated throat lozenges. |
| **Concentration/Maximum Dose:** | For topical applications: The concentration must not exceed 16 %. |
| **Health Claim:** | Cooling sensation and/or soothing action for the (skin) (mouth) (throat) <*specify area of application*>. |

## Annex 3: CAMPHOR

## GUIDANCE FOR USE AS PART OF A COMPLEMENTARY MEDICINE

| **Camphor** | |
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| *2-bornanone*<br>*2-camphanone*<br>*2-hydroxybornane*<br>*2-hydroxycamphane*<br>*bornan-2-one*<br>*Borneol*<br>*borneo camphor*<br>*Bornyl alcohol*<br>*d-camphor* | The synthetic form (dl-camphor and l-camphor) is not permitted for use in Health Supplements where the intention is instead to include substances from natural origin.<br>When used in Discipline-Specific medicines, d-camphor is the preferred form and synthetic forms (dl-camphor and l-camphor) must be suitably motivated including evidence of its safety. Substances of synthetic origin remain unacceptable as active ingredients.<br>Inclusion of dl-camphor and l-camphor as a health supplement requires an Annexure B submission in terms of Guideline 7.04 as required. |
| **Accepted Sources:** | Camphor is derived from steam distillation of bark and/or wood from *Cinnamomum camphora* (L.) J. Presl. (camphor laurel, camphor tree, camphorwood)<br>Camphor Laurel = *Cinnamomum camphora* (L.) J. Presl.<br>d-camphor is the extract after distillation<br>Other acceptable sources for d-camphor: |

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| *Achillea millefolium* L. | (Leaf) | *Cinnamomum camphora* (L.) J.Presl | (Leaf, Stem, bark) |
| *Coriandrum sativum* L. | (Fruit) | *Foeniculum vulgare* Mill. | (Fruit) |
| *Hyssopus officinalis* L. | (Flower, Leaf) | *Juniperus communis* L. | (Fruit) |
| *Lavandula latifolia* Medik. | (Flower, Leaf and Stem) | *Nepeta cataria* L. | (Whole plant) |
| *Ocimum basilicum* L. | (Whole plant) | *Origanum vulgare* L. | (Whole plant) |
| *Peumus boldus* Molina | (Leaf) | *Rosmarinus officinalis* L. | (Whole plant) |
| *Teucrium polium* L. | (Shoot) | *Thymus vulgaris* L. | (Whole plant) |
| *Zingiber officinale* Roscoe | (Rhizome) | | |

| **Camphor** | |
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| **Use:** | In the case of discipline-specific medicines the use must align with the principle of the discipline from which it arises, e.g.: in line with Unani, TCM and Ayurveda principles – but is not confined to discipline-specific use only.<br><br>Topical use and administration in preparations including but not limited to liquids, rubs, sprays, patches, roll-ons, use in chest rubs with warning: "For external use only."<br><br>Camphor must not be used in patch forms applied on the skin. This restriction does not apply to patches that are only used on clothing.<br><br>Forms suitable for indirect inhalation with warning: "Do not use in chronic lung conditions or asthma."<br><br>As an essential oil.<br><br>In medicines for oral administration, a maximum of 0,3 % camphor will be permitted as a flavourant, and no claims for medicinal activity may be made. |
| **Concentration/Maximum Dose:** | *In all forms:* can be used by adults, adolescents, and children >2 years.<br><br>*In solid or semisolid preparations:* the concentration must not exceed 12,5 %.<br><br>*In liquid preparations, other than essential oils:* the concentration must not exceed 2,5 %.<br><br>*In essential oil products:* restricted flow inserts/closures must be fitted to the container when:<br>• the concentration is greater than 2,5 % but less than or equal to 10 % and the nominal capacity of the container is 25 ml or less;<br>• the concentration is greater than 10 % and the nominal capacity of the container is 15 ml or less; or<br>• the concentration is greater than 10 % and the nominal capacity of the container is greater than 15 ml but less than or equal to 25 ml, in which case the container must also be fitted with a Child Resistant Closure.<br><br>*Preparations intended for inhalation* are limited to 7 % camphor.<br><br>*Antitussive lozenges* may contain up to 15 mg camphor per lozenge.<br><br>Exposure to camphor should not exceed 2 mg/kg body weight on a single day in any age group. |
| **Claim:** | Other than specified traditional uses in TCM, Unani and Ayurveda, the following health claims are permitted:<br>• Temporary relief of mild nasal congestion<br>• Temporary relief of chest congestion<br>• Improves blood circulation in microvessels |

| **Camphor** | |
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| | • Decrease sensation of “heavy legs“<br>For creams and ointments with 0,1 – 3,0 %: “Temporary relief of pain and itching associated with minor burns, sunburn, insect bites and other minor skin irritations.”<br>For all topical preparations: “Temporary relief of muscular cramps and rheumatic pain.” |
| **Cautions and Warnings:** | *Boxed warnings must be included for all camphor-containing products on all packs of topical applications including the words:*<br>"WARNING: Contains CAMPHOR. Harmful if swallowed. For external use only. Keep out of the reach of children."<br>*Boxed warnings must be included for all camphor-containing products on all packs of medicines for oral administration, with a maximum of 0,3 % camphor* permitted as a flavourant only:<br>"WARNING: Contains CAMPHOR. Use only as directed – excess quantities may be harmful if swallowed. Keep out of the reach of children."<br>*General warnings for all camphor-containing products on labels:*<br>Avoid use in pregnancy, epilepsy, and chronic lung conditions.<br>*General warnings for all camphor-containing products on Patient Information Leaflets and Professional Information:*<br>If accidental ingestion occurs, seek urgent medical attention, or contact a Poison Information Centre.<br>Do not use topically on broken, irritated, or sensitive skins.<br>Avoid direct contact with eyes, mucous membranes, genitals, and nose and mouth.<br>Avoid exposure of applied area to the sun.<br>Do not use with other products containing camphor, menthol, eucalyptol and/or eucalyptus essential oil. |

## Annex 4: CANNABIDIOL (CBD)

## GUIDANCE FOR USE AS PART OF A COMPLEMENTARY MEDICINE

| **Cannabidiol** | |
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| *CBD*<br>*Cannabidiolum*<br>*(−)-cannabidiol*<br>*2-[(1R,6R)-6-isopropenyl-3-metylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (IUPAC)* | **General**: 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 on safety on their combined use is available. |
| **Accepted Sources:** | *Cannabis sativa* L. |
| **Product Names:** | The total pack size should be reflected appropriately in such a manner that it would not be misconstrued for the individual dose value or concentration. As such, the total pack size is discouraged from being represented in the name of the medicine and should rather refer to the strength of dose if used. |
| **Use:** | Duration of use: No longer than 3 months without advice from a relevant health care provider.<br>Not to be taken:<br>• by children under the age of 18 years; or<br>• during pregnancy or breastfeeding.<br>Health supplements: preparations intended for oral use only.<br>Discipline-specific: preparations for oral or topical use. |
| **Concentration/Maximum Dose:** | **<u>Health Supplements</u>**<br>*Schedule 0*<br>Permitted:<br>• as a stand-alone health supplement (single substance formulation or in multiple substance formulations):<br>  ○ Maximum Daily Dose: 20 mg cannabidiol; and<br>  ○ No more than 600 mg cannabidiol per sales pack; or |

| **Cannabidiol** | |
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| | • when CBD is a natural constituent of Hemp Seed Protein and Hemp Seed Oil. In such cases, refer to SAHPRA Guideline 7.04 Annexures G and H for requirements related to these substances. Fortification of such products is not permitted (as per the schedule inscription only the natural quantity of cannabinoids is permitted).<br><br>**<u>Discipline-specific medicines</u>**<br>Permitted as part of a:<br>• herbal preparation which naturally contains CBD used traditionally for specified indications in any of the stated disciplines, where origin and use are to be justified with relevant literature as per Guideline 7.01; or<br>• 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.<br>*Schedule 0*<br>As per the Schedules published in terms of the Medicines Act, CBD will be a Schedule 0 substance when:<br>• Low-risk indication(s) is (are) used;<br>• THC content is lower than 0,001 %;<br>• Maximum Daily Dose: 20 mg cannabidiol; and<br>• No more than 600 mg cannabidiol per sales pack.<br>*Schedule 4*<br>As per the Schedules published in terms of the Medicines Act, CBD will be a Schedule 4 substance when:<br>• High-risk indication(s) are used;<br>• THC content is lower than 0,001 %;<br>• providing more than 20 mg daily; or<br>• pack size greater than 600 mg total CBD. |
| **Accepted Low-Risk Claim:** | **<u>Health Supplements</u>**<br>• Contributes to nervous system health |

| **Cannabidiol** | |
|---|---|
| | • Contributes to healthy sleep<br>• An antioxidant<br><br>**<u>Discipline-specific medicines</u>**<br>Claims which can be substantiated by (a) traditional use or (b) traditional use and clinical evidence, related only to:<br>• General health enhancement without any reference to specific diseases;<br>• Health maintenance, or<br>• Relief of minor symptoms (not related to a disease or disorder) |
| **Precautions/Warnings:** | **<u>Medicine Label</u>**<br>The statements:<br>• *All products containing CBD:*<br>o "If symptoms persist or get worse, consult a relevant health care provider for advice."<br>o "Adults only" or similar statement.<br>o "Do not take during pregnancy or breastfeeding."<br>o "Do not drive or operate machinery until you know how CBD affects you."<br>• *If schedule 0, the additional statements to those for all products:*<br>o "Do not exceed maximum daily dose of 20 mg."<br>o "May have side effects including drowsiness See enclosed leaflet for important use and safety information."<br>• *If schedule 4, the additional statement to those for all products:*<br>o "May cause light-headedness or drowsiness and/or worsen Parkinson's disease. See enclosed leaflet for important use and safety information."<br><br>**<u>Professional Information and Patient Information Leaflet</u>**<br>The statements:<br>• *All products containing CBD:* |

| **Cannabidiol** | |
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| | ○ "If symptoms persist or get worse, consult a relevant health care provider for advice."<br>○ "Do not take during pregnancy or breastfeeding."<br>○ "Oral preparations of cannabidiol (CBD) taken at doses more than 20 mg per day may worsen symptoms of Parkinson's disease."<br>○ "Taking CBD may cause light-headedness, dry mouth or drowsiness. Do not drive or operate machinery until you know how CBD affects you."<br>○ "The use of CBD together with opioids and caffeine should be avoided."<br>• *If schedule 0 the additional statements to those for all products:*<br>○ "Do not exceed maximum daily dose of 20 mg."<br><br>**Professional Information**<br>The additional statements:<br>• "CBD may interact with numerous medicines.<br>○ Taking CBD may (theoretically) cause additive effects when taking sedatives or anaesthetics enhancing the effect of the sedatives beyond what is intended.<br>○ CBD inhibits Cytochrome P450 (CYP) system in vitro. The effect of CBD in humans has not been fully established.<br>○ 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.<br>○ Avoid use of CBD with clobazam, stiripentol or valproate."<br><br>**Patient Information Leaflet**<br>The additional statement:<br>• "CBD may interact with numerous medicines. Consult your health care provider before starting CBD if you are taking any other medicine, particularly antifungals, ARVs, antibiotics, TB medicines, anti-epileptic medicines and herbal medicines." |

Following publication for comment, additional aspects have been raised which SAHPRA seeks comment on. Public comment is therefore invited to be submitted by Table 4.1 only by **30 April 2022**.

**Table 4.1: Public comment sought on the proposed introductions to the guidance related to Cannabidiol when used in Complementary Medicines**

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| **Packaging:** | The use of child-resistant closure for products with a concentration exceeding 20 % or a total pack dosage of 400 mg is required. |
| **Concentration/Maximum Dose:** | Health Supplements:<br>As a stand-alone health supplement (single substance formulation or in multiple substance formulations) a minimum 5 % concentration is required. |