NHAA Submission

Rescheduling of cannabidiol (CBD) in the Australian Poisons Standard (SUSMP)

Date

Send with cover letter to

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On or before 22 May 2020

Executive Summary

- Cannabidiol has drawn local and international interest as a safe and effective medicine, with significant public demand.
- Australia faces a local scheduling challenge to ensure public access to high quality, safe, and cost-effective cannabidiol products.
- Cannabidiol requires re-scheduling to enable wider use, however current international drug law may present a barrier to complete de-scheduling. However Australia has an opportunity to pre-empt the outcome of international scheduling discussions to best serve its population.
- Cannabidiol has been shown to cause drug interactions, however this should not be a reason for scheduling as evidenced by the absence of St John's wort (Hypericum perforatum) from the Schedules.
- It is possible to have exemption clauses in the Poisons Standard to allow the general availability of scheduled substances, as is the case for Kava (Piper methysticum).
- The scheduling of cannabinoids, cannabidiol and potential stereoisomers requires special attention to ensure access to products representative of natural cannabis.

Scheduling of cannabidiol

Re: Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS #25

There has been considerable public interest in using the cannabis plant for medicinal purposes, both in Australia, and internationally. Of particular interest has been cannabidiol (CBD), a phytochemical constituent of *Cannabis* spp., which confers many of the therapeutic actions of cannabis, including its use in central nervous system disorders such as epilepsy, pain management, nausea, cancer, and immunological disorders (Pisanti et al., 2017). An inquiry into the current barriers to patient access to medicinal cannabis in Australia, conducted by the Australian Senate Community Affairs References Committee, recommended that the Australian Government support the process of down-scheduling or de-scheduling CBD and other non-psychoactive cannabinoids (Senate of Australia Community Affairs References Committee, 2020). Submissions to the Senate by many groups were in favour of increasing access to CBD for medicinal purposes, and proposals for the rescheduling of CBD have been submitted to the Advisory Committee on Medicines and Scheduling. Submissions have come from the Delegate of the Secretary of the Commonwealth Department of Health, and a private applicant, requesting changing the scheduling of CBD.

Currently, cannabis and its phytocannabinoid constituents (CBD, tetrahydrocannabinol (THC), and others), are scheduled in Australia in the Poisons Standard (February 2020), in Schedules 4, 8 and 9 in various forms (Therapeutic Goods Administration (TGA), 2019). The scheduling is in alignment with international drug law. Cannabis is included in the United Nations Single Convention on Narcotic Drugs 1961 (United Nations, 2013). In recent years, there has been global interest in reducing restrictions around cannabis. The World Health Organization (WHO) Expert Committee on Drug Dependence has suggested that "[cannabis] preparations containing predominantly cannabidiol and not more than 0.2 per cent of delta-9-tetrahydrocannabinol are not under international control.", and this suggestion is being considered by the United Nations Commission on Narcotic Drugs (United Nations Commission on Narcotic Drugs, 2020). Australia is signatory to United Nations drug control treaties (United Nations, 2013), so while Australia would be in contravention of these treaties by de-scheduling CBD at this time, Australia has the

opportunity to pre-empt the decisions of the UN to act upon the WHO's recommendations, and tailor its local laws to best serve its population.

Cannabidiol

Cannabidiol (CAS number 13956-29-1), and its precursor carboxylic acid, cannabidiolic acid, is found in the cannabis plant, alongside structurally related phytocannabinoids such as tetrahydrocannabinol (THC). Many other pharmacologically active phytochemicals are present, including volatile terpenoids such as beta-myrcene (Lewis et al., 2018), and classes such as flavonoids, stilbenes, coumarins, polysaccharides, and sterols (Alves et al., 2020; Upton et al., 2014), The proposals for rescheduling of cannabidiol focus mainly around ensuring high concentrations of CBD (98%+) and low levels of THC (<0.2-2%), but give no consideration to the remaining phytochemicals in the plant.

Cannabidiol risks and toxicity

The risk and toxicity associated with low-dose cannabidiol is low, as supported by the TGA's safety review in April 2020 (Therapeutic Goods Administration (TGA), 2020), and the World Health Organization's review (World Health Organization, 2018). The most important safety issue appears to be that cannabidiol has been shown to cause pharmacokinetic drug interactions. In doses of 8-25mg/kg/day (far exceeding the rescheduling proposals), CBD has the potential to cause interactions via numerous CYP450 enzymes, including CYP1A1, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 (Zendulka et al., 2016, p. 450). Interactions have been observed with the anti-epileptic drug clobazam (20–25 mg/kg CBD; increased concentration of clobazam active metabolite), and warfarin (>5mg/kg/day CBD; decreased warfarin metabolism) (Alves et al., 2020). These doses far exceed the Australian Department of Health's proposed recommendation of 60mg CBD per day, which qualifies as low dose (Zendulka et al., 2016, p. 450).

The CBD-induced drug interactions should not present a barrier to down-scheduling (or de-scheduling) CBD. Within the domain of herbal medicines, similar potential for pharmacokinetic interactions exists for hyperforin, a constituent of Hypericum perforatum (Chrubasik-Hausmann et al., 2019; Nicolussi et al., 2020), at normal therapeutic doses. H. perforatum is a widely-used herb that is well known for its

pharmacokinetic drug interactions and readily available in many unscheduled products in Australia.

Precedence exists for other herbal products on the Australian market which have entries in the Poisons Standard, and are available without prescription. An example of this is Piper methysticum (kava), which has strict dosage and manufacturing requirements detailed in the Poisons Standard under a Schedule 4 entry (Therapeutic Goods Administration (TGA), 2019). The major active constituents of the plant (the kavalactones) are explicitly controlled, with exemption clauses allowing products to be manufactured and supplied for general use. It is therefore possible to create scheduling entries to allow the manufacture of cannabidiol products which are not captured by the Schedules, and would allow listing on the Australian Register of Therapeutic Goods under AUST-L(A) listings, enabling more cost-effective access to the Australian public while not compromising safety.

Cannabis products, including CBD, are currently produced and supplied through unlawful black market channels. These supply channels are not regulated in any way, and present significant risk to public safety due to potential inconsistent phytochemical profiles, contamination, adulteration and substitution with other substances. As a requirement for lawful manufacture and supply of therapeutic goods in Australia, facilities must adhere to good manufacturing practices to ensure purity and consistency of products in accordance with the Therapeutic Goods Act 1989 (Commonwealth of Australia, 2019).

Response to scheduling proposals

Submission by the Delegate of the Department of Health

Re: https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-joint-acmsaccs-meetings-june-2020

NHAA's response: The NHAA generally agrees with the Delegate of the Department of Health's proposal on the controls around cannabidiol, its stereoisomers, and the composition of cannabis products only containing natural cannabinoids. The NHAA believes the dosage range could be increased to accommodate for the larger average body size in Australia. The dosage range of 60mg per day based on 1mg/kg/day suggests a body weight of 60kg. This doesn't represent the typical Australian adult, to

which the scheduling is referring. The average body weight for Australian adult males is 87kg and females 72kg (Australian Bureau of Statistics, 2018), suggesting a dose of at least 85mg CBD per day be available for these average weights.

Submission by Private Applicant

Re: https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-acms-and-joint-acmsaccs-meetings-june-2020#s22

The NHAA believes it is important to be very specific about the phytochemistry of *Cannabis* spp., and has the following suggestions to the private applicant's submission about CBD rescheduling:

> Private applicant proposal:
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> Schedule 8
>
> *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).*

NHAA's response: Whole-plant cannabis extracts, depending on extraction method and solvents used, can contain other phytochemical classes such as volatile terpenoids, flavonoids, stilbenes, coumarins, polysaccharides, sterols and others (Upton et al., 2014). It is the cannabinoid content that is subject to legal controls locally and internationally, therefore any mention of "whole-plant" should focus on the cannabinoid content, like in the the following amended example:

iv) it is a whole plant cannabis product or distillate or isolate which, of the cannabinoid content, contains at least 98 per cent cannabidiol and less than or equal to 0.2 per cent tetrahydrocannabinol (THC).

The current scheduling doesn't distinguish between cannabinoids and their carboxylic acid precursors which occur in the plant (Bonini et al., 2018), however this level of

distinction hasn't been necessary, and legislation on cannabinoids appears to simply mention the decarboxylated versions of these phytochemicals and treats the precursors as equivalent.

Private applicant proposal:

Schedule 4 - Amend Entry

CANNABIDIOL in preparations for therapeutic use where:

a. cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation 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

b. ~~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.~~ 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.

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.

NHAA's response: The terms synthetic or semi-synthetic are ambiguous and can introduce confusion. If a molecule is a copy of cannabidiol (with due attention to stereoisomerism), then it is a copy. How a manufacturing process produced the copy is not relevant. The terms synthetic or semi-synthetic should not be used so as to avoid confusion with the term synthetic cannabinoids and cannabimimetics referred to in Schedule 9 of the Poisons Standard (Therapeutic Goods Administration (TGA), 2019), which can be hazardous to human health (Courts et al., 2016; Le Boisselier et al., 2017).

Stereoisomers of CBD are important, as (+)-CBD binds to cannabinoid CB1 and CB2 receptors, whereas (-)-CBD does not (Bisogno et al., 2001). (-)-CBD is found in cannabis, whereas (+)-CBD is not (ElSohly & Slade, 2005), so any efforts to create synthetic CBD or other cannabinoid products should be diligent in recreating only the stereoisomers present in cannabis. A more suitable wording may be the following:

b. ~~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.~~ cannabidiol is a copy of the naturally occurring molecule and comprises 98 per cent or more of the total cannabinoid content of the preparation and other cannabinoids, other than cannabidiol, must comprise 2 per per cent or less of the total cannabinoid content of the preparation, and must also be identical to naturally occurring cannabinoids.

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.

Impact and consequences of the proposed scheduling amendments

The impact to naturopaths and Western herbalists with CBD being moved to Schedule 3 would have minimal impact to practice, as neither have authority to prescribe products which are captured by the Schedules. On the other hand, a de-scheduling of CBD would allow naturopaths and Western herbalists to prescribe CBD products. The NHAA would recommend that practitioners of Western herbal medicine undertake specific training in the use of cannabidiol and/or other cannabis products as the legal status allowed. While naturopaths and Western herbalists are trained in plant chemistry and the medicinal use of plants, and are certainly in a good position to integrate new plant knowledge and utilise it effectively, due to the legal status of Cannabis spp. and its phytochemicals in Australia, education on Cannabis spp. has been very limited. Additionally, the use of cannabidiol as a phytopharmaceutical does not represent traditional use of the plant, nor typical preparations of herbal medicines as commonly used by naturopaths and Western herbalists (Bone & Mills, 2013; Bonini et al., 2018; Grieve, 1996).

Western herbal medicine commonly utilises hydroethanolic extracts of plants which contain a broad range of phytochemicals, all of which have the potential to be

pharmacologically active, acting in synergy with each other to create the observed biological effects. Synergy involves diverse pharmacokinetic and pharmacodynamic mechanisms, and physicochemical interactions between molecules (Caesar & Cech, 2019). Like with other plants, this phenomenon is observed in Cannabis spp. where various cannabinoids affect the pharmacology of other cannabinoids (Pisanti et al., 2017). Cannabis phytochemistry is also not limited to cannabinoids, but includes various terpenoids, flavonoids and other phenolics, polysaccharides and sterols (Upton et al., 2014). These classes of molecules, from cannabis (Bergman et al., 2019; Lewis et al., 2018) and other plant species, are known to have extensive biological activity (Bone & Mills, 2013). The traditional use of cannabis is typically whole-plant (or whole plant part) preparations (Bonini et al., 2018), so to isolate a single phytochemical such as cannabidiol, does not represent what would be considered common practice in Western herbal medicine.

Despite naturopaths and herbalists having the requisite knowledge to adopt cannabidiol and other cannabis products into their practice, the ability to do so hinges on the legal status and scheduling of Cannabis spp. in Australia. Currently neither profession is registered with the Australian Health Practitioner Regulation Agency (AHPRA), however work is ongoing in this area by organisations such as Australian Register of Naturopaths and Herbalists (ARONAH) (ARONAH, 2020; Victorian Department of Health, 2013). As such, the requirements of ARONAH reflect the requirements of other AHPRA-registered professionals but specifically catering for naturopaths and herbalists.

The NHAA would recommend specific cannabis education to its members (who are also registered with ARONAH) in the context of naturopathic and Western herbal medicine practice before widespread use of cannabis as a traditionally-prepared herbal product by these professions. It would also be recommended that herbal products made from cannabis be restricted by scope of practice, however the current regulations do not have provision for authorising naturopaths and herbalists to prescribe particular substances or products like they do for medical doctors.

The NHAA supports the intent to down-schedule cannabidiol to enable increased access to this phytochemical for medicinal purposes, with reduced costs and increased safety for patients using this medicine. A complete de-scheduling of CBD does not appear to be possible at this time due to international law associated with

cannabis and its constituents, however this situation is changing. Australia may decide to pre-empt the outcome of international discussions on cannabidiol scheduling, and change local laws in favour of the requirements of its population.

Due to the acceptable safety profile within the proposed dosage ranges, significant public demand for high quality, cost-effective CBD preparations, the NHAA believes it is in the public interest to change the scheduling of CBD to reduce costs and barriers to supplying CBD products.

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