Medicinal Cannabis Industry Australia (MCIA)

Submission to the TGA: Interim Decision on Amendments to the Poisons Standard (Medicines/Chemicals)

October 2020

1.0 About Medicinal Cannabis Industry Australia (MCIA)

Medicinal Cannabis Industry Australia (MCIA) welcomes the opportunity to make this submission to the TGA regarding the Interim Decision on Amendments to the Poisons Standard (Medicines/Chemicals).

MCIA is the peak industry organisation for Australia's licensed medicinal cannabis industry. This encompasses all activities of medicinal cannabis licence holders across research, cultivation and manufacturing and interaction with patients, the medical profession and communities.

MCIA's focus is on building an industry that enhances wellbeing through facilitating access to quality Australian medicinal cannabis products for Australian and global patients.

Medicinal cannabis has an important role to play in improving health outcomes. MCIA supports a holistic healthcare approach built around patients and their regular medical practitioner determining if medicinal cannabis is an appropriate medicine for their current medical condition. MCIA believes that patients should have easy and affordable access to a quality controlled, true to label, compliant product that is demonstrating the potential to positively contribute to a broad range of conditions.

2.0 Introduction

MCIA makes this submission in response to the proposed scheduling of cannabidiol (CBD) as provided by the interim decision of the Joint ACMS-ACCS #25 meeting, June 2020 (Item 4.1 in relation to cannabidiol (private application) and cannabidiol (delegate initiated)).

MCIA welcomes the consideration of CBD scheduling by the Therapeutic Goods Administration (TGA), the Advisory Committees on Medicines and Chemicals Scheduling (ACMS and ACCS) and the Delegate of the Secretary. Many other countries have CBD more readily available than Australia, and this scheduling review provides an opportunity to improve quality, safety and access for consumers, while ensuring health care professional involvement in provision. This pragmatic approach to CBD availability could be world-leading, and also has the potential to provide a clear path forward for the local industry.

MCIA **supports** the general proposition of down-scheduling of CBD to S3 as it has the potential to provide patients with improved access to a safe low dose cannabis product for medical use. Any down-scheduling should aim to provide the consumer with GMP-certified product and enable contact with a healthcare professional before provision, which has obvious safety advantages.

However, MCIA notes that the current proposal has **limitations** in terms of delivering the desired patient access and for the Australian industry looking to bring products to market. Our comments on the elements of the interim decision raised by the Delegate are discussed in Section 3.0.

On the basis of the evidence presented below MCIA recommends that CBD be down scheduled to S3, but with a higher daily dose, and with the other requirements proposed by the Delegate.

Potential benefits of widening access through S3 supply

Many of the safety benefits of the S3 down-scheduling will largely be derived by enabling patients who are currently obtaining their medicinal cannabis from the illicit market to obtain it from pharmacies. Currently, most patients indicate that they use illicit cannabis for medical purposes and many purchase this illicit product via the internet[1]. It is important that patients have assurance around the quality and source of products they are receiving.

MCIA believes that the down-scheduling of CBD will benefit patients by allowing them to move from the illicit market and providing easier and more affordable access to high quality products.

[1] *Cannabis As Medicine Survey (CAMS:18)*, conducted by staff at the Discipline of Addiction Medicine in conjunction with the Lambert Initiative for Cannabinoid Therapeutics at the University of Sydney

The use and marketing of low dose CBD "nutraceutical" products continues to be prevalent in Australia, specifically through online suppliers. As a result of the accessibility of CBD products elsewhere in the world, many patients are purchasing these products without understanding that they are illicit. Nor do many patients appreciate the potential risks associated with their consumption including that content may not match the product label resulting in products with lower CBD content than advertised, or products with potentially hazardous contaminants and/or high levels of THC (or a variety of other potential quality issues). Finally, the illegality of their actions may come with significant criminal penalties for the unsuspecting user, including, but not limited to the risk of roadside drug test failure, workplace drug test failure or for the import of prohibited goods.

Thus, there is a clear safety and quality use of medicines benefit of having CBD down-scheduled to Schedule 3.

3.0 Comments on the interim decision

Dose

As indicated above, MCIA supports a Schedule 3 – Pharmacist Only medication registration option for CBD products at appropriate dosage levels. The TGA registration process would ensure that efficacy, safety, and quality are pre-assessed. However, MCIA encourages the Delegate to review the capping of daily dose, which is proposed at 60 mg per day.

The key driver for the down-scheduling proposal is to deliver improved access and benefit for patients (a key issue identified in the Senate Inquiry report released in March this year[2]). On the basis of the evidence provided in McGregor et al Report[3], the proposed daily dose of 60 mg will make it difficult for products to achieve registration, due to the difficulty of meeting the evidentiary requirements for efficacy. Therefore, it is likely down-scheduling will not achieve the desired outcome of patient access to low dose CBD products, which in turn will result in the continuance of accessing products through the illicit market.

The McGregor et al Report, commissioned by MCIA, indicates that a dose well above 60 mg per day is safe. Therefore the down-scheduling could be increased to a more efficacious dose without compromising safety. Key conclusions of this Report supporting a higher dosage rate were that:

i. clinically-relevant CBD effects tend to become more robust as dosage is increased - with the review assessing evidence up to and including 400 mg, and

ii. CBD appears exceptionally safe, with very few concerns even at the highest dose range considered in the report i.e. up to 400 mg.

MCIA recommends the dose be increased based on the following factors and evidence:

1. Maximum daily dose should be increased based on dose calculations drawn upon by the TGA

   From the TGA low-dose CBD review the daily dose of 60 mg was based on a dose rate of 1 mg/kg/day for a **60kg person[4]**. The representation that "above 2 mg/kg/day" was a dose typically used for epilepsy, and thus inappropriate for a S3 medicine due to crossover with a condition requiring medical supervision, is misrepresentative. The recommended ***starting dosage*** of Epidyolex™[5] (a CBD product) is 2.5 mg/kg ***twice daily***, increasing to a ***maintenance dosage*** of 5 mg/kg ***twice daily***, and further adjustment to 10 mg/kg twice daily is the recommended maximum dose i.e. the expected dosage range is 10-20 mg/kg/day for certain seizure disorders.

[2] Current barriers to patient access to medicinal cannabis in Australia, **March 2020,** Senate Standing Committees on Community Affairs

[3] *The Efficacy and Safety of Oral Cannabidiol at Oral Doses up to 400 mg: An Evaluation of Current Evidence*, A Report Commissioned by the Medical Cannabis Industry Australia (MCIA), Iain S. McGregor, Danielle McCartney, Anastasia Suraev & Jonathon C. Arnold, The Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Brain and Mind Centre

[4] Note the TGA *Safety of low dose cannabidiol* Review noted the global average body mass of 62 kg, but used the approximate of 60kg in developing the recommended low dose

[5] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02277-1&d=202010101016933 AUSTRALIAN PRODUCT INFORMATION – EPIDYOLEX® (CANNABIDIOL) ORAL SOLUTION. Emerge Health Pty Ltd, 21 Sep 2020

There is considerable scope between the 1 mg/kg/day informing the classification of a low dose in the review and the delegate-initiated submission, and the recommended maintenance dose for a condition that should have medicinal oversight – that is, 10-20 mg/kg/day or 600-1200 mg daily dose for a 60kg person.

Based solely on the position of the appropriate dose being below the starting dose highlighted above, the maximum daily dose should be 120 mg (1mg/kg for a 60kg person, twice daily).

2. Maximum daily dose should be increased based on body mass calculations

   Secondly, the dose should also be recalculated for body mass calibrated to Australian body mass data. The TGA calculation is based on body mass of a 60kg person, while the Australian average body mass for men is 87kg and women 72kg[6]. Thus, we suggest, using an **average of 80kg** for persons 18 years or over. If calibrated at 1 mg/kg twice per day, the maximum dosage would be 160 mg.

   On this basis, the maximum daily dose is more realistically represented at 160 mg

3. Safety data supports a higher dose rate

   Evidence from available literature supports a higher dose. The McGregor et al Report concluded that CBD appears exceptionally safe, with very few concerns even at the highest dose range considered (301- 400 mg per day). Further the Report identified "that several high-quality systematic reviews and meta-analyses of CBD safety have recently been conducted (Chesney et al., 2020; Dos Santos et al., 2020; Iffland and Grotenhermen, 2017; Larsen and Shahinas, 2020) and these generally conclude that CBD has a remarkably safe profile."

   The McGregor et al Report found few concerns around safety across the studies analysed of up to 400 mg per day. Where side effects were reported these were typically minor, often in studies that lacked a placebo control, and therefore could not be unambiguously attributed to CBD itself. Few adverse events were reported in any of the studies considered even at the 300-400 mg per day dose range where efficacy was most often reported. The only minor concerns around safety were altered metabolism of CBD in hepatically impaired patients (Taylor et al., 2019) and limited tolerance in patients with advanced cancer who were medicated with many other drugs (Good et al., 2020).

   Non-prescription CBD products in the US and EU typically involve relatively low daily doses of CBD (<1 mg/kg) obtained from products such as capsules containing 10-50 mg CBD, or from orally administered oils containing 15–240 mg/ml CBD (typically dosed with a few drops i.e., 0.1-0.5 ml per day). Recommended daily oral dosing of such products tends to be less than 100 mg CBD/day and often in the range of 10-25 mg per day, an order of magnitude lower than the doses confirmed by clinical trials as efficacious (i.e., 300-1500 mg) (McGregor et al., 2020). This widespread availability of CBD-containing products without a prescription is consistent with few safety concerns about this cannabinoid. For example, in 2019 the World Health Organisation (WHO) proposed changes through its Expert Committee of Drug Dependence to exclude CBD from international drug control. This was on the basis that CBD does not intoxicate and has little potential for abuse or dependence (World Health Organisation, 2017, 2019). While this low dose use supports the safety of the product, there is not corresponding evidence of efficacy at these low levels (refer section below).

   Specifically at the different dose ranges, the McGregor Report found:

   - No major issues with safety in the studies conducted in the 61-100 mg oral CBD dose range
   - No obvious problems relating to side effects or adverse events were seen at the 101-200 mg dose range
   - The 300 mg oral dose of CBD is the threshold at which higher quality evidence accumulates around CBD efficacy, in the absence of significant safety concerns. There are no obvious safety concerns with this dose of CBD across the hundreds of patients treated either acute or chronically in the studies in the 201-300 mg dose range

[6] ABS' National Health Survey

- The tendency towards positive clinical trial outcomes with 300 mg CBD were further consolidated at doses of 400 mg CBD. Despite occasional reports of minor side effects, sometimes above placebo, the overall safety profile of CBD at this dose level appears favourable at the 301-400 mg dose range.

On this basis, MCIA suggests that the maximum daily dose could be 300 mg (which is a 2.5mg/kg twice daily, in a 60kg person; or <2mg/kg twice daily in a 80kg person), where there is a maximum of 2% other cannabinoids, and THC should not exceed 2 mg per dose.

As a Schedule 3 drug this would only apply to conditions that do not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.

4. CBD fits well within the criteria for S3, at appropriate doses.

   The medicine would be substantially safe with pharmacist intervention. The WHO 2017 report states CBD "is generally well-tolerated, with a good safety profile" [7]. There is no dependency[7]. Misuse, abuse or illicit use would be unlikely with a minimum age of 18 years, which the pharmacist would manage. While the risk profile is not as clear as for many medicines, the WHO 2017 report notes the good safety profile[8], drug interactions concerns have mainly arisen from in vitro (theoretical) data at concentrations above those used clinically in seizure disorders, and are no more than for other non-prescription medicines (refer next section). Contraindications are few[8]. Conditions that CBD could be registered for would need to be those a consumer could self-manage or manage with help from a pharmacist (potentially in some cases after a prescriber's recommendation). Examples would be insomnia or anxiety, already self-managed with non-prescription medicines or remedies. CBD would not mask the symptoms or delay diagnosis of a serious condition.

   There are many other medicines available without a prescription that similarly fit the scheduling criteria for S3, with all having different risks. For example, triptans for migraine can have overuse headaches if used excessively and have important contraindications and precautions, oral diclofenac has important contraindications and precautions, omeprazole has potential drug interactions and the potential for use with a serious condition. CBD has no greater risk than these.

5. Low potential for drug-drug interactions

   While drug interactions were identified as a concern by the TGA in their document "Safety of low dose cannabidiol" April 2020, and the ACMS and Delegate, we share the following data/points of interest.

   Much recent information has been derived from high dose CBD developed for epilepsy, dosed at 10-20 mg/kg/day (700-1400 mg/day for a 70kg person), and at least some interactions are considered theoretical[9]. For some theoretical interactions (e.g. CYP1A2, CYP2C8, CYP 2C9, and CYP2B6) inhibition occurred in vitro at concentrations far greater than used as an anti-seizure drug[9], so these would have even less relevance to non-prescription CBD doses. Increased liver enzyme concentrations when CBD and valproate are used together are very likely to reflect the high doses used for epilepsy (up to 50 mg/kg/day) rather than a concern likely to occur at lower CBD doses. A Sept 2020 published review concluded in the evidence concerned that *"…trials indicate an overall low potential for drug-drug interactions between CBD and other anti-seizure drugs except CLB [Clobazam]".* The review, and Stockley's Drug Interactions[9] (the authoritative drug interactions database for clinicians) also reported that CBD did not affect CYP3A4 activity, based on research in combination with midazolam, a marker for CYP3A4 interactions. Stockley's reports very few clinically significant interactions – either CBD affecting another drug, or CBD being affected.

[7] World Health Organisation. Cannabidiol Pre-review Report for the Expert Committee on Drug Dependence 39th meeting. 2017

[8] MacCallum CA and Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 2018; 49: 12-19. Review. DOI: 10.1016/j.ejim.2018.01.004

[9] Stockley's Drug Interactions [online]. In: Preston C, (ed.). London: Pharmaceutical Press, 2020

Earlier, the 2017 WHO Pre-Review Report noted *"it is not clear whether [inhibition of some CYP enzymes] occur at physiological concentrations."*[7] The single case report with warfarin and CBD showed a significant effect on INR requiring a warfarin dose reduction, with increasing effect as the dose increased from 5 mg/kg/day to 25 mg/kg/day, suggesting a dose relationship[10]. A single case report of a CBD-tacrolimus interaction was seen at a dose of 2000 mg/day.

CBD is a CYP2C19 inhibitor and therefore could increase bioavailability of CYP2C19 substrates. While there is clearly a significant increase in plasma concentration for an active metabolite of clobazam (thought to be affected by this mechanism), the amount of this increase varies between studies[9] and this could easily be avoided with Schedule 3 use requiring the pharmacist's intervention, and with appropriate label warnings, as for other S3 medicines with interactions. Furthermore, substrates for CYP2C19 are relatively few with only one listed as sensitive (omeprazole).

As CBD is metabolised by CYP2C19 and CYP3A4, inhibitors and inducers of these enzymes might affect CBD levels. However, even potent inhibitors of these enzymes have relatively little effect, e.g. ketoconazole a potent CYP3A4 inhibitor was reported by Stockley's Drug Interactions to cause a *"slight"* increase in exposure for CBD (nearly double bioavailability)*[9]*. Ketoconazole has a greater effect on other non-prescription medicines such as loperamide (5-fold increase), ulipristol (5.9-fold increase), and loratadine (2.8-4.5-fold). Similarly, omeprazole 40 mg daily (a potent CYP2C19 inhibitor) had no effect on the bioavailability of CBD.

For context it is useful to consider that other non-prescription medicines have drug interactions which are navigated. For example, fluconazole is a potent CYP2C9 inhibitor, a moderate CYP3A4 inhibitor and inhibits CYP2C19*[9]*. Omeprazole has drug interactions through inhibition of CYP2C19 and acid suppression. For example, omeprazole increased the AUC of carbamazepine by 75-90% and affects methotrexate and reduces the bioavailability of mycophenolate mofetil[9]. NSAIDs (some of which are general sales) have dangers used with warfarin (because of the potential for a stomach bleed),and have the well-known triple whammy reaction given with a diuretic and ACE inhibitor.

The effect of CBD on CYP2C19 could well be dose-related, as with omeprazole as a CYP2C19 inhibitor where 20 mg has much less effect than 40 mg*[9]*. Low dose CBD or cannabis are well-used worldwide, increasingly including legal use. Yet there are minimal reports of interactions at these lower doses of CBD (noting that smoked cannabis has considerably higher bioavailability of CBD than when used orally).

6. Efficacy data supports higher dose

The McGregor Report found little compelling evidence of efficacy at CBD doses below 150 mg per day. Therapeutic benefits of CBD (across a range of indications) became more clearly evident at doses of 300 and 400 mg. Increased dosing from 60 to 400 mg did not appear to be associated with an increased frequency of adverse effects. No serious adverse events were evident in the studies evaluated. At 300-400 mg oral dosing there is evidence of efficacy with respect to reduced anxiety (in both normal and clinical populations) as well as anti-addiction effects in drug-dependent individuals. More marginal effects on insomnia, neurological disorders and chronic pain were also apparent.

The McGregor Report noted that the 300 mg oral dose of CBD is the threshold at which higher quality evidence accumulates around CBD efficacy, in the absence of significant safety concerns. Reduction in anxiety with single dosing is reported in three studies with healthy volunteers, while efficacy in social anxiety disorder patients is apparent in one study. The observational study of Gulbransen et al. (2020) provides further confirmation of the anxiolytic effects of CBD as well as evidence of pain reduction in a real-world setting, albeit without a placebo control. Gulbranson, an experienced medical practitioner with CBD, recommended dosing at least 100 mg per day to 400 patients who took 40-300 mg/day.[11]

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[10] Grayson L, Vines B, Nichol K, et al. An interaction between warfarin and cannabidiol, a case report. *Epilepsy Behav Case Rep* 2017; 9: 10-11. DOI: 10.1016/j.ebcr.2017.10.001.
Leino A, Emoto C, Fukuda T, et al. Evidence of a Clinically Significant Drug-Drug Interaction between Cannabidiol and Tacrolimus: A Case Report. *Am J Transplant* 2017; 17

[11] [Ref: Gulbransen, G., W. Xu and B. Arroll (2020). "Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand." BJGP Open: bjgpopen20X101010.

In a different application, chronic CBD at 300 mg appears to have potential as a treatment in GVDH, although, again, placebo controlled clinical trials are required to confirm this. The effects on quality of life in Parkinson's disease also appear promising. There are no obvious safety concerns with this dose of CBD across the hundreds of patients treated either acute or chronically in the studies reviewed in this section.

It is suggested that an absolute cap for total THC (acid and neutral form) is provided to remove any ambiguity and, based upon the stipulations outlined in the Delegate's proposal (not more than 2% for a 60mg CBD dose), it is recommended that the maximum THC presence for a Schedule 3 CBD product not exceed 2mg per day.

Registration pathway (Appendix M)

The current down-scheduling proposal i.e. a maximum daily dose of 60 mg with a registration pathway through an Appendix M requirement, will severely limit the likelihood of products being able to achieve registration and thus, further support the illicit market. The McGregor et al Report noted that "A major potential problem for product registration is the lack of evidence that low doses of CBD (≤60 mg or ≤1 mg/kg/day oral doses) have any therapeutic benefits. Thus, products may fail the efficacy requirement for registration of OTC products."

Proposing a Schedule 3 entry which is constrained to a dose limit where existing evidence indicates that therapeutic value will not be achieved seems counter to the intent of making the quality-controlled, safe and efficacious therapeutic good available for patients. As outline above, MCIA recommends that the dose limit be raised, which would address this barrier.

Even where a therapeutic benefit can be demonstrated, the registration pathway for products to come to market will be long and arduous, as each will need to generate data for the specific product/formulation that is being registered and thus, will not provide a solution to patient access barriers (many of which were outlined in the Senate Inquiry report[2]), in the short to medium term. Given the safety profile of CBD, MCIA encourages the TGA to consider options for an expedited pathway.

Such a pathway could concentrate on quality and safety. This would enable consumer access to CBD with a pharmacist's help (as was well-supported by various submitters to the Senate enquiry). Importantly, it would mean that Australians would be able to have access to a product with known ingredients, without inappropriate levels of contaminants (such as heavy metals, pesticides, THC or prescription medicines), and with health professional advice.

Advertising (Appendix H)

The MCIA notes that advertising to consumers would not be allowed. While we see advantages in consumers being informed of the availability through advertising, MCIA is supportive of this entry strategy to down-scheduling CBD. We note that for other medicines in S3 where advertising may have been prohibited initially that it has been allowed over time. MCIA recommends a similar approach for CBD.

4.0 Summary

In conclusion, MCIA strongly recommends that CBD be down-scheduled to S3; with a higher maximum daily dose. MCIA recommends that based on the evidence provided a maximum daily dose of 300 mg be considered, but that at a minimum the dose should be increased to 160 mg/day based upon the dose calculations drawn upon by the Delegate.

The evidence indicates safety at this level, and this is more consistent with already accepted dosing rates and Australian patient profiles. It could be expected that products would be accompanied with appropriate dose rates for different body weights as is common with other OTC products.

This higher dose would also provide greater opportunity for products to be able to meet registration requirements for efficacy, thereby delivering outcomes for patients.

MCIA acknowledges the Appendix M requirement for registration of products, but would encourage the Delegate to consider options for an expedited pathway. In respect of Appendix H, we recommend that a schedule of requirements be published that would allow advertising to occur once those requirements are met.

We believe this approach balances benefits and risk. It will minimise the perverse incentives driving Australians to use illicit cannabis for medicinal purposes and will ensure a health care professional is involved in the OTC supply. It will ensure a quality product with known CBD doses and minimal levels of THC or contaminants will be used by consumers instead of personal importation/purchase of product that is of unknown quality, unknown strength and with potential for high levels of THC and contaminants

This regulatory clarity will provide stronger signals to patients, practitioners, and business than in comparable jurisdictions, providing better safety, quality, and efficacy outcomes for the Australian people.