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Submission regarding proposed amendments referred for scheduling advice to the Joint ACMS-ACCS #25

as outlined in the Public Notice of 24 April 2020 (item 2.5)

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1.0 About Applied Cannabis Research

Applied Cannabis Research, a division of Southern Cannabis Holdings, is a contract research organisation (CRO) focused on clinical research within the medicinal cannabis sector.

Applied Cannabis Research is currently conducting several observational cohort studies of medicinal cannabis prescribing within the Australian clinical practice context. As such, we are in a position to understand the current clinical cohort/s for which low dose CBD is being prescribed and the associated patient reported outcomes of this treatment.

Further, our team is comprised of those from an academic research background who have expertise in cannabinoid clinical research and have an in-depth understanding of the existing medicinal cannabis evidence base, including that for CBD only products.

ACR is actively engaged with patients, clinicians, researchers, industry suppliers and also government bodies on the topic of medicinal cannabis and are therefore well placed to provide input on the proposed SUSMP amendment.

2.0 Summary

- ACR supports the proposal to make low dose CBD available as a Schedule 3 medicine as outlined in the Public Notice of 24 April 2020 (item 2.5).
- Use of illicit CBD products is occurring which exposes patients to potential harms associated with unregulated products including contamination.
- Amendment of the SUSMP may lead to increased registration of CBD products on the ARTG which is beneficial to Australian patients.
- Increased ARTG registration activities within the industry will require and promote further clinical research in the area of low dose CBD products, adding to the knowledge base.
- There is potential for a decreased burden on the unregistered medicines pathway (i.e. SAS-B) due to some products being potentially made available via S3.
- TGA guidance will be required to clarify what evidence level is sufficient for an S3 low dose CBD application.

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3.0 Sufficient safety and lack of addiction potential to support low dose CBD S3 classification

The safety profile of CBD has been explored explicitly in a number of Phase I clinical trials, as well as being a primary outcome of a number of pilot randomised controlled trials (RCTs) and observational open-label studies. Existing evidence has shown that doses of up to 6000mg of CBD taken orally are safe and generally well tolerated in adult subjects, and that repeated dosing of 1500mg/day is tolerated, with only mild and moderate adverse events reported at these high doses[1].

Furthermore, a recent trial of hepatically impaired patients confirmed that 200mg doses of CBD were safe and tolerated in these patients, with no severe adverse events being reported[2]. The existence of evidence from studies such as these, in combination with other published trials[8] and observational learnings from current clinical practice[3], support the conclusions reached by the Department of Health in their submission and report [14].

Further, the potential for CBD to become a drug of abuse has not been found, which is in part due to its molecular signalling mechanisms. Unlike THC, CBD does not directly activate the receptors responsible for triggering reward circuits within the brain, and hence lacks the addictive potential of THC and certain other synthetic cannabinoids[7]. Specifically, an RCT in polydrug users using moderate to high CBD doses (400-1500mg) concluded that there was a significantly low abuse potential of CBD in a highly sensitive polydrug user population[4]. In fact, CBD has been suggested as a possible novel treatment for drug addiction given the anti-craving and anti-addiction effects that have been observed in preclinical and early phase human experimental studies [5,10]. Results from recent clinical studies have shown promise for CBD in areas such as opiate abuse[6], which are ongoing.

4.0 Unregulated CBD consumption is posing a risk to Australian patients

The widespread use and marketing of low dose CBD “nutraceutical” products continues to rise. Recent data from the United States and the UK suggest approximately 9-14% of the population have used some form of CBD product [11,12].

Further to this, the purchase of these products online by Australians is ongoing and, due to marketing of these products and the apparent accessibility of CBD elsewhere in the world, many Australians are

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purchasing these products without understanding that they are in fact illicit, or appreciating the potential risks associated with their consumption.

Studies of CBD products purchased and tested for content in the USA have shown that in only 30% of cases did the content match the product label[9]. Patients were either receiving products with lower CBD content than advertised, affecting potential efficacy, or receiving products with potentially hazardous contaminants including THC in 20% of cases[9]. This is a further concern if patients are unaware and are driving or operating heavy machinery. Another similar study in the UK also showed mislabelling as well as contamination of CBD products with harmful solvents and heavy metals[13]. This further supports why amendments such as the proposed, which may lead to increased access to regulated low dose CBD products, are beneficial to Australian patients and help to mitigate existing public health risks.

5.0 SUSMP amendment will promote greater ARTG registrations of CBD products

From the perspective of research organisations, the proposed amendment is a positive step that may provide incentive for greater registration uptake for CBD products within the Australian market. Unlike in a traditional pharmaceutical development framework, there are already competing "generic" products within the current medicinal cannabis market, meaning that the traditional motivations to register a patent protected medicine (ensuring a period of market exclusivity) are absent.

Given the existing challenges with approval pathways in Australian states and territories for medicinal cannabis products (including low dose CBD), the opportunity to provide an alternative legitimate path that overcomes these approval pathway challenges, for a subset of products, is positive for the industry and for patient access.

6.0 S3 registration option will provide an incentive for more clinical research with CBD products

For low dose CBD products to be made available as Schedule 3 medicines, we understand that drug sponsors will be required to demonstrate efficacy and safety of their product for the selected indication. At present, the literature to support a dose of 1mg/kg/day (~60mg/day) of CBD for any indication is scarce. The few existing placebo-controlled studies using doses ≤150mg of CBD alone

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have not shown any significant effect over placebo in a range of indications including insomnia[17], anxiety [21,22]and inflammatory bowel disease (IBD)[15]. This is despite the Department of Health claiming that CBD in doses of up to 1mg/kg/day "has possible utility in the management of chronic and generalised pain of broad aetiologies through both systemic and localised administration and in anxiety and insomnia"[14]. There are, however, isolated case reports and case series supporting low dose CBD in cases of refractory illness such as insomnia[19] and anxiety[20].

Interestingly, IBD is one of the few indications where doses ≤1mg/kg/day of CBD have been evaluated in an RCT (20mg/day oral CBD for 56 days)[15]. The study however concluded there was a lack of effect of low dose CBD on disease progression markers or remission rates when compared to placebo. A recent survey of Australian IBD patients[16] reported that a proportion were taking (mostly illicit) CBD products and suggested patient reported benefits, however in line with the prior RCT outcomes, benefits were not reported in the areas of disease pathology, but rather associated symptom relief. Patients reported better sleep, less stress/anxiety and pain associated with their IBD.

This potentially highlights one applicable indication where supplementary low dose CBD may have benefit to a patient's ability to manage their chronic disease status. That is, when taken in adjunct to existing clinically proven therapies. These are potential areas where low dose CBD research programs could explore efficacy; in management of secondary symptoms of chronic disease such as stress and anxiety.

The evidence to support low dose CBD efficacy is limited as few studies have directly assessed its effects in isolation. There are numerous cases in the literature where low dose CBD has been placed in an RCT but in combination with THC[18], making conclusions about its effects alone immeasurable. For this reason the literature to support low dose CBD alone is even more scarce.

This provides an excellent opportunity for new clinical research to be undertaken with low dose CBD products that addresses the question of efficacy in a range of indications including in secondary symptom control. This is beneficial to the knowledge base as it will stimulate greater research interest and further our understanding of CBD and its utility as a medicine more broadly.

7.0 Potential to ease burden on unregistered medicines pathway

Facilitating access to low dose CBD products through the S3 registered medicines pathway may inadvertently allow for easing on the unregistered medicines pathways, in particular the Special

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Access Scheme B (SAS-B), that has suffered from large volumes of applications since medicinal cannabis products have become available to prescribe within Australia.

During some periods it has been noted that SAS-B approval turnaround times are lengthy/delayed which is predominantly due to high volumes of applications to review and process given the limited staff resources available. Increased use of S3 registered CBD medicines will reduce the number of SAS-B applications currently submitted for low dose CBD products and should allow for increased facilitation of patient access via faster decision turnaround.

8.0 ACR supports the proposed amendments, noting that drug sponsors must be provided with clarity on the path to S3 registration for low dose CBD products

We agree with the assessment made by the Department of Health that CBD in low doses is safe and should be captured in Schedule 3 of the SUSMP. Given the lack of clarity around what an initial Schedule 3 submission for low dose CBD would entail, it would be beneficial for the TGA to present to the industry and research groups that will be involved in evidence gathering, to clarify what requirements are necessary to demonstrate efficacy and safety of low dose CBD products.

Questions around the necessity to include placebo or active comparator groups, the number of patients to be considered a representative indication cohort and the ability to use existing published data from other low dose CBD products for an individual application, will need to be clarified. This will be highly informative for both industry and research organisations to understand the level of evidence being sought by the TGA and the types of clinical research that may be considered and included in S3 registration submissions.

Submitted by Dr Melissa Benson
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