THC GLOBAL GROUP

Submission by THC Global Group Limited
Proposed amendments to the Poisons Standard - ACMS and Joint ACMS/ACCS meetings, June 2020

Submission for Item 2.2

Summary position on suggested amendments.

1	Schedule 8 amendment: "or iv) it is a whole plant cannabis product or distillate or isolate which contains at least 98 per cent cannabidiol and less than or equal to 0.2 per cent tetrahydrocannabinol (THC)."	Disapprove
2	Schedule 4 amendment: "and any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation; or"	No comment (rewording of existing)
3	Schedule 4 amendment: "cannabidiol is a synthetic or semi-synthetic copy of the molecule and comprises 98 per cent or more of the total cannabinoid content of the preparation and any other synthetic or semi-synthetic cannabinoids, other than cannabidiol, must comprise 2 per per cent or less of the total cannabinoid content of the preparation."	Disapprove
4	Schedule 4 amendment: "except when cannabidiol comprises 98 per cent or more of the total cannabinoid content and the tetrahydrocannabinol (THC) content is less than or equal to 0.2 per cent of the total cannabinoid content of the preparation."	Disapprove

Detailed Submission

Item 1

Our overall view is that CBD should be regulated as a Schedule 3 medicine, and not removed from scheduling, due to the need for ongoing engagement with health care professionals for safe use. Safety concerns include:

(1) CBD is not risk-free in animal models of human disease

In animals, CBD reported adverse effects (AEs) at high doses include developmental toxicity, embryo-foetal mortality, central nervous system inhibition and neurotoxicity, hepatocellular injuries,

spermatogenesis reduction, organ weight alterations, male reproductive system alterations, and hypotension[1].

(2) CBD is not risk-free in clinical studies

Human CBD studies for epilepsy and psychiatric disorders have reported CBD AEs including hepatic abnormalities, diarrhea, fatigue, vomiting, and somnolence[1]. The length of treatment is another important factor because data on AEs is much more limited following chronic CBD administration. Research is still needed on larger cohorts of CBD patients, and evaluation of CBD effects following long term exposure on genotoxicity and cytotoxicity, hormones, and the immune system are still needed[1].

In addition, CBD is still psychoactive (i.e. it modulates brain activity in epilepsy)[2], just not intoxicating, although a clinical study has reported some intoxicating properties of CBD compared to placebo[3].

(3) There is potential for drug-drug interactions

Human CBD studies for epilepsy and psychiatric disorders have reported CBD-induced drug-drug interactions (DDIs)[1]. Bidirectional effects may occur with concomitant administration of agents via affected membrane transporters (P-glycoprotein, P-gp; breast cancer resistance proteins, BCRP or ABCG2; and multidrug resistance proteins, MDRP), as well as via metabolising enzymes, particularly cytochrome P450 (CYP450) CYP2C9, CYP2C19, CYP2D6 and CYP3A4[4].

For example, an increase in blood concentrations of strong immunosuppressants have been described with concomitant administration of CBD at high doses (10-50 mg/kg/day)[5,6].

In epilepsy patients on clobazam, increased active metabolite N-desmethylclobazam (nCLB) concentrations were noted, likely due to CYP2C19 and CYP3A4 inhibition by CBD[7]. Higher nCLB concentrations were associated with a higher frequency of reports of sedation[8].

Concomitant administration of valproic acid may increase CBD hepatotoxicity[8,9].

The current scientific literature recommends that caution should be undertaken to closely monitor the responses to CBD of patients with certain drugs to guard their safety, especially for the elderly and people with chronic diseases or kidney and liver conditions[10,11]. Removal of scheduling will place some patients at risk by removing the need for medical monitoring of AEs and DDIs, as well as follow-up hepatic and renal function tests in relevant patients . This could lead to serious health consequences.

(4) Variability of formulations could affect CBD efficacy and adverse events

Variability in CBD formulations (tablet, spray, capsule, tablet, plant material, oil), route of administration (oromucosal, oral, inhaled), and the wide CBD dose range (≤1 to 5 mg/kg/day) can influence CBD efficacy and the incidence, type and number of AEs[12]. Medical supervision is necessary to monitor AEs and adjust dosages.

Due to the need of medical supervision to adjust dosing to maximise effect and reduce AEs, and to monitor AEs and DDIs, CBD should NOT be regulated as a complementary medicine in the same way that other plant medicines (herbal medicines) are regulated in Australia. This agrees with the findings of the TGA review which states that “the potential for drug-drug interactions with other commonly used medications is high”, and that “Therefore, whilst CBD has been reported to be well tolerated with minimal adverse effects at the low dose range of 60 mg daily and below, the potential for drug-drug interactions should be a consideration for the scheduling of the substance for therapeutic use and the designation to the required level of medical supervision”[13].

Item 2

No comment is provided due to this being a formatting requirement of other alterations.

Item 3

Our overall view is that the allowance of synthetics under Schedule 4 is proposed with little understanding of what may eventuate, and therefore this modification is not consistent with public safety. Our concerns are as follows:

(1) (+)-CBD enantiomers are known to be psychoactive

The TGA review, *Safety of Low Dose Cannabidiol*, *version 1, April 2020*[13] (see Box 1), found that unlike non-psychoactive (-) CBD enantiomers found uniquely in cannabis plants, (+) CBD enantiomers which are likely to be present in synthetic or semi-synthetic preparations, have been shown to bind to both CB1 and CB2 receptors, but to display selectivity toward CB1[14]. The (+) CBD enantiomer has also been shown to bind to vanilloid VR1 receptors *in vitro* and in rats[15], but the implication of this in humans has not been investigated. Therefore, since (+) CBD synthetic forms may be potentially psychoactive and/or have pharmacological activity which has not yet been well defined in clinical studies, this highlights a risk for the therapeutic use of synthetic formulations.

> ***Box 1. TGA Review recommendation***
> *"Cannabidiol is a chiral compound. Only the (-) CBD enantiomer is present in the Cannabis plants. Consequently, plant derived cannabidiol is present only as (-) CBD and has low affinity for the CB1 and CB2 receptors, and thus is not psychoactive. Synthetic cannabidiol has the potential to be a racemic mixture, the non-psychoactive (-) CBD or the alternative (+) CBD enantiomer. (+) CBD and its derivatives have been reported to bind to both CB1 and CB2 receptors, displaying selectivity towards CB1[14,16] and is therefore likely to be psychoactive and present different pharmacological activity. Therefore, the use of synthetic CBD may have psychoactive potential that would not be found in plant-derived cannabidiol. This should be considered in any decision to down-schedule CBD."[13]*

The TGA review points out that "the use of synthetic CBD may have psychoactive potential that would not be found in plant-derived cannabidiol. This should be considered in any decision to down-schedule CBD."[13] Thus, including synthetic or semi-synthetic molecules of (+) CBD under Schedule 4b would go against the findings of the TGA's own review. It could potentially place patients at risk of undefined psychoactive effects or other adverse events.

(2) Synthetic CBDs have not been shown without exception to have the same clear safety profile as naturally sourced CBDs

The effects of natural CBD on psychological and behavioral measures have been investigated in numerous experimental, placebo-controlled studies, giving us valuable information on its risk profile[1]. In contrast, comparable studies with synthetic cannabinoids in humans are in their infancy. Consequently, reliable and well-validated information on individual health risks is missing. It has been proposed that the complexity of the pharmacological processes of CBD and CBD analogs calls for a better understanding of their mechanism of action before the development of safe synthetic CBD-based drug therapies[14].

Therefore, there is no evidence to support that a 2% maximum content of synthetic cannabinoid molecules is consistent with no activity and safe consumption.

(3) There is no definition of what constitutes an allowable other synthetic cannabinoid

In addition to (+) CBD, synthetic formulations may include, but may not be limited to, hydrogenated derivatives of (+) CBD; dimethylheptyl (DMH)-CBD derivatives; CBD analogs modified on the C4'-alkyl chain; chlorinated, brominated, fluorinated and iodinated CBD derivatives; CBD derivatives modified at the hydroxyl groups; diacetylated-CBD analogs; and quinones related to CBD[14].

There is still limited evidence for the safety and efficacy of many of these molecules. However, in animals, the safety of four diacetylated-CBD analogs (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-triacetate, and 9hydroxy-CBD-triacetate), was found to be lower than that of CBD in the same assays[17].

The physiological effects of synthetic cannabinoids may vary based on the specific molecule modification. Chemically, synthetic cannabinoids and traditional cannabinoids like THC are vastly different. As opposed to THC, which is a partial agonist at the CB1 receptor, synthetic cannabinoids are full agonists. They exhibit a markedly higher affinity for CB receptors. As such, the effects of synthetic cannabinoids can be much more potent than THC thus increasing the effects seen physiologically and toxicologically[18].

It is therefore concerning that the proposed modification does not require that any additional cannabinoids be those found naturally in cannabis. In the absence of a definition of what constitutes an allowable other synthetic cannabinoid, formulations may also include synthetic molecules of THC which may be more potent that natural THC. Whereas the psychotropic effects associated with natural cannabis are related to the presence of THC, synthetic cannabinoid products potentially containing a wide range of high-potent full agonists of the cannabinoid receptors could induce "THC-like" effects, but be more unpredictable, severe and enduring[19,20]. Pharmacological effects of synthetic THC are 2-100 times more potent than natural THC[19]. Synthetic THC has been associated with a plethora of acute and long-term neuropsychiatric, affective, cognitive, cardiovascular, neurologic, gastrointestinal and other adverse effects[21].

A placebo-controlled, cross over study in 17 cannabis-experienced healthy volunteers evaluating the safety and efficacy of a single, very low dose (2.0-2.6 mg) of JWH-018, a synthetic analog of THC, found that serum concentrations of JWH-018 were significantly higher in the responders. Overall, JWH-018 increased heart rate within the first hour and significantly impaired critical tracking and memory performance. Responders to JWH-018 performed more poorly in tests measuring reaction time and showed increased levels of confusion, amnesia, dissociation, derealisation, and depersonalisation and increased drug liking after JWH-018[22].

In addition to this study, it is noteworthy that a number of clinical reports describe various adverse effects, including seizures, after exposure to synthetic cannabinoid products[23-26]. In agreement with this, a recent study in mice investigating potential adverse effects of the synthetic THC analogs, JWH-073 and AM-2201, found that these synthetic cannabinoids generally resulted in more seizures and hypothermia than THC[27].

Finally, some synthetic cannabinoids, due to their many and varying chemical structures, are not detected by standard hospital or other drug screens and testing, when and if needed, would have to be through a comprehensive drug screen at a reference laboratory[18].

(4) Synthetic cannabinoids are still investigational molecules

Jung *et al*[28] reviews (-)-CBD and structural analogues obtained through synthesis, which are claimed to have varying efficacy and safety profiles. It is clear from review of this document that the synthesis of (-) CBD is a highly active and emergent area of research and commercialisation. We submit that the definition of a synthetic (-) CBD should not inadvertently include in its definition one of the included analogues in this review, or one yet to be developed, which does not have an understood safety profile.

(5) There is no limitation on activity of minor constituent molecules

As a result, a formulation could potentially contain synthetic derivatives of cannabinochromene (CBC), cannabivarin (CBV) and/or cannabigerol (CBG). For example, a synthetic quinone derivative of CBG, VCE-003, has shown biological activity *in vitro* and physiological activity *in vivo*[29,30]. However, these molecules are still under investigation and have unclear efficacy and safety profiles in a clinical setting.

Item 4

Our comments listed in Item 1 apply in Item 4.

[redacted]

Dr Liliana Endo-Munoz
Medical Affairs/Scientific Writer

[redacted]

Dr Andrew Beehag
COO Australasia

18 May 2020

References

1. Huestis, M.A*., et al.* Cannabidiol Adverse Effects and Toxicity. *Curr Neuropharmacol* **17**, 974-989 (2019).
2. Bhattacharyya, S*., et al.* Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* **35**, 764-774 (2010).
3. Solowij, N., Broyd, S.J., van Hell, H.H. & Hazekamp, A. A protocol for the delivery of cannabidiol (CBD) and combined CBD and 9-tetrahydrocannabinol (THC) by vaporisation. *BMC Phamacol Toxicol* **15**, 58 (2014).
4. Gaston, T.E. & Friedman, D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav* **70**, 313-318 (2017).
5. Wiemer-Kruel, A., Stiller, B. & Bast, T. Cannabidiol Interacts Significantly with Everolimus-Report of a Patient with Tuberous Sclerosis Complex. *Neuropediatrics* **50**, 400-403 (2019).
6. Leino, A.D*., et al.* Evidence of a Clinically Significant Drug-Drug Interaction between Cannabidiol and Tacrolimus. *Am J Transplant* **19**, 2944-2948 (2019).
7. Geffrey, A.L., Pollack, S.F., Bruno, P.L. & Thiele, E.A. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* **56**, 1246-1251 (2015).
8. Gaston, T.E., Bebin, E.M., Cutter, G.R., Liu, Y. & Szaflarski, J.P. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia* **58**, 1586-1592 (2017).
9. McCoy, B*., et al.* A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. *Ann Clin Transl Neurol* **5**, 1077-1088 (2018).
10. Alsherbiny, M.A. & Li, C.G. Medicinal Cannabis-Potential Drug Interactions. *Medicines* **6**, 3 (2018).

11. Lucas, C.J., Galettis, P. & Schneider, J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol* **84**, 2477-2482 (2018).
12. Khoury, J.M.*, et al.* Is there a role for cannabidiol in psychiatry? *World J Biol Psychiatry* **20**, 101-116 (2019).
13. Safety of low dose cannabidiol. Version 1.0, April 2020. Therapeutic Goods Administration.
14. Morales, P., Reggio, P.H. & Jagerovic, N. An Overview on Medicinal Chemistry of Synthetic and Natural Derivatives of Cannabidiol. *Front Pharmacol* **8**, 422 (2017).
15. Bisogno, T.*, et al.* Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* **134**, 845-852 (2001).
16. Cannabidiol (CBD). Pre-Review Report. Expert Committee on Drug Dependence. World Health Organization, 39th Meeting, Geneva, 6-7 November 2017. https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf.
17. Carlini, E.A., Mechoulam, R. & Lander, N. Anticonvulsant activity of four oxygenated cannabidiol derivatives. *Res Commun Chem Pathol Pharmacol.* **12**, 1-15 (1975).
18. Kelly, B.F. & Nappe, T.M. Cannabinoid Toxicity. in *StatPearls* (StatPearls Publishing). Copyright © 2020, StatPearls Publishing LLC., Treasure Island (FL), 2020).
19. Castaneto, M.S.*, et al.* Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend* **144**, 12-41 (2014).
20. Weinstein, A.M., Rosca, P., Fattore, L. & London, E.D. Synthetic Cathinone and Cannabinoid Designer Drugs Pose a Major Risk for Public Health. *Front Psychiatry* **8**, 156 (2017).
21. Cohen, K. & Weinstein, A.M. Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective. *Front Public Health* **6**, 162 (2018).
22. L., T.E.*, et al.* Neurocognition and Subjective Experience Following Acute Doses of the Synthetic Cannabinoid JWH-018: Responders Versus Nonresponders. *Cannabis Cannabinoid Res* **4**, 51-61 (2019).
23. Wolfe, C.E.*, et al.* Seizures as a complication of recreational drug use: Analysis of the Euro-DEN Plus data-set. *Neurotoxicology* **73**, 183-187 (2019).
24. Tatusov, M., Mazer-Amirshahi, M., Abbasi, A. & Goyal, M. Clinical effects of reported synthetic cannabinoid exposure in patients admitted to the intensive care unit. *Am J Emerg Med* **37**, 1060-1064 (2019).
25. Lapoint, J.*, et al.* Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol* **49**, 760-764 (2011).
26. Schneir, A.B. & Baumbacher, T. Convulsions associated with the use of a synthetic cannabinoid product. *J Med Toxicol* **8**, 62-64 (2012).
27. Breivogel, S.S., Wells, J.R., Jonas, A., Mistry, A.H., Gravley, M.L., Patel, R.M., Whithorn, B.E., Brenseke, B.M. Comparison of the Neurotoxic and Seizure-Inducing Effects of Synthetic and Endogenous Cannabinoids with Δ9-Tetrahydrocannabinol. *Cannabis Cannabinoid Res* **5**, 32-41 (2019).
28. Jung, B.*, et al.* Synthetic Strategies for (-)-Cannabidiol and Its Structural Analogs. *Chem Asian J* **14**, 3749-3762 (2019).
29. Granja, A.G.*, et al.* A cannabigerol quinone alleviates neuroinflammation in a chronic model of multiple sclerosis. *J Neuroimmune Pharmacol* **7**, 1002-1016 (2012).
30. Valdeolivas, S.*, et al.* Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice. *Neurotherapeutics* **12**, 185-199 (2015).

THC GLOBAL GROUP

Submission by THC Global Group Limited
Proposed amendments to the Poisons Standard - ACMS and Joint ACMS/ACCS meetings, June 2020

Submission for Item 2.5

Summary position on suggested amendments.

1	Schedule 8 amendment: “or Schedule 3.”	Approve
2	Schedule 4 amendment: “**except** when included in Schedule 3.”	Suggested rewording for clarity
3	Schedule 3 entry: “CANNABIDIOL in preparations for therapeutic use when:”	Approve
4	Schedule 3 entry: “a. the cannabidiol is either plant derived”	Approve
5	Schedule 3 entry: “or when synthetic only contains the (-) CBD enantiomer; and”	Disapprove
6	Schedule 3 entry: “b. the maximum recommended daily dose is 60 mg or less of cannabidiol; and”	Approve
7	Schedule 3 entry: “c. in packs containing not more than 30 days' supply; and”	Approve
8	Schedule 3 entry: “d. cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and”	Approve
9	Schedule 3 entry: “e. any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation; and”	Disapprove
10	Schedule 3 entry: “f. for adults aged 18 years and over.”	Disapprove

Detailed Submission

Item 1

Our overall view is that CBD in a controlled form should be regulated as a Schedule 3 medicine. We agree with the findings of the TGA Safety Review on this matter, as there is a growing evidence base supporting its acceptable safety profile in various patient groups[1-17].

Item 2

We suggest the wording "except when captured by the CANNABIDIOL entry in Schedule 3" to have consistency with the suggested modification for Schedule 8 Cannabis.

Item 3

Our overall view is that CBD in a controlled form should be regulated as a Schedule 3 medicine. We agree with the findings of the TGA Safety Review on this matter.

Item 4

We agree with the TGA Safety Review that CBD has an acceptable safety and tolerability profile at the proposed dose.

Item 5

Our overall view is that the allowance of synthetics under Schedule 4 is proposed with little understanding of what may eventuate, and therefore this modification is not consistent with public safety. Our concerns are as follows:

(1) The TGA Report on low dose cannabidiol safety has a logical flaw

The TGA report on the safety of low dose CBD[18] states: "Cannabidiol is a chiral compound. Only the (-) CBD enantiomer is present in the Cannabis plants. Consequently, plant derived cannabidiol is present only as (-) CBD and has low affinity for the CB1 and CB2 receptors, and thus is not psychoactive. Synthetic cannabidiol has the potential to be a racemic mixture, the non-psychoactive (-) CBD or the alternative (+) CBD enantiomer."

In our view there is a logical non sequitur within this statement which may have consequence for the safe use of S3 CBD.

There is a first statement that plant derived CBD is present only as (-) CBD, a second statement that plant derived CBD has a low affinity for the CB1 and CB2 receptors, and a third statement that plant derived cannabidiol is thus not psychoactive. We submit that there is significant evidence in the literature that plant-based CBD is not psychoactive, and the TGA report infers this, and it is clarified elsewhere in the TGA report that there is an acceptable safety profile for CBD. However, the above statement within the TGA report does not contain a clear line of logic, nor is there clear literature supporting the following argument: due to (-) CBD having low affinity for CB1 and CB2 receptors in the brain there is no psychoactive activity, likewise due to the (-) CBD configuration there are no other uncontrolled or undesirable events in other regions of the body that would warrant elevated safety concerns, and that exclusivity of (-) CBD is the reason for the acceptable safety profile of cannabidiol, and therefore plant sourced cannabidiol is safe.

It is important that this line of logic is clear before it can be applied to the use of synthetic cannabinoids including (-) CBD, particularly as the proposal is for availability of synthetic (-) CBD without ongoing medical supervision as a S3 product.

We further question the conclusion of the TGA report[18], stating "Given that the safety profile is based on cannabidiol having low affinity for the CB1 and CB2 receptors, and thus is not exhibiting psychoactive effects". The safety profile is not based on having no psychoactivity; no psychoactivity is only one of the features of a positive safety profile. We again restate that plant-based cannabidiol has been well researched and well understood through widespread use and extensive study to have a good safety profile.

(2) (+)-CBD enantiomers are known to be psychoactive

The TGA review, *Safety of Low Dose Cannabidiol*, *version 1, April 2020*[18] (see Box 1), found that unlike non-psychoactive (-) CBD enantiomers found uniquely in cannabis plants, (+) CBD enantiomers which are likely to be present in synthetic or semi-synthetic preparations, have been shown to bind to both CB1 and CB2 receptors, but to display selectivity toward CB1[20]. The (+) CBD enantiomer has also been shown to bind to vanilloid VR1 receptors *in vitro* and in rats[21], but the implication of this in humans has not been investigated. Therefore, since (+) CBD synthetic forms may be potentially psychoactive and/or have pharmacological activity which has not yet been well defined in clinical studies, this highlights a risk for the therapeutic use of synthetic formulations.

> ***Box 1. TGA Review recommendation***
> *"Cannabidiol is a chiral compound. Only the (-) CBD enantiomer is present in the Cannabis plants. Consequently, plant derived cannabidiol is present only as (-) CBD and has low affinity for the CB1 and CB2 receptors, and thus is not psychoactive. Synthetic cannabidiol has the potential to be a racemic mixture, the non-psychoactive (-) CBD or the alternative (+) CBD enantiomer. (+) CBD and its derivatives have been reported to bind to both CB1 and CB2 receptors, displaying selectivity towards CB1[20,22] and is therefore likely to be psychoactive and present different pharmacological activity. Therefore, the use of synthetic CBD may have psychoactive potential that would not be found in plant-derived cannabidiol. This should be considered in any decision to down-schedule CBD."[18]*

The TGA review points out that "the use of synthetic CBD may have psychoactive potential that would not be found in plant-derived cannabidiol. This should be considered in any decision to down-schedule CBD."[18] Thus, including synthetic or semi-synthetic molecules of (+) CBD under Schedule 4b would go against the findings of the TGA's own review. It could potentially place patients at risk of undefined psychoactive effects or other adverse events.

(3) Synthetic CBDs have not been shown without exception to have the same clear safety profile as naturally sourced CBDs

The effects of natural CBD on psychological and behavioral measures have been investigated in numerous experimental, placebo-controlled studies, giving us valuable information on its risk profile[23]. In contrast, comparable studies with synthetic cannabinoids in humans are in their infancy. Consequently, reliable and well-validated information on individual health risks is missing. It has been proposed that the complexity of the pharmacological processes of CBD and CBD analogs calls for a better understanding of their mechanism of action before the development of safe synthetic CBD-based drug therapies[20].

(4) Precedent indicates synthetic CBD should have an independent entry in SUSMP

Dronabinol is a distinct entry in the SUSMP that enables a specific single molecule entry for delta-9-tetrahydrocannabinol. This separation enables dronabinol to be obtained by synthesis rather than plant extraction, as indicated in the entry for cannabis, tetrahydrocannabinols and nabiximols. Dronabinol has undergone significant clinical research, and it is understood this is the basis for its entry into SUSMP. We support a similar process for a synthetic cannabidiol, which clarifies the specific definition of the synthetic cannabidiol and distinguishes it from near analogues, and that the synthetic

cannabidiol has been assessed for its safety profile. At this time the appropriate schedule for entry can be established.

(5) There is no clarity on whether other synthetic cannabinoids are allowable

In addition to (+) CBD, synthetic formulations may include, but may not be limited to, hydrogenated derivatives of (+) CBD; dimethylheptyl (DMH)-CBD derivatives; CBD analogs modified on the C4'-alkyl chain; chlorinated, brominated, fluorinated and iodinated CBD derivatives; CBD derivatives modified at the hydroxyl groups; diacetylated-CBD analogs; and quinones related to CBD[20].

There is still limited evidence for the safety and efficacy of many of these molecules. However, in animals, the safety of four diacetylated-CBD analogs (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-triacetate, and 9-hydroxy-CBD-triacetate), was found to be lower than that of CBD in the same assays[24].

The physiological effects of synthetic cannabinoids may vary based on the specific molecule modification. Chemically, synthetic cannabinoids and traditional cannabinoids are vastly different. For example, as opposed to THC, which is a partial agonist at the CB1 receptor, synthetic cannabinoids are full agonists. They exhibit a markedly higher affinity for CB receptors. As such, the effects of synthetic cannabinoids can be much more potent than THC, thus increasing the effects seen physiologically and toxicologically[25].

Thus, in the absence of a definition of what constitutes an allowable other synthetic cannabinoid, formulations may also include synthetic molecules of THC which may be more potent that natural THC. Whereas the psychotropic effects associated with natural cannabis are related to the presence of THC, synthetic cannabinoid products potentially containing a wide range of high-potent full agonists of the cannabinoid receptors could induce "THC-like" effects, but be more unpredictable, severe and enduring[26,27]. Pharmacological effects of synthetic THC are 2-100 times more potent than natural THC[26]. Synthetic THC has been associated with a plethora of acute and long-term neuropsychiatric, affective, cognitive, cardiovascular, neurologic, gastrointestinal and other adverse effects[28].

A placebo-controlled, cross over study in 17 cannabis-experienced healthy volunteers evaluating the safety and efficacy of a single, very low dose (2.0-2.6 mg) of JWH-018, a synthetic analog of THC, found that serum concentrations of JWH-018 were significantly higher in the responders. Overall, JWH-018 increased heart rate within the first hour and significantly impaired critical tracking and memory performance. Responders to JWH-018 performed more poorly in tests measuring reaction time and showed increased levels of confusion, amnesia, dissociation, derealisation, and depersonalisation and increased drug liking after JWH-018[29].

In addition to this study, it is noteworthy that a number of clinical reports describe various adverse effects, including seizures, after exposure to synthetic cannabinoid products[30-33]. In agreement with this, a recent study in mice investigating potential adverse effects of the synthetic THC analogs, JWH-073 and AM-2201, found that these synthetic cannabinoids generally resulted in more seizures and hypothermia than THC[34].

Finally, some synthetic cannabinoids, due to their many and varying chemical structures, are not detected by standard hospital or other drug screens and testing, when and if needed, would have to be through a comprehensive drug screen at a reference laboratory[25] (see comment (2) under Item 9).

(6) Synthetic cannabinoids are still investigational molecules

Jung *et al*[19] reviews (-)-CBD and structural analogues obtained through synthesis, which are claimed to have varying efficacy and safety profiles. It is clear from review of this document that the synthesis of (-) CBD is a highly active and emergent area of research and commercialisation. We submit that the definition of a synthetic (-) CBD should not inadvertently include in its definition one of the included analogues in this review, or one yet to be developed, which does not have an understood safety profile.

(7) There is no limitation on activity of minor constituent molecules

As a result, a formulation could potentially contain synthetic derivatives of cannabinochromene (CBC), cannabivarin (CBV) and/or cannabigerol (CBG). For example, a synthetic quinone derivative of CBG, VCE-003, has shown biological activity *in vitro* and physiological activity *in vivo*[35,36]. However, these molecules are still under investigation and have unclear efficacy and safety profiles in a clinical setting.

Item 6

We agree with the TGA Safety Review that CBD has an acceptable safety and tolerability profile at the proposed dose.

Item 7

We agree with the TGA Safety Review that CBD has an acceptable safety and tolerability profile at the proposed dose.

Item 8

We agree that the noted minimum percentage is required to keep Schedule 3 CBD in the same understood safety profile as Schedule 4 CBD.

Item 9

We agree that naturally occurring cannabinoids are the only valid cannabinoids, and we agree that the noted maximum percentage is required to keep Schedule 3 CBD in the same understood safety profile as Schedule 4 CBD. However, as full acceptance of the submitted modifications may allow an interpretation that the naturally occurring cannabinoids are produced synthetically, we request the following words are used instead:

> any cannabinoids, other than cannabidiol, must be only those sourced from the cannabis plant and comprise 2 per cent or less of the total cannabinoid content of the preparation

Note that the requirement for this adjustment is removed where our suggested modifications are made (noted below under Clarification of Cannabidiol from a Natural and Legal Source).

(1) Concentration of minor cannabinoids may change dramatically

The safety profile of cannabis plants is well researched and understood, in particular in reference to the safety profile of cannabidiol preparations from plants (see references 1-17). Within the cannabinoid profile of these preparations are up to 140 different cannabinoids in small to undetectable concentration. We submit that the safety profile of cannabidiol from plants requires an understanding that the minor concentration of other cannabinoids remains minor. The ability to process and significantly raise concentration of minor to undetectable cannabinoids sourced from a plant is exceptionally unlikely due to the cost involved. Therefore, the risk is extremely low that a minor cannabinoid sourced from the cannabis plant will rise to a concentration level to give safety outcomes inconsistent with the well-researched safety profile of cannabidiol.

However, where synthesis of these same molecules is allowed, the ability of the molecules to be produced inexpensively and at scale is clear. This means that the safety profile of formulations containing up to 2% concentration is no longer understood and cannot be stated categorically to be consistent with the well-researched safety profile of plant-sourced cannabidiol and its associated minor plant-sourced cannabinoids.

(2) Synthetic cannabinoid variants may not be detected
The criteria that minor cannabinoids must be natural and less than 2%, where synthesis of cannabinoids is permitted, is an exclusion criterion that is difficult to police. The reliance on the Certificate of Analysis to indicate correct detection of a cannabinoid and its correct reporting relies on the accuracy of method development. It is unclear that an analogue of a natural cannabinoid will be detectable through the chromatographic assessment means generally used for cannabinoid medicines to enable release of therapeutic goods. However, the safety profile may differ significantly.

We submit that the plant based cannabinoids, which have been in widespread use and have a well-researched safety profile, will be contained to the approximately 140 known cannabinoids, and where additional cannabinoids are discovered, they are likely to be in exceptionally small concentration, and we submit these are likely to pose an extremely low safety risk.

Item 10
The logic underlying restriction of supply to persons under 18 as a Schedule 3 medicine is understood and supported in principle. However, we also note that medications manufactured to the proposed Schedule 3 medications are valid Schedule 4 medications and are likely to have the same production and packaging. There should be no restriction on a doctor prescribing a CBD product meeting proposed Schedule 3 requirements to a minor while under strict medical supervision.

Our view is that appropriate warnings on the packaging, noted by the relevant pharmacy staff, can achieve the objective of restricting OTC supply to persons under 18 years of age. An example warning statement for suggested inclusion in Appendix F would be “Not for supply to persons under 18 years without prescription”.

Additional Suggested Modifications

Additional References to Cannabidiol
We note an additional location where reference to Cannabidiol as Schedule 3 should be included, being:

- Schedule 8 definition of Tetrahydrocannabinols

Warning Labels for Cannabidiol
We request the following alterations with regard to sedation effects of Cannabidiol:

- Appendix K: that the Cannabis entry have the exception for cannabidiol removed
- Appendix K: that the Tetrahydrocannabinols have the exception for cannabidiol removed

Our opinion is that cannabidiol may have the potential for sedation at lower dose levels (25-175 mg/day) in a subset of patients[5], or may potentiate the sedative effect of concomitant medications[37].

Exception in Appendix D
We suggest a specific exception for prescribing is made for the Cannabis and Tetrahydrocannabinols entry in Appendix D for Cannabidiol as defined in Schedule 3 for the purpose of clarity.

Clarification of Cannabidiol from a Natural and Legal Source

We would like to suggest a modification to the definition of Cannabidiol, due to the disparity between Cannabidiol and other cannabis-sourced product definitions in SUSMP including Tetrahydrocannabinol and Nabiximols.

We would like the following inclusion made for Cannabidiol Schedule 4, as well as any future entry for Cannabidiol under Schedule 3, to contain the following text (similar to the entry for Cannabis under Schedule 8):

Cannabidiol when prepared or packed for human therapeutic use, when:

a. in products manufactured in accordance with the Narcotic Drugs Act 1967; and/or
b. for use in products manufactured in accordance with the Narcotic Drugs Act 1967; and/or
c. imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
d. in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989,

and the entry to have appropriate exceptions.

The reasoning for this suggested modification is as follows:

- The current Schedule 4 entry is insufficiently clear, given Cannabidiol is an exception to the Schedule 8 Cannabis entry for the purpose of listing in Schedule 4 (and potentially Schedule 3), and we suggest is not an exception to the supply under the Narcotic Drugs Act or Therapeutic Goods Act
- The entries for Cannabis, Tetrahydrocannabinol and Nabiximols clearly identify plant or botanical source; it is appropriate Cannabidiol is not separated from this group by the omission of clarifying text
- The entry can be clarified further at a future date when the safety profile of cannabinoids from other sources, including synthetic cannabinoids, is clear
- The clarification that cannabidiol is a manufactured good (as addressed by the truncated definition in line “a” above), and not a redefinition of a cannabis plant or its flower where cannabidiol is at least 98% of all cannabinoids (and is subject to variation)

Modification of Schedule 9 Entry for Cannabis

The current Schedule 9 entry for Cannabis appears to be at odds with FSANZ Gazette #169 for the supply of hemp food.

We suggest an additional exception to account for hemp seed products for internal human use as outlined in FSANZ Food Standards Code Amendment No. 169 – 11 May 2017, including specific limits on cannabinoids within the food products, and the presence of cannabinoids only from the source cannabis seed as outlined in Amendment 169. We believe this can be achieved with reference to the Food Standards Gazette.

A suggested entry is:

Definitions

"Hemp seed food" means a seed food or food product obtained from the seeds of low THC Cannabis sativa

Cannabis entry Schedule 9, additional exception

d) when in hemp seed food and where standards for Low THC Hemp Seeds as Food are met as determined in the Commonwealth of Australia Food Standards Gazette

[redacted]

Dr Liliana Endo-Munoz
Medical Affairs/Scientific Writer

[redacted]

Dr Andrew Beehag
COO Australasia

18 May 2020

References

1. Hobbs, J.M*., et al.* Evaluation of pharmacokinetics and acute anti-inflammatory potential of two oral cannabidiol preparations in healthy adults. *Phytother Res*, 10.1002/ptr.6651 (2020). In Press.

2. Gulbransen, G., Xu, W. & Arroll, B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open* **4**(1). pii: bjgpopen20X101010 (2020).

3. Miller, I*., et al.* Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. *JAMA Neurology* **77**, 613-621 (2020).

4. Silvestro, S., Mammana, S., Cavalli, E., Bramanti, P. & Mazzon, E. Use of Cannabidiol in the Treatment of Epilepsy: Efficacy and Security in Clinical Trials. *Molecules* **24**, pii:E1459 (2019).

5. Shannon, S., Lewis, N., Lee, H. & Hughes, S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J* **23**, 18-041 (2019).

6. Mitelpunkt, A*., et al.* The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study. *Epilepsy Behav* **98**, 233-237 (2019).

7. Laux, L.C*., et al.* Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Res* **154**, 13-20 (2019).

8. Thiele, E.A*., et al.* Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* **391**, 1085-1096 (2018).

9. Taylor, L., Gidal, B., Blakey, G., Tayo, B. & Morrison, G. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. *CNS Drugs* **32**, 1053-1067 (2018).

10. Szaflarski, J.P., *et al.* Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav* **87**, 131-136 (2018).

11. Devinsky, O., *et al.* Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* **90**, e1204-e1211 (2018).

12. Devinsky, O., *et al.* Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *New Engl J Med* **378**, 1888-1897 (2018).

13. Naftali, T., *et al.* Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. *Dig Dis Sci* **62**, 1615-1620 (2017).

14. Cannabidiol (CBD). Pre-review Report. Agenda Item 5.2. Expert Committee of Drug Dependence. 39th Meeting (Geneva, 2017). World Health Organization.

15. Devinsky, O., *et al.* Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* **55**, 791-802 (2014).

16. Devinsky, O., *et al.* Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* **15**, 270-278 (2016).

17. Shannon, S. & Opila-Lehman, J. Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report. *Perm J* **20**, 16-005 (2016).

18. Safety of low dose cannabidiol. Version 1.0, April 2020. Therapeutic Goods Administration.

19. Jung, B., *et al.* Synthetic Strategies for (-)-Cannabidiol and Its Structural Analogs. *Chem Asian J* **14**, 3749-3762 (2019).

20. Morales, P., Reggio, P.H. & Jagerovic, N. An Overview on Medicinal Chemistry of Synthetic and Natural Derivatives of Cannabidiol. *Front Pharmacol* **8**, 422 (2017).

21. Bisogno, T., *et al.* Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* **134**, 845-852 (2001).

22. Cannabidiol (CBD). Pre-review Report. Agenda Item 5.2. Expert Committee of Drug Dependence. 39th Meeting (Geneva, 2017). World Health Organization.

23. Huestis, M.A., *et al.* Cannabidiol Adverse Effects and Toxicity. *Curr Neuropharmacol* **17**, 974-989 (2019).

24. Carlini, E.A., Mechoulam, R. & Lander, N. Anticonvulsant activity of four oxygenated cannabidiol derivatives. *Res Commun Chem Pathol Pharmacol* **12**, 1-15 (1975).

25. Kelly, B.F. & Nappe, T.M. Cannabinoid Toxicity. in *StatPearls* (StatPearls Publishing LLC., Treasure Island (FL), 2020).

26. Castaneto, M.S., *et al.* Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend* **144**, 12-41 (2014).

27. Weinstein, A.M., Rosca, P., Fattore, L. & London, E.D. Synthetic Cathinone and Cannabinoid Designer Drugs Pose a Major Risk for Public Health. *Front Psychiatry* **8**, 156 (2017).

28. Cohen, K. & Weinstein, A.M. Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective. *Front Public Health* **6**, 162 (2018).

29. Theunissen, E.L*., et al.* Neurocognition and Subjective Experience Following Acute Doses of the Synthetic Cannabinoid JWH-018: Responders Versus Nonresponders. *Cannabis Cannabinoid Res* **4**, 51-61 (2019).

30. Wolfe, C.E*., et al.* Seizures as a complication of recreational drug use: Analysis of the Euro-DEN Plus data-set. *Neurotoxicology* **73**, 183-187 (2019).

31. Tatusov, M., Mazer-Amirshahi, M., Abbasi, A. & Goyal, M. Clinical effects of reported synthetic cannabinoid exposure in patients admitted to the intensive care unit. *Am J Emerg Med* **37**, 1060-1064 (2019).

32. Lapoint, J*., et al.* Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol* **49**, 760-764 (2011).

33. Schneir, A.B. & Baumbacher, T. Convulsions associated with the use of a synthetic cannabinoid product. *J Med Toxicol* **8**, 62-64 (2012).

34. Breivogel, C.S*., et al.* Comparison of the Neurotoxic and Seizure-Inducing Effects of Synthetic and Endogenous Cannabinoids with Delta(9)-Tetrahydrocannabinol. *Cannabis Cannabinoid Res* **5**, 32-41 (2020).

35. Granja, A.G*., et al.* A cannabigerol quinone alleviates neuroinflammation in a chronic model of multiple sclerosis. *J Neuroimmune Pharmacol* **7**, 1002-1016 (2012).

36. Valdeolivas, S*., et al.* Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice. *Neurotherapeutics* **12**, 185-199 (2015).

37. Kerstin, I. & Franjo, G. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis and Cannabinoid Research* **2**, 139-154 (2017).