The Honorable Greg Hunt,

Minister of Health,

Parliament House,

Canberra.

14. December, 2018

Dear Mr Hunt,

Thank you for your letter dated 29 November 2019, in which you responded to the key recommendations of a position paper on medicinal cannabis written by Associate Professor Kylie O'Brien PhD and Professor Ian Brighthope, supported by myself and many representatives of the cannabis and hemp industry in Australia.

We thank you for the direction to contact the Department of Infrastructure, Regional Development and Cities regarding changing the current roadside drug testing practices and decriminalising the presence of THC in the body whilst driving, provided the driver is not impaired. We will be following up on this shortly.

You have stated that there have been changes to expedite the process by which doctors may apply, through the SAS scheme, to prescribe medicinal cannabis, and that the turnaround time for processing is two days. Whilst having one online form which goes to both the TGA and state/territory health departments is an improvement with respect to reducing the amount of paperwork required of busy doctors, and time taken for processing, this does not address the real issues at hand. The issues are that the regulatory structures set up around medicinal cannabis are unnecessarily restrictive and not in the best interests of the public. They will also restrict the growth of the medicinal cannabis industry in Australia.

It is incorrect that *'Any registered Australian doctor may apply to the TGA to access an unapproved medical cannabis product for their patient for any medical condition/indication if they feel it is appropriate to do so'*. There is a lack of harmonisation across the states and territories- some states do not allow general practitioners to prescribe medicinal cannabis products. See **Attachment 1** for a summary of state/territory prescriber access.

Your main arguments against CBD being off-scheduled are that:

a) it has a number of significant side effects at the dosages required to treat epilepsy in children,

b) it interacts very strongly with a number of other prescription medicines, and

c) the conditions it is prescribed for to treat require the diagnosis and management of a doctor

We would like to address these three points.

a) it has a number of significant side effects at the dosages required to treat epilepsy in children

In relation to epilepsy, the main concerns have been around potential drug-herb interactions, rather than CBD treatment alone. There are some studies which have reported side-effects in association with drug-CBD interactions. However, several studies have indicated that there have not been serious adverse events and that side effects were mild:

- In a study of 39 adults and 42 children with treatment-resistant epilepsy who were taking concomitant anti-epileptic medication and CBD, increases in serum levels of three drugs (topiramate, rufinamide, and N-desmethylclobazam) were found in children and adults, increases in serum levels of two drugs (zonisamide and eslicarbazepine) were found in adults, and decreases in clobazam serum levels were seen (children and adults) with increasing CBD dose. Except for clobazam and desmethylclobazam, all noted mean level changes were *within the accepted therapeutic range*. Abnormal liver function test results were noted in participants taking concomitant valproate (Gaston et al. 2017)[1].

- In a survey of 117 parents of children with high refractory epilepsy, who gave their children CBD (median latency from epilepsy onset to CBD initiation of five years, during which the child's seizures failed to improve after a median of eight anti-epilepsy medications), not only was there a significant reduction in the number of seizures, but the side effects were found to be uncommon except for an increase in appetite (in 30%) (Hussain et al. 2012). In addition, a high proportion of the children had improved sleep (53%), mood (63%) and alertness (71%) during CBD therapy. These children were taking a median number of two anti-epileptic drugs concurrently with CBD. The study found that 74% reported the successful discontinuation of at least one anti-seizure drug during CBD exposure [2].

- In another survey of Mexican parents of 43 children with refractory epilepsy (47% of cases had previously been treated with 9 or more anticonvulsant therapies), the parents reported a decrease in convulsions when CBD was used in 81% of cases (a moderate to significant decrease occurred in 51% of cases, and 16% of cases were free from seizure), and a reduction in number of anti-epileptic drugs in 9/43 cases. No serious adverse effects were reported, with only some mild adverse effects in 37% of cases, such as increased appetite (10/43) or changes in sleep patterns (4/43, one insomnia, three broken sleep) (Aguirre-Velazquez et al. 2017)[3]

- A paper by Devinsky et al. (2014)[4] states that: '*Few data exist regarding drug interactions with CBD in humans, although there are some theoretical concerns that could have implications for its use in people with epilepsy (PWE)'*. They go on to say that: *'CBD is a potent inhibitor of CYP isozymes, primarily CYP2C and CYP3A classes of isozymes, in vitro and in animal models. This*

[1] Gaston TE, Bebin EM, Cutter GR et al. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017; 58(9):1586-1592.

[2] Hussain SA et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. Epilepsy Behav 2015; 47():138-41.

[3] Aguirre-Velazquez CG. Report from a survey of parents regarding the use of cannabidiol (medicinal cannabis) in Mexican children with refractory epilepsy. Neurol Res Int 2017; 2985729

[4] Devinsky O et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014 Jun;55(6):791-802.

is particularly important because many medications are substrates for CYP3A4. However, inhibition has typically not been observed at concentrations used in human studies'.

No-one would argue that the treatment of childhood epilepsy or any other serious disease requires the care of a neurologist, nor that care should be taken with the concomitant use of CBD or any other herb and epilepsy medication. The potential increased availability of CBD, should it be off-scheduled, would not necessarily result in parents self-treating their child's epilepsy with CBD. The same risk of parents treating their own children is already present with any herb, for any condition. The fact remains that overall, CBD is quite safe. That doesn't mean it is safe for everyone, just as for any herb or supplement. Vitamin A and Vitamin D, for example, can be very toxic in high doses; however they are not scheduled on the SUSMP.

A World Health Organization (WHO) Expert Committee on Drug Dependence Pre-Review Report on CBD published in 2017 states that: '*In general, CBD has been found to have relatively low toxicity, although not all potential effects have been explored*'. It concluded that: *'Across a number of controlled and open label trials of the potential therapeutic effects of CBD it is generally well tolerated, with a good safety profile'* (WHO 2017, p.13)[5]. It also states that '*To date, there is no evidence of recreational use of CBD or any public health related problems associated with the use of pure CBD*' and '*In humans, CBD exhibits no effects indicative of any abuse or dependence potential'* (WHO 2017)[5].

The WHO Pre-Report on CBD states that the following has been found from <u>in-vitro</u> and <u>animal studies</u>:

- 'CBD affects growth of tumoral cell lines, but has no effect in most non-tumour cells. However, a pro-apoptotic effect has been observed in lymphocytes.
- It has no effect on embryonic development (limited research)
- Evidence on potential hormonal changes is mixed, with some evidence of possible effects and other studies suggesting no effect, depending on the method used and the particular hormone
- It has no effect on a wide range of physiological and biochemical parameters or significant effects on animal behaviour unless extremely high doses are administered (eg, in excess of 150 mg/kg iv as an acute dose or in excess of 30 mg/kg orally daily for 90 days in monkeys)
- Effects on the immune system are unclear; there is evidence of immune suppression at higher concentrations, but immune stimulation may occur at lower concentrations.
- There is potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes, but it is not yet clear whether these effects occur at physiological concentrations' (WHO 2017)[5]

b) that it interacts strongly with a number of other prescription medicines

The fact is that many herbs potentially may interact with pharmaceutical medications. The question for regulators is why single out CBD as a special case and quarantine it as a Schedule 4 medicine? What is the evidence that it interacts 'very strongly' and with which medications?

[5] World Health Organization WHO Expert Committee on Drug Dependence Pre-Review. Cannabidiol. Geneva: WHO 2017.

The WHO report on CBD states: 'There is potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes, *but it is not yet clear whether these effects occur at physiological concentrations*' (WHO 2017)[5]. This is similar to the conclusion of Devinsky et al. (2014)[4] quoted earlier, that potential inhibition of CYP isoezymes by CBD has typically not been observed at concentrations used in human studies.

In general, many of the proposed interactions between drugs and herbs are theoretical, based on cell and animal studies, rather than real interactions in humans. However, it is also true that there are studies which do substantiate drug-herb interactions in humans. The Chinese herb Radix Salviae Miltiorrhizae for example, interacts with warfarin (as does CBD) and there have been some case studies reported of such interactions. Responsible herbalists check potential drug-herb interactions and avoid prescribing herbs that may potentially interact with medications. Over 70% of Australians use some form of complementary medicine. St John's Wort interacts with the antipsychotic drug Clozapine, anti-viral drugs Cobicistat and Atanazavir, anti-malarial medication, the hypolipidaemic agent Atorvastatin, anti-coagulant Clopidogrel, antidepressant Citalopram, narcotic analgesic Bupenorphrine[6], to name just a few. St John's Wort is regulated as a complementary medicine and listed on the ARTG. Labelling on bottles of St John's Wort warns patients that if they are taking other medication, they should consult a doctor. Such labelling would be important if CBD was to be regulated as a listed complementary medicine or a registered medicine on the ARTG.

c) that the conditions it is prescribed for require the diagnosis and management of a doctor

It is true that in order to label a disease, it must be diagnosed by a medical practitioner. However, there is a strong movement towards self-care of illness in Australia, and the high use of complementary medicines (over 70% of the population in Australia) bears this out. Australians consult other healthcare practitioners such as Chinese medicine practitioners (regulated via statutory regulation in Australia) and naturopaths and western herbalists for the management of a range of labelled diseases or conditions that have been diagnosed (by a medical practitioner). This includes anxiety, insomnia, pain, diabetes, inflammatory conditions and many others, for which CBD has been shown to be efficacious. Responsible practitioners practise within their scope of practice, and this includes western medicine and allied healthcare practitioners.

CBD is an extract from the plant Cannabis sativa. It has been shown to provide a range of beneficial actions, to be safe and have low toxicity. Like any other herb, there can be drug-herb interactions. In this, CBD is nothing special. Given its lack of potential for addiction and abuse, there is no logical reason to treat CBD any differently than any other herbal medicine.

Canada faced the possibility that their medicinal cannabis market would plummet following legalisation of adult use. However, a report suggests that this is not the case. Canadians are still consulting their healthcare practitioner for advice on how to use medicinal cannabis[7]. There is no evidence that Australians would suddenly start self-medicating, in particular for serious diseases if CBD were to be off-scheduled, any more than they are self-medicating with other herbs.

In addition, the US Senate voted 87-13 to pass the *Agriculture Improvement Act 2018* (the 'Farm Bill') which, if it passes, will amend the *Controlled Substances Act* to exempt the entire hemp plant and all of its derivatives from the Schedule 1 designation. This may also open a path for the federal approval

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[6] IMGateway. Available at: https://www.imgateway.net [accessed 13 Dec 2018]

[7] Marijuana News. The number of patients enrolled in Canada's medical marijuana program is increasing despite cannabis legalization. Available at 420intel.com [accessed 14 Dec 2018]

and regulation of CBD products for medicinal and therapeutic use. As you are aware, 35 states in the US have already legalised commercial hemp[7].

The public are clearly in support of medicinal cannabis. A 2016 survey of 1748 Australians who were using cannabis for medicinal purposes prior to legalisation found that most respondents (960 of 1081 who responded, 88.8%) believed that cannabis use should be legal for all purposes (recreational and medical), whilst 11.0% believed it should be legal only for medical reasons, and 0.2% believed that all use should remain illegal (Lintzeris et al. 2018)[8].

As Minister for Health, you are likely to gain significant support from a large percentage of the Australian voters if you were to de-schedule CBD. One in five Australians suffer from chronic pain alone (one in three over the age of 65 years). This population alone represent a significant proportion of the voters in this country. A strong public health campaign about medicinal cannabis, including CBD, would be an important part of an overall strategy, in a similar way to Canada which has also launched its own public health and awareness campaigns in relation to the legalisation of adult use of cannabis.

Any opposition from professional bodies could be addressed by providing the evidence in support of its safe and effective use by your advisor Richard Temperly with input from experts, academics and researchers from integrative medicine institutions.

We look forward to further discussions on this matter in early 2019.

Yours sincerely

Charles Kovess

Professor Brighthope

A/Professor Kylie O'Brien

[8] Lintzeris N et al. Medicinal cannabis in Australia, 2016: the Cannabis as Medicine Survey (CAMS-16). Med J Aust 2018; 209 (5): 211-216.